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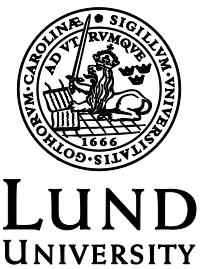
Auditory event-related potentials and cognitive outcome after very preterm birth

Holger Hövel



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Auditory event-related potentials and cognitive outcome after very preterm birth

Children born before 32 gestational weeks have a high incidence of neuropsychological deficits. The structural and functional correlates of such impairments in preterm infants are incompletely understood, and early diagnostic tools are needed, but still lacking. Auditory event-related potentials (AERPs) are neurophysiological measures of cortical sound detection, encoding, discrimination, and attentional processes. Abnormal AERPs have been associated with cognitive and behavioral problems. To date, there has been very little research into AERP in preterm infants. Therefore, our aim was to investigate if AERPs in infants and children born very preterm correlate with cognitive outcome, and whether AERPs are related to findings on magnetic resonance imaging (MRI) at term. We investigated 70 children at 4-5 years of age who had been born very preterm, using AERPs and psychological testing, and compared them with more mature preterm and full-term children of the same age. Furthermore, we performed AERPs and MRI in another 42 very preterm infants at term, and these infants had a follow-up testing at 2 years of age.

AERPs at preschool age in children born very preterm showed abnormalities in comparison with more maturely born children. Similar abnormalities have been reported in full-term children with cognitive and behavioral problems (especially smaller amplitudes of early AERP deflections). Within the very preterm group, faster early sound processing was associated with better psychological test results, and sound differentiation was different between children with normal and abnormal test results. We showed that immaturity at birth, neonatal morbidity, and neonatal brain damage had an impact on different aspects of auditory processing, and that this impact still was present at 5 years of age. In the infants investigated at term age, we showed that later sound processing as well as sound differentiation has a high correlation with both cognitive and neurological outcome. Neonatal morbidity rather than prematurity itself had a strong impact on sound differentiation. AERPs showed stronger associations with outcome than brain volumes.

We conclude that AERPs are promising as a prognostic tool for outcome in very preterm infants. They can add considerably to established anatomical methods such as MRI. However, more research is needed before AERPs can be applicable in clinical praxis.

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Auditory event-related potentials and cognitive outcome after very preterm birth

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‘The average Ph.D. thesis is nothing but a transference of bones from one graveyard to another.’

J. Frank Dobie (1888-1964)

To Oma,

Because you have shown me the right way, at the right time.

To Hillevi,

Because you fill this way with love and joy and all that is important to me.

To my family,

Because you have given and give me the safety and confidence to grow, although all too far away from you.

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II. Hövel H, Partanen E, Tideman E, Stjernqvist K, Hellström-Westas L, Huotilainen M, Fellman V. Auditory event-related potentials are related to cognition at preschool age after very preterm birth. *Pediatric Research,* Doi:10.1038/pr.2015.7 (e-pub ahead of print)

III. Hansen-Pupp I, Hövel H (equal contribution), Hellström A, Hellström-Westas L, Löfqvist C, Larsson E, Lazeyras F, Fellman V, Hüppi PS, Ley D. Postnatal decrease in circulating Insulin-like growth factor-I and low brain volumes in very preterm infants. *J Clin Endocrinol Metab* 2011;96:1129-1135.

IV. Hövel H, Hansen-Pupp I, Partanen E, Hüppi PS. Rosén I, Ley D, Huotilainen M, Fellman V. Clinical value of auditory event-related potentials after very preterm birth. *In Manuscript, to be submitted to Cortex*

Summary

Children born before 32 gestational weeks, even those without severe disabilities, have a high incidence of neuropsychological deficits, including reading, learning, language, and memory disorders, as well as behavioral problems. There is only an incomplete understanding of the structural and functional correlates of such impairments in preterm infants. And although there is need for early diagnostic tools, they are still lacking.

Auditory event-related potentials (AERPs) are neurophysiological measures of cortical brain activity related to auditory stimuli which may be extracted from an electroencephalogram. They have been used in neuropsychological and developmental research for more than 50 years. AERPs have been shown to reflect various cortical processes such as sound detection, encoding, and discrimination as well as attentional processes. These processes are essential for pre-conscious orienting in a sound environment, and for cognitive processes such as language learning. In full-term children and adults, abnormal AERPs have been associated with cognitive and behavioral problems that have an increased incidence after very preterm birth. However, to date, there has been little research into AERPs in preterm infants. Therefore, the aim of this thesis was to investigate if AERPs in preschool children born very preterm are different from more mature preterm and term-born children, and whether these differences are associated with cognitive outcome. Furthermore, we investigated if AERPs at term (40 gestational weeks) were associated with outcome during toddler age, and we compared this association with that of brain volumes as measured by magnetic resonance imaging (MRI) at term.

For this purpose, we first investigated 70 children at 4- 5 years of age who had been very preterm, and compared them with more mature preterm and full-term children of the same age. These children were investigated with AERPs and psychological testing. Furthermore, we performed AERPs and MRI with another 42 very preterm infants at term, and these infants had follow-up testing at the age of two.

Our results demonstrate that AERP measures at preschool age in children born very preterm are different from those of children who are born more mature, and that the abnormalities (especially reduced amplitudes of early AERP deflections) were similar to findings in full-term children with cognitive and behavioral problems. However, we did not find any differences in general sound differentiation capacity between study groups at this age. In the very preterm group, faster early sound encoding and processing were associated with better psychological test results, and sound differentiation was different between children with normal and abnormal test results. Neonatal morbidity had an impact on auditory processing even at five years of age and affected processes which were different from those affected by prematurity itself and by neonatal brain damage seen on ultrasound.

In the infants investigated with AERPs at term, we showed that later processes of sound processing (after 250 ms), as well as sound differentiation, have a high correlation with both

cognitive and neurological outcome at the age of two. Furthermore, neonatal morbidity rather than prematurity itself had a strong impact on sound differentiation. AERPs showed stronger associations with outcome than brain volumes. However, brain volumes were associated with concentrations of Insulin-like growth factor-I during the neonatal period, while AERPs were not.

We conclude that AERPs are promising as a prognostic tool for outcome in very preterm infants. As a measure of cortical function, this technique can add considerably to the established methods for demonstration of structural abnormalities, such as MRI. However, more research is needed before AERP can be applicable in clinical praxis.

List of abbreviations

ADC	Apparent diffusion coefficient
ADHD	Attention deficit hyperactivity disorder
aEEG	Amplitude-integrated electroencephalography
AERP	Auditory event-related potential
AGA	Appropriate for gestational age (birth weight)
BSID	The Bayley Scales of Infant Development
BW	Birth weight
CP	Cerebral palsy
cPVL	Cystic periventricular leukomalacia
CSF	Cerebrospinal fluid (volume)
cUS	Cranial ultrasound
DEHSI	Diffuse excessive high signal intensity
DWI	Diffusion-weighted imaging
DTI	Diffusion-tensor imaging
DTT	Diffusion-tensor tractography
EEG	Electroencephalography
ELGA	Extremely low gestational age
fMRI	Functional magnetic resonance imaging
GM	Gray matter
GW	Gestational weeks
H-MRS	Proton magnetic resonance spectroscopy
IGF-I	Insulin-like growth factor-I
IQ	Intelligence quotient
IUGR	Intrauterine growth restriction
IVH	Intraventricular hemorrhage
MDI	Mental developmental index (of the BSID)
MEG	Magnetoencephalography
MMN	Mismatch negativity
MMR	Mismatch response(s)
MRI	Magnetic resonance imaging
MWM	Myelinated white matter (volume)
NEPSY	A Developmental Neuropsychological Assessment
NICU	Neonatal intensive care unit
N-MMR	Negative mismatch response
NOS	Neurological optimality score (Hammersmith assessment)
PDI	Psychomotor developmental index (of the BSID)
PHVD	Posthemorrhagic ventricular dilatation

PLIC	Posterior limb of the internal capsule
P-MMR	Positive mismatch response
PVHI	Periventricular hemorrhagic infarction
PVL	Periventricular leukomalacia
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SGA	Small for gestational age
SOA	Stimulus-onset asynchrony
TBV	Total brain volume
TGM	Total gray matter (volume)
UMWM	Unmyelinated white matter (volume)
VAco	Visual attention subtest of NEPSY, number of correct markings
VAt	Visual attention subtest of NEPSY, time to complete the test
VERP	Visual event-related potential
VLBWI	Very low birth weight infants (birth weight <1500 g)
VP	Very preterm (born < 32 gestational weeks)
WISC	Wechsler Intelligence Scale for Children
WM	White matter
WMI	White matter injury
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised

Background

Outcome after very preterm birth

In the literature, the term very preterm (VP) birth is commonly, but not always, used for infants delivered before 32 gestational weeks (GW). Extremely low gestational age (ELGA) infants are those born before 28 GW. In this thesis, we define VP birth as birth before 32 gestational weeks (GW).

Survival and impairment

Preterm birth is a major risk factor for brain damage, inflicted by perinatal and postnatal mechanisms such as fetal inflammation, hypoxia, reperfusion injury, postnatal cerebrovascular insults, and nutritional deficiency.[1-3] The infants of youngest gestational ages (GA) have the greatest risk of brain damage and death.[4-6] Although survival of the most immature infants is increasing, the proportion of survivors affected by major neonatal morbidity and severe neurodevelopmental impairment seems no to have unchanged over the last 20 years.[5-8] There are major differences in survival at equal GA between different countries and neonatal intensive care units (NICUs).[4, 7, 8] Moderate and severe impairments such as cerebral palsy (CP), impaired hearing and vision, and developmental quotients more than two standard deviations (SD) below the mean for their age are common after VP birth and persist throughout childhood, with incidences above 20% in the most immature preterm infants.[5, 9, 10] Brain injuries such as periventricular leukomalacia (PVL), severe intraventricular hemorrhage (IVH), periventricular hemorrhagic infarction (PVHI), and posthemorrhagic ventricular dilatation (PHVD), which all are easily identifiable by brain imaging, are major risk factors for such impairments.[11-13]

Neurocognitive and behavioral outcome

Very preterm children without obvious neurological problems or impairments and without serious neonatal morbidity still show a below average intelligence quotient (IQ) later in life, as well as neuropsychological and behavioral problems.[14-16] About half the survivors of VP birth are affected by such problems, which leads to considerable educational burdens and has important social and economic implications.[14, 15]

The IQ of VP children is estimated to be 11 points (about 0.7 SD) below their term peers for children born between 28- 32 GW, and 14 points (0.9 SD) for ELGA children. IQ is

estimated to decrease by 1.5 points per week for those born below 33 GW. No major improvements have been seen over the last 25 years.[16] However, while IQ scales are reliable in the assessment of the general cognitive ability, they are not ideal for the detection of mild deficits or specific strengths and difficulties.[16] Moreover, developmental testing at toddler age often underestimates the amount of cognitive problems in later years.[15, 17]

Children born VP are vulnerable to impairments in all cognitive domains, and explicit impairment patterns that are specific to this risk group are difficult to find, because there are multiple relations and interdependencies between cognitive functions.[16] Most types of cognitive problems have been described in preterm infants, often as part of complex combinations of impairments. Typical problems after VP birth difficulties with learning and mathematics, language-related problems,[14, 16, 18-20] impaired motor and sensori-motor skills,[20, 21] as well as visual problems.[16, 22] There is a high degree of coherence in the results of studies concerning impaired executive functions and processing speed, both of which involving numerous different skills.[14, 16, 20, 23] All memory domains may be impaired by preterm birth, including working memory, verbal memory, recognition memory, and explicit memory.[16, 20, 21, 24, 25]

Behavioral and emotional problems also have an increased incidence after VP birth. Typically, these children have difficulties with attention, are distractible with or (often) without hyperactivity, and show internalizing rather than externalizing behavior.[14, 16, 18, 20, 21, 26-28] Emotional issues are often associated with social and communication problems and may involve anxiety disorders.[26-28] An increased incidence of autism spectrum disorders has also been reported in VP born children.[27-29]

Of special significance because of its critical importance for relations and social interactions, and its high correlation with academic achievement,[16] is the high frequency of problems with speech and language.[14, 16, 18, 20, 21, 24, 30] Very preterm born children show poorer performance in all language subdomains,[24] including verbal comprehension and memory, phonological short-term memory, verbal learning, verbal and reading fluency, spelling, and delays in the acquisition of expressive language, receptive language processing, and articulation. Many of these differences increase with increasing age, while others decrease.[14, 16, 18-20, 24]

In spite of the increased risk for all these problems, the majority of children born VP have mild or no problems at all.[31] Furthermore, similar quality of life, even after birth before 28 GW, is reported in adolescence and adulthood in the absence of severe impairments, and a majority show no major differences compared to adolescents born at term during their transition to adult life.[31-33] However, adults born VP are more likely to be unemployed, have lower incomes, are less likely to live in relationships, and have fewer children of their own.[22]

Because neuropsychological skills mediate the relationship between achievement and prematurity and birth weight (BW),[20] improvements in cognitive functions and capabilities as well as early help with cognitive and behavioral problems have the potential to improve adaptation in society, and education and social functioning in a longer perspective. Prognostic tools which identify individual needs in these children before they become evident in everyday life are a prerequisite for interventions aiming at improving cognitive functions. Many prognostic variables and methods have been investigated, such as perinatal variables, neonatal risk factors, biochemical markers, neurological examinations, electrophysiological and

neuroimaging methods. Many have shown potential to explain part of the inter-individual outcome variability. But as yet, none has been sufficiently reliable to become a gold standard for prognostication of neuropsychological, cognitive, and behavioral outcome after very preterm birth.[34,35]

Brief summary of early development of the auditory system and speech perception

The neurological auditory pathway starts in the inner ear where vibrations of the middle ear ossicles are converted to neural impulses in the organ of Corti. These impulses are transmitted by the auditory nerve to the dorsal and ventral cochlear nuclei of the brainstem. Ascending auditory pathways lead through the superior olivary nucleus to the lateral lemniscus, the inferior colliculus, and the medial geniculate body of the thalamus. From the thalamus, ascending fibers lead to the auditory cortex in the superior temporal gyrus. The main location of human auditory cortical areas for primary and secondary auditory processing is the posterior part of the Sylvian fissure.[36, 37]

The development of these neurological structures begins as early as 3- 6 GW, with early cochlear function appearing around 20 GW and brainstem myelination starting as early as at the end of the second trimester. Basal functioning of perception and discrimination, and the storing of auditory information and reaction to it, is present as early as around 25- 26 GW.[24, 36, 38-40] However, many essential processes of brain development are still taking place during the last trimester of gestation, such as final migration of neurons to their correct position in the cortical plate, creation of the final six-layered cortical lamination, dendritic and axonal growth, synaptogenesis, myelination, and cortical folding.[41-43] During the last trimester, genetically determined structural left- right asymmetries in the temporal lobes are formed.[43,44] Preterm birth thus has the potential to disturb or disrupt a number of processes essential for normal brain function later in life.

Human fetuses are able of to perceive and discriminate sound *in utero*. Behavioral evidence for fetal hearing starts between 19- 28 GW,[39, 45] and electrophysiological evidence of hearing and of change discrimination at 27 GW and 33 GW, respectively.[46]

The intrauterine environment is different from the extrauterine environment in several aspects. Because of the filtering effects of the uterus, it is mainly low-frequency acoustic signals which reach the fetal ear, including those from the surrounding auditory environment and physiological maternal sounds. Thus, prosodic information of maternal and surrounding speech may be processed prenatally, while high-frequency phonetic and phonotactic information (a prerequisite of phoneme and syllable discrimination) is not accessible before birth. After birth, the entire frequency range is transmitted, albeit distorted by the incubator walls in VP infants during the first weeks.[47-49]

The auditory environment after VP birth is even more different, exposing these infants to an auditory stimulation that is completely different from both the intrauterine environment and an extrauterine environment at home.[39, 50] Mean exposure time to sounds in a NICU

include 19- 36% of electronic sounds including monitors and 25- 29% of noise, but only 1-5% of total language exposure and 27- 39% of silence.[24] Because part of these exposures are high-frequency and may reach peaks far above recommended levels, the auditory system in VP infant's may not be prepared to process them. A limited ability of self-regulation further increases this risk.[39] Sensory overload, sleep deprivation, and impairment to the auditory system and brain development may be a consequence, and may be further exacerbated by ototoxic medications.[39, 51]

Furthermore, separation from the mother and other family members for most of the day is still the rule in NICUs, in contrast to the intrauterine and home environment.[24, 52] Although preterm infants hear the complete range of speech earlier and experience social interactions with their mother, family, and caregivers at an earlier date, for developmental reasons, this theoretical advantage does not result in a faster maturation of speech discrimination.[25, 47-49, 53]

Discrimination of different types of speech sounds during infancy is an essential skill for language learning.[54] In an unsorted sound environment, newborns and infants show a preference for speech sounds, which facilitates language learning by selecting acoustic signals that are relevant for social communication.[55] Prenatal exposure filtered by the uterus seems to provide sufficient experience for the newborn to be able to distinguish their mother's voice from that of a stranger as early as the first postnatal days.[25, 56, 57] They also begin to be able to distinguish languages belonging to different rhythmic classes from each other[58] and are sensitive to prosodic cues present in spoken utterances.[59] Discrimination of phonemes is also a connate skill present in newborn infants.[48] However, at birth, they are broadly tuned to any speech sound and phoneme differentiation, irrespective of the surrounding adult languages. It is during the second half of the first year of life, that they first develop the ability to differentiate phonemes belonging to the ambient language from phonemes which are different (phonetic attunement).[47, 48, 60, 61] This process is triggered by exposure rather than maturation.[47] At this developmental stage the infant also has a so-called statistical language, meaning that at the beginning of a word auditory processing already predicts its most probable termination.[62] Over the following years, continued experience further refines specialization of discrimination and processing of ambient language features, a process that extends beyond 4 years of age. It is not known at what age the highly automatic adult speech perception is attained.[61]

Imaging for prognostication of outcome after preterm birth

Cranial ultrasound versus magnetic resonance imaging

For several decades, cranial ultrasound (cUS) has been in use for clinical evaluation of brain development and brain damage in both preterm and term-born infants, because it is non-invasive, widely available, relatively inexpensive, and accessible without moving the unstable

preterm baby. It is a better predictor of school-age neurological and cognitive outcome than GA.[63] Its major role is the early detection of bleeding in the germinal matrix, ventricles (IVH), and cerebral parenchyma (such as PVHI) as well as of connate, postinfectious, and post-hemorrhagic ventricular dilatation (PHVD).[64] Because severe IVH, PVHI, and PHVD are associated with serious neurological and cognitive impairments in later life, such as cerebral CP and severe mental retardation,[64, 65] early and repeated neonatal cUS is part of clinical routine, and is of great help for decision making at the limit of viability in most NICUs. However, more recently, even the presence of germinal matrix and minor intraventricular hemorrhage has been shown to be associated with outcome and an increased risk of CP, especially in extremely preterm infants and if white matter injury (WMI; see below) is present at the same time.[66, 67] Hemorrhages in atypical locations such as the frontal or temporal lobes also carry an increased risk of various unfavorable outcomes, even if CP is uncommon with these hemorrhages. Temporal hemorrhages seem to lead to more serious problems than frontal ones.[68]

In the last decade, neonatal cerebellar hemorrhage after VP birth has been increasingly investigated. As this damage is present in 1.3- 15% of VP infants and is difficult to detect in conventional cUS images, imaging through the posterior fontanel or transtemporally is mandatory.[65, 69] MRI is clearly superior to cUS in detecting cerebellar hemorrhages, and the importance of this topic has been confirmed by evidence for the prognostic value of such hemorrhages for later outcome.[69-72]

Other characteristic types of brain damage associated with preterm birth are PVL and other WMI, which most often present bilaterally. The most serious form, cystic PVL (cPVL), is readily detected by serial cUS examinations (but not always by a single late one). The presence of cPVL is associated with a very high incidence of serious impairments such as cerebral palsy, severe cognitive, developmental, and visual impairments. Fortunately, the incidence has markedly decreased to well below 1% in recent studies.[64] Far more prevalent after VP birth are subtle WMIs. Even this form carries an increased risk of (often milder) CP and cognitive deficits, but not all cases are revealed by cUS, while it is readily seen on conventional magnetic resonance imaging (MRI) around term. Therefore, MRI has become the gold standard for detection of WMI and other brain damage.[64, 65] The presence of periventricular echolucencies in cUS is also difficult to interpret, and is, in addition, a subjective finding. If it persists for several weeks or is inhomogeneous, it predicts abnormal WM on MRI and carries a risk of up to 10% for diplegic CP. However, its absence on cUS does not predict normal WM on MRI.[65, 73] Ventricular dilatation on cUS is also associated with motor outcome when caused by WM loss.[64, 74, 75]

Most cases of severe CP are detectable by repeated cUS examination.[76] Several studies have compared the predictive value of cUS and MRI for motor outcome in infants and children after VP birth. These studies have consistently shown a higher sensitivity of MRI for adverse outcome as compared to cUS, while cUS has a higher specificity for CP.[76-79] The detection of cognitive and behavioral difficulties related to preterm birth usually requires MRI,[80] even though some studies have shown associations between increased ventricular size or brain atrophy and neurodevelopmental test results at 2- 3 years of age.[75, 81] On the other hand, the association of mild WMI on MRI with outcome is not so strong, as will be discussed later.

Magnetic resonance imaging

Over the last two decades, research on MRI and its value for prognostication of outcome after VP birth has increased exponentially, and MRI is increasingly used in routine clinical settings. New MRI-based neuroimaging techniques such as three-dimensional morphological imaging and volumetry, diffusion-based imaging, functional MRI (fMRI), and MR-spectroscopy have added new insights into normal and pathological brain development, cerebral microanatomy, pathophysiology and the anatomy of neonatal brain damage, post-damage plasticity, and brain function in preterm-born infants, children and adults. A complete discussion of these methods is beyond the scope of this thesis. Instead, there follows a short summary of current knowledge regarding prognostication of neurological, cognitive, and behavioral outcome by means of different MRI methods.

Conventional MRI

MRI has a better sensitivity for prediction of CP either cUS,[76-78] or clinical or physical examinations.[82] On the other hand, data on specificity are more contradictory, and the predictive values achieved are strongly dependent on the MRI findings used for prediction.[79, 83]

A high risk of CP is associated with severe IVH and PVHI, PHVD, cPVL, abnormalities of the thalamus including bleedings and infarcts, and the absence of myelination in the posterior limb of the internal capsule (PLIC) on MRI performed at 40 GW or later. These findings are all primarily associated with WMI, and are easily diagnosed with MRI.[12, 64] More subtle findings, such as uncomplicated germinal matrix and intraventricular hemorrhage, punctate WM lesions, and ventricular dilatation associated with reduced WM volumes, all of which are common after VP birth and are assumed to represent milder forms of PVL, also entail an increased risk of (often mild) CP and other neurological problems, while they have a low specificity for these outcomes.[12, 64] In most studies, diffuse excessive high signal intensity seen on fast spin echo T2-weighted images (DEHSI) does not imply an increased risk.[83, 84] The use of grading scores for WMI and brain injury has improved prognostication, highlighting the high predictive value of moderate-to-severe WM abnormality.[79, 83, 85] Generally, severely abnormal MRI implies a very high risk for adverse neurological outcome, including non-ambulatory CP (OR 9.6), and completely normal MRI nearly precludes CP. However, a high degree of uncertainty remains for the prognosis of individual infants following the frequent finding of subtle WM abnormalities.[76, 79, 83] Even after exclusion of children with CP, WM abnormalities are associated with motor impairment at 5 years of age.[86] An increasing severity of PVL and cPVL also correlates with impaired later cognitive outcome. However, prediction of cognitive outcome is limited by an insufficient sensitivity below 50% for cognitive delay.[35]

Cerebellar injury, which often coexists with supratentorial lesions, has a high correlation with adverse neurological and neurodevelopmental outcome.[71, 87]

The presence of cPVL or other forms of severe PVL is highly predictive of cortical visual impairment. Lesions in the optic radiations and the occipital cortex have been associated with abnormal visual acuity and function.[88]

Associating abnormalities in conventional MRI with cognitive outcome in infants and children without CP and severe neurological impairment is even less straightforward. Studies

vary greatly regarding MRI abnormalities and outcome assessments, as well as the timing of the MRI examination and follow-up. The largest number of studies have been performed with MRI between birth and term, with follow-up neurodevelopmental tests at toddler age. A smaller number of studies have investigated the predictive value of conventional MRI for outcomes at higher ages.

Badr et al.[89] compared early outcome predictors such as neonatal morbidity, early motor development, neurological examination, MRI at term-equivalent age, head circumference, and postnatal environmental factors for mental and motor development at 12 and 18 months of age. Interestingly, the simple MRI classification into normal or abnormal was not a better predictor than head circumference and neonatal neurological assessment for scores on the 18-months Bayley Scales of Infant Development (BSID)-II.

DeBruine et al.[90] demonstrated that punctate WM lesions and ventricular dilatation at term were significantly associated not only with neurological and psychomotor outcome, but also with mental outcome at 2 years of age as assessed by BSID. Contrarily, in a different cohort studied by Dyet et al.,[91] similar WM abnormalities were not associated with 18-months outcomes on the Griffiths Mental Development Scales.

Scoring systems have been developed to characterize the severity of brain injury. Increasing severity scores of WMI were associated with poorer performance on both cognitive and psychomotor scales of the BSID-II at 2 years of age, as well as with increased risks of severe cognitive delay (OR 3.6).[79] Moderate to severe WM abnormalities were associated with lower object working memory performance at 2 years of age[92] and with decreased verbal and visuospatial working memory abilities at 6 years of age.[93] Executive functioning including behavioral inhibition, cognitive flexibility, planning ability, and selective attention at 2, 4, and 6 years of age were also associated with the presence of any WM abnormalities and VP children with the most severe abnormalities showed the smallest improvements in executive functions with age.[94-96] Abnormal WM at term predicted lower scores in all subscores of the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) and Wechsler Intelligence Scale for Children (WISC)-III at 4, 6, and 9 years of age.[95, 97] Language development was impaired in children with abnormal WM at term, both at 4 and 6 years of age.[95] Data on correlations between WM abnormalities at term and inattention and hyperactivity during childhood are contradictory.[98, 99]

Normal WM at term was associated with measures of intelligence, language, and executive functioning at 4 and 6 years of age that were no different from term-born controls.[95]

Several groups have demonstrated the absence of an association between DEHSI and toddler outcome.[83, 90, 100, 101] However, Dyet et al.[91] found an association with 18-months developmental quotient on the Griffiths scales. This emphasizes the high prevalence and subjectivity of this finding. Using an automated, atlas-based WM signal abnormality quantification method, He and Parikh[102] reported an association of the extent of DEHSI-like WM abnormalities with language and cognitive scores at 2 years of age (BSID-III).

Increasing gray matter (GM) abnormality scores at term are associated with poorer performance on both scales of BSID-II at 2 years of age.[79] They have also been demonstrated to correlate with impaired performance in tests of memory and learning at 7 years of age.[103]

Small isolated cerebellar hemorrhages were not associated with BSID-II at 2 years of age[69] but with lower expressive and receptive language scores and cognitive deficits, problems

with internalizing behavior, higher scores on autism screeners, and limitations during everyday activities during childhood.[70, 87] These associations were independent of simultaneous supratentorial abnormalities, and damage to the vermis had the strongest association with such deficits.[70]

3D- and volumetric MRI

Three-dimensional or volumetric MRI methods have made it possible to calculate the volumes of different tissue classes, either of the whole brain or of different brain segments. The 3D data set is acquired in only one plane but with isotropic resolution (all three dimensions of the voxel are the same), and images can then be reconstructed in any plane. or as a volume. Initially, manual brain segmentation has been the gold standard, but it is extremely time-consuming.[104] Semi-automated and, in recent years, automated brain tissue segmentation techniques have been introduced, allowing for volume calculation of a great number of different brain areas.[105, 106] Calculations of cortical thickness in particular cortical areas and measures of cortical area and cortical folding have also become possible. Brain volumes have been used for prediction of outcome after VP birth, although many of these studies have been performed with MRI after the neonatal period.

Global brain volumes are decreased after VP birth and are associated with outcome. Higher total brain volumes (TBV) at term were associated with higher cognitive and motor scores at 2 years of age,[107, 108] including better object working memory.[92] An increased cerebrospinal fluid (CSF) volume correlated with impaired object working memory at 2 years of age and with inattention/hyperactivity at 4, 6, and 9 years of age,[92, 98] but not with developmental outcome during the first 3 years of life, nor with motor outcome or IQ.[35] Faster cortical growth, including faster growth of the cortical surface from birth to term, was related to mental and cognitive outcomes at both 2 and 6 years of age, including improved attention, learning, memory, planning, and numeric and conceptual abilities, while motor skills showed no association with cortical growth.[109] Likewise, faster WM growth from birth to term was associated with higher BSID-III language scores at 2 years of age.[110]

Local brain volumes at term have also been associated with measures of neurodevelopmental and behavioral outcome. Peterson et al. demonstrated correlations between larger WM volumes in sensorimotor and midtemporal regions, and higher mental and motor BSID-II scores at 18- 20 months of age.[111] Smaller inferior occipital brain volumes, especially when cortical GM was reduced, were predictive of impaired visual function at 2 years of age.[112]

Cortical folding after preterm birth differs during the first postnatal months between preterm singletons, twins, and preterm infants born with intrauterine growth restriction (IUGR), and these differences are predictors of neurobehavioral development at term.[113] Cortical growth from birth to term age was directly related to cognitive test results both at 2 and 6 years of age.[109]

Larger cerebellar diameter and volumes at term correlated with better mental and motor development in young infants and toddlers.[107, 108, 114] However, one study demonstrated that this association might be mediated by WMI.[115] Larger basal ganglia and thalami at term-equivalent age were correlated with better motor development but not with mental

development at 2 years of age.[107, 108] Smaller hippocampal volumes at term were associated with lower mental and psychomotor IQ (BSID-II) and impaired performance on a working memory task at 2 years of age,[116, 117] with emotional problems at 5 years of age,[118] and with lower verbal and visual memory scores at 7 years of age, while a less infolded shape at term did not correlate with memory.[119]

In the majority of studies on associations between brain volumes and outcome, MRI has been performed during childhood, adolescence, or early adulthood, often at the same time as outcome measurements. In such studies, patients with CP had reduced GM volumes in sensorimotor (especially pre- and postcentral), parietal, temporal, and occipital cortical areas as well as in basal ganglia, and the thalamus and cerebellum.[120]

Total brain WM volume as well as global GM and WM volumes were smaller after VP birth and correlated with IQ and educational performance in adolescents and young adults born VP, both with and without neonatal brain damage, explaining up to 40% of the outcome differences between VP infants and controls.[121-124]. Smaller global GM and WM volumes have been associated with impaired language, memory, executive functioning, and motor skills.[124, 125]

In adolescents born with a BW below 1500 g, higher IQ was associated with thicker cortex in most brain areas, including areas in the frontal and temporal lobe important for auditory processing, language, and memory.[126] Thinning of the entorhinal cortex correlated with low performance on perceptual and cognitive scores, executive tests, and impaired working memory and behavioral and attentional difficulties correlated with a thinner cortex in frontal areas.[127, 128] Conversely, increased cortical thickness in the frontal cortex, possibly due to disruptions in synaptic pruning, was associated with internalizing and externalizing scores as measured by the Child Behavior Checklist.[129] A thicker insular cortex at 2 years of age was associated with better BSID-III language scores.[110]

Most local brain volumes of both GM and WM were decreased in VP born children and adolescents, and larger local volumes in different cerebral areas, including the frontal and temporal areas, were positively associated with IQ, including all subscales.[123, 130-134] Focal brain volumes explained about 20- 30% of the variance of global IQ, executive functions, language, and non-verbal memory scores.[135, 136] Gross motor scores were correlated with sensorimotor cortical volumes.[132] Gyrification of the temporal lobe seemed to be most vulnerable to prematurity, and an increased left temporal gyrification index correlated negatively with left temporal GM volume and reading scores at 7 years of age.[137] In adults born as very low birthweight infants (VLBWI, with a birth weight below 1500 g), reduced cortical surface in multiple areas, including the inferior frontal gyrus, inferior temporal and parahippocampal gyri, correlated with IQ scores, the strongest correlations being with working memory and processing speed indices.[138] However, a few studies showed no associations between local brain volumes and cognitive outcome.[139]

Reduced hippocampal volumes have been associated with VP birth, and the decrement correlated with global IQ, impaired memory functions such as working memory and developmental amnesia, and emotional problems in some studies,[135, 140-142] but not all.[143-145] Bilateral hippocampal volumes were almost 12% smaller in individuals with attention deficits.[129]

Decreased caudate volumes were found in adolescents born VP and the volumes were influenced by early neonatal nutrition. They correlated positively with global IQ, verbal and performance IQ, and spelling performance but not with motor outcome.[135, 143, 146] Hyperactivity and social problems correlated with smaller caudate volumes[147]. Smaller striatal volume at 2 years of age correlated with BSID-III.[110]

Thalamic volumes have also been demonstrated to be smaller after VP birth, and smaller volumes have been linked to lower global IQ, impaired working memory, and verbal fluency.[148, 149]

The lateral lobes and vermis of the cerebellum were also smaller in individuals born VP.[150] Smaller volumes were associated with supratentorial damage and reduced cerebral WM volume.[151] While no significant associations were reported in ex-preterm infants before school age,[87] in older children, cerebellar lobe volumes were associated with total and performance IQ, executive, cortical visual, and language functions.[121, 125, 141, 150, 152] The vermis did not show such associations.[150] From 14- 19 years of age, the cerebellum shrank by 3% in adolescents born VP, as compared to full-term controls, and these changes were associated with worse self-reported mental health including concentration, confidence, and decision-making capacity.[129]

Although corpus callosum has been extensively studied using diffusion MRI techniques (as discussed below), few studies have investigated the correlation between the size of this WM structure and outcome. Several studies have shown that VP infants have reductions in different parts of corpus callosum, mainly in its posterior areas.[153-155] Reductions of different parts of this structure, both anterior and posterior, were associated with motor function during childhood, and with full-scale IQ and IQ subscores as well as with verbal and executive frontal cortical functions during adolescence.[153-156]

Diffusion-based MRI

Modern imaging techniques such as diffusion-weighted imaging (DWI) allow for measurements of increased diffusion of water molecules within the brain, quantified as an increase of the apparent diffusion coefficient (ADC). More advanced techniques (diffusion-tensor imaging, DTI) add information on the three-dimensional characteristics of diffusion, and are able to describe the extent of diffusion restriction in each three-dimensional direction (including the relation between diffusion in the most and in the least restricted directions; i.e. the anisotropy). They thus give important information the alignment and qualities (such as density, premyelination, and myelination) of WM fibers within the brain. Even more advanced techniques (diffusion-tensor tractography, DTT) allow for the description of the pathways of WM tracts, including tract qualities, throughout the brain. In the last 15 years, these techniques have enabled detailed descriptions of early human (mainly) WM maturation *in-vivo*, as well as of modification and disruption of these processes after VP birth and the consequences for outcome.[157]

In general, very preterm infants show higher ADC and lower anisotropy in their WM throughout the brain compared to term-born infants.[157-159] A lower anisotropy increase from preterm birth to term-equivalent age in basal ganglia and WM was predictive for adverse cognitive and motor outcomes at 18 months of age.[88] Furthermore, higher ADC in the corona radiata at term was associated with poorer gross motor outcome at 2 years of age,[160] and higher ADC in the centrum semiovale with a reduced developmental quotient at 2 years of age.[84]

WM alterations in periventricular regions as well as in fronto-striatal and fronto-cerebellar connections were associated with ADHD and overall mental health functioning scores.[129] Higher ADC in the right orbitofrontal cortex, a region implicated in autism spectrum disorders, was associated with social-emotional problems at age 5 years.[118] Anisotropy in various WM tracts, mainly the arcuate fasciculus connecting Wernicke's and Broca's areas, and with typical left lateralization, has been associated with a variety of language and reading skills.[157, 161] However, Thompson et al.[159] found little evidence for associations between WM diffusion measures at term and IQ. Instead, motor problems were associated with increased ADC in posterior brain regions, and impaired executive functions with higher ADC in the orbitofrontal, inferior occipital, and cerebellar regions at 7 years of age. In adolescents, abnormal DTI measurements in the corticospinal and speech-motor corticobulbar tract correlated with impaired speech and oromotor control.[162] Disturbed connectivity between the posterior and prefrontal brain regions correlated with executive functions.[163] In early adulthood, higher anisotropy in most WM regions was associated with higher global IQ, but not with verbal IQ and executive function.[164] In conclusion, higher anisotropy and lower ADC in most WM areas of the brain have been associated with increased IQ and better performance in a variety of cognitive functions.[157]

The association between impaired myelination in the PLIC shown on conventional MRI has been confirmed in DTI studies, showing a robust association between increased ADC and decreased anisotropy in the PLIC and corticospinal tract from term-equivalent age up to childhood and adverse motor outcome, including CP, from 2 years of age to school age.[120, 165-168] In one of these studies, 7 of 10 VP infants with abnormal anisotropy in the PLIC at term had CP at 4 years of age, while none of the infants with normal anisotropy was diagnosed with CP, which implied a more accurate prediction of CP than with conventional MRI.[35, 167] Decreased anisotropy in the posterior thalamic radiation during childhood was also associated with CP.[169] Even attention deficits and autism spectrum disorders in school children born preterm have been associated with microstructural disorganization in the internal and external capsule, but also in the superior longitudinal fasciculus and in occipital brain regions.[129]

A similar pattern of correlations between abnormal DTI measurements and outcome has been shown for the corpus callosum. Higher anisotropy in the corpus callosum at 2 years of age correlated with higher global developmental scores, performance subscores, and hand-eye coordination, but not locomotor, personal- social, or hearing- language scores at the same age.[170] Abnormal DTI at school age was associated with adverse motor outcome,[120, 166] attention deficits,[129] and language impairment, when interhemispheric temporal connectivity was reduced.[171]

While DEHSI on conventional MRI did not correlate with outcome (see above), several DTI studies on infants and children presenting DEHSI have demonstrated patterns of delayed maturation (increased ADC, decreased anisotropy) in WM structures such as periventricular WM, centrum semiovale, optic radiation, and PLIC.[101, 172, 173] This delayed maturation was not associated with neurodevelopmental outcome at 18- 24 months of age.[173] However, Parikh et al.[174] used diffusivity-based measurements of DEHSI extension, and the resulting DEHSI volumes correlated significantly with Bayley scores at 2 years of age, explaining 35% of the score variability. In the same study, subjective DEHSI definition by neuroradiologists did not correlate with Bayley scores.

Increased ADC in the cerebellar hemispheres at term was associated with worse motor outcome at 2 years of age.[74] In adolescents, anisotropy in the cerebellar peduncles correlated with reading abilities.[175]

Associations between diffusion measurements of visual tracts and visual outcome have been investigated in several studies. Higher anisotropy and lower ADC in the optic radiation during the neonatal period and up to adolescence were accompanied with better visual performance at the same age.[176-179]

Other MRI techniques

More recently, fMRI and proton MR-spectroscopy (H-MRS) have been introduced in research on patients born preterm, from the neonatal period up to adult age. Studies using these techniques have mostly used small study groups. Here, the focus is on studies that have investigated associations of these techniques with outcome after VP birth.

Functional MRI is based on the MRI signal in specially adapted sequences that is given by changes in local cerebral blood oxygenation and blood flow (BOLD: blood oxygen level dependent activation).[180] With the help of this technique, it is possible to investigate which parts of the brain are involved in processing the cognitive processes studied. Recently, a rapidly increasing focus has been placed on the functional brain connectivity present without a special cognitive performance, so-called resting-state fMRI.

An altered BOLD- signal of cortical activation following sensorimotor stimulation was correlated with altered neurodevelopmental outcome at 4- 6 months of age.[181]

Studies using fMRI have demonstrated that preterm infants develop alternative pathways for language processing. Connectivity between the left cerebellum and bilateral inferior frontal gyri was decreased in adults born preterm, and this connectivity was associated with language outcomes.[182] School age children and adolescents showed activation patterns for language processing tasks that differed from term-born children (in part, showing stronger activation of Wernicke's and Broca's areas in VP patients), and correlated with language testing results.[183-185] PT children at 8 years of age showed activation patterns to a semantic processing task that resembled those of term-born children to a phonological processing task. Interestingly, the greater this resemblance was, the lower verbal comprehension was in the VP children.[180]

PT born children showed different activation from term-born children in a working memory/selective attention task, but these differences did not explain their lower task performance or lower cognitive test results as these correlated with activation in different brain areas.[186] In a test of action inhibition, VP children showed poorer inhibition control, which was not associated with any differences in cortical activation patterns, but with decreased DTI anisotropy in involved WM fibers.[168] Among 41 VP children, only those with impaired visuospatial working memory had working memory network activations which differed from those of term-born children.[187]

H-MRS has the potential to measure specific metabolites in regions of interest in the brain, which can give information on dysfunction, or ongoing or recent damage, or on

permanent changes in brain metabolism caused by harmful processes during the neonatal period.[188]

Motor scores on BSID-III up to 2 years of age have been associated with some cerebral metabolite ratios (choline-CHO/creatine-CR and inositol-INS/CR) when scanned postnatally after VP birth,[110] and with other metabolite ratios in cortical and WM areas (N-acetylaspartate-NAA/CHO, CHO/CR) and in the subventricular zone (NAA/myoinositol-MI) when scanned at term.[188, 189] In one of these studies, H-MRS reached a sensitivity and specificity of 0.80 for impaired motor outcome at 1 year of age, and it was a more reliable predictor of outcome than conventional MRI at term.[189] In VP infants developing severe WMI and adverse outcome at 18 months of age (BSID-III), the NAA/CHO ratio in the basal nuclei and WM was increasing more slowly from birth to term age than in VP infants with normal motor development,[88] and NAA/CHO and NAA/CR ratios in the posterior periventricular WM were decreased at term.[190] Higher cerebellar NAA/CHO ratios at term were significantly correlated with cognitive scores on BSID-III at 2 years of age, but not with motor performance.[114] However, another earlier study failed to find any associations between term H-MRS results and the 2-years Griffiths' developmental quotient.[191]

Conclusions

Postnatal and term MRI has increasingly been adopted as a diagnostic and prognostic method in infants born VP. It is perfectly applicable to the identification of severe brain damage associated with adverse motor and cognitive outcome, and a completely normal MRI at term almost definitely excludes such an outcome. DTI of PLIC and specific WM tracts can enhance the prediction of adverse outcome even further.

On the other hand, an important subsection of infants born VP show some kind of brain abnormality but no severe brain damage. These infants are still a major challenge for prognostication of cognitive and behavioral outcome.[35] Furthermore, even completely normal MRI images do not preclude minor cognitive impairment. Different MRI techniques have demonstrated associations between local maturational, anatomical, and functional brain abnormalities and several cognitive and behavioral outcomes. Modern MRI techniques have shown that focal damage leading to impaired cerebral growth or WM tract development may be associated with functional impairments in these brain areas. However, few of these results have been reproduced in sufficiently large studies, and sensitivity and specificity are often too poor to allow for reliable prognostication in the individual infant. Furthermore, cerebral plasticity and a variety of postnatal factors will have an impact on the infant's future development. Much research is still needed before MRI can be used for prognostication of cognitive and behavioral outcome in this group of preterm infants and children.[35, 192]

Neurophysiology and AERP for prognostication of outcome after preterm birth

Brief summary of neurophysiological methods other than AERP

Neurophysiological methods have been used for several decades for examination and prognostication of outcome in preterm infants.[36] Electroencephalography (EEG) and amplitude-integrated EEG (aEEG) are long-established clinical methods in neonatology, mainly after hypoxic-ischemic encephalopathy, and for diagnosis of neonatal seizures. In recent years, several studies have shown that aEEG within a few hours of VP birth is prognostic for both short-term and long-term outcome.[193, 194]

Evoked potentials such as brainstem auditory-evoked potentials, visual-evoked potentials, and somatosensory-evoked potentials have been used to investigate the integrity and normal development of sensory function after preterm birth and the predictive value for both sensorimotor impairment and cognitive outcomes.[36, 45, 195, 196] More recently, using an indirect measure of brain physiology, namely changes in cerebral blood flow and tissue oxygenation as a result of neuronal activity, near-infrared spectroscopy is been increasingly introduced into clinical praxis for monitoring of sick term and preterm infants.[197]

In analogy to AERP, visual event-related potentials (VERPs) have been used to investigate cortical processing of visual information after VP birth, although outcome data are sparse. Delayed or absent onset of orientation-reversal VERPs during the first year of age has been shown to be a sensitive indicator of perinatal brain damage in preterm-born infants.[198] Among 24 VLBWI, four had abnormal VERPs, and these infants had abnormal postnatal cUS findings and an abnormal neurological outcome.[199] Another group of 17 healthy VP infants showed abnormal VERPs reflecting delayed maturation at 2- 4 months of age.[200] At four months of age, 16 NICU- infants (9 of whom were born preterm) showed abnormal VERPs as compared to 16 healthy newborn infants, possibly indicating altered patterns of synaptic organization.[201] VERPs before 1 year of age were about as effective as a behavioral attention-fixation test for prediction of the Griffith's developmental quotient at 2 years of age, with a sensitivity of 86% and specificity of 65% for a quotient ≤80, and they were better than the behavioral test in predicting visual outcomes at 3- 6 years of age.[202] Delays in many systems within the visuomotor, spatial, and attentional domains have been shown to correlate with VERPs in VP infants.[203] However, the predictive value of VERPs for cognitive outcome after VP birth has yet to be established.

Studies combining MRI and neurophysiological methods

Early EEG and aEEG during the first days and weeks after preterm birth has been used to monitor neuronal activity and investigate early brain damage. Postnatal EEG maturity patterns, especially inter-burst interval and sleep-wake cycling, correlated with cortical folding during the first week of preterm life,[204] and with maturity scores at term on conventional MRI.[205] Increased early brain activity seen on EEG has been shown to correlate with faster brain growth by term, mainly of cortical and deep nuclear GM, as assessed by volumetric MRI.[206] Pineda et al.[194] investigated the impact of different NICU environments on postnatal

aEEG, term MRI, postnatal neurobehavior, and outcome at 2 years of age as assessed by BSID-III. Infants cared for in private rooms showed a slower aEEG maturation, decreased physiological hemispheric asymmetry in the insular and temporal cortexes, and lower language and motor scores, and more externalizing behavior. These effects were not mediated by brain damage.

Glass et al.[207] compared DTT data of the optic radiation before term with visual-evoked potentials recorded between 6- 20 months after birth in infants born before 34 GW. The amplitudes correlated with increasing anisotropy and decreasing diffusivity in some, but not all, visual-evoked potential modes. In school-age children born preterm but without any major neuromotor impairment, no differences with term-born controls in ophthalmological and cortical tests of vision were found, and conventional MRI, volumetric MRI, and DTI data did not show any correlations with visual-evoked potential results.[208] A study by Atkinson et al.[202] compared VERPs in an orientation-reversal paradigm and a behavioral visual attention-fixation test before 1 year of age for prediction of an abnormal Griffith's developmental quotient at 2 years of age and of abnormal cortical visual function at 3- 6 years of age. The behavioral visual test and visual event-related potentials showed comparable predictive values, with sensitivities close to 100% and specificities around 50%, for abnormal Griffith's developmental quotient, and VERPs were more predictive of visual outcomes at preschool age. In this study, term conventional MRI was scored for brain abnormalities. Unfortunately, no data on the predictive value of MRI for the outcome measures were given.

In VP infants with birth weights below 1000 g and with no major brain lesions, MRI was performed at term and ADC was measured in pons and WM regions known to contain motor fibers. Brainstem auditory-evoked potentials were registered at term age and gross motor outcome assessed at 2 years of age. Higher ADC- values in the pons (implying immature or impaired maturation) correlated with longer latencies of auditory potentials.[160] In analogy, Reiman et al.[209] reported associations between lower anisotropy and higher ADC-values in the inferior colliculus and longer brainstem auditory-evoked potential latencies in VP infants at term. In normally developing term-born children and adolescents, using magnetoencephalography (MEG; see below) and DTI, Roberts et al.[210] demonstrated an association between increasing WM anisotropy in auditory pathways and decreasing latencies of the first event-related auditory response around 100 ms from stimulus onset. Brainstem size as measured by MRI at term predicted neurosensory impairment (CP, hearing loss) at 30 months of age with a sensitivity of 23- 31% and a specificity of 97- 100%, while abnormal brainstem auditory-evoked potentials at term showed a sensitivity of 93% and a specificity of 57- 59% for the same outcome.[211]

Auditory event-related potentials

Auditory event-related potentials (AERPs) have been in use for half a century, but this use has expanded dramatically over the last 20 years because of the availability of commercial recording systems, and the relatively low expense of AERP compared to neuroimaging. AERPs are small changes in electrical activity of the brain recorded at the scalp and elicited by specific auditory stimuli. They are portions of the EEG time-locked to the stimulus.[36, 37]. This

stimulus-induced EEG activity is small in relation to basic EEG activity and thus can only be isolated by averaging of a large number of equal stimuli. By this means, the unrelated, non-time locked EEG activity (noise) will cancel out as the number of trials is increased, while the time-locked, stimulus-related activity will remain.[36, 212] This AERP activity is usually recorded from multiple scalp locations with a temporal resolution of the order of a few milliseconds.[55, 212] It provides information on the strength and speed of electrical signals in the brain related to the cortical processing of the stimulus. AERPs reflect the cortical processing of the stimuli, and high temporal resolution makes them a powerful tool to investigate the timing of these cognitive processes non-invasively.[53]

Brain activity recorded at the scalp surface largely consists of the combined effect of inhibitory and excitatory postsynaptic potentials generated by the firing of tens of thousands of cortical neurons. An AERP component or response is part of the waveform with a circumscribed scalp distribution and neuronal activity, and with a relationship to a particular cognitive function. Different AERP components are sometimes generated by distinct neural sources, but they may also reflect the sum of superimposed activities and may receive contributions from generators in different cerebral areas and from several layers of the cerebral cortex. Therefore, the source of the electrical activity in the brain is not easily deductible from the scalp distribution.[212, 213]

An alternative way of recording electrical brain activity is by recording the magnetic fields created by the cerebral electrical currents, as is done in MEG. It combines the advantage of the high temporal resolution of EEG-derived AERPs with a far higher spatial resolution and the possibility of recording even when EEG is not accessible, as in fetal investigations.[46, 55, 214] However, it is far more expensive to perform and needs equipment that will not be easily accessible in normal clinical settings.

Cortical AERP responses are usually classified into two types: exogenous (obligatory) and endogenous (cognitive) responses.[215] Exogenous components (mainly synonymous with late evoked potentials) are those that are obligatorily elicited by the occurrence of a single stimulus. Their response characteristics are determined by the stimulus parameters such as physical features, or the energy or energy change of the stimulus, all of which are 'exogenous' to the listener. Exogenous responses may correspond to the conscious detection of sounds and transient encoding of the stimulus features.[36, 213, 216]

Endogenous components are recorded in response to two or more different stimuli and reflect internally generated mental events related to the cognitive assessment of the stimuli (e.g. discrimination, memory, learning).[36, 217] They are triggered by the sound, but not elicited by the stimulus and its physical parameters per se, but rather by the cognitive response to a perceived event in the auditory environment.[37] Endogenous components are often elicited in so-called oddball paradigms in response to an infrequent stimulus ('deviant') randomly inserted into a train of identical stimuli ('standards'). In the classical oddball paradigm, around 80- 90% of trials consist of standards and 10- 20% of deviants, and it allows the assessment of the response to one or a few different types of deviants only.[36, 37] However, in the last ten years, multi-feature paradigms have been developed, allowing for a higher proportion of deviants and thus for a higher number of different deviants to be tested without sacrificing the size of the endogenous responses or increasing the recording time.[218-220] Endogenous components are generally seen on the difference curve, derived by subtracting the response to

the standard stimulus from that to the deviant stimulus (the deviant-minus-standard difference curve).[37, 216, 221]

AERPs in adults

Exogenous responses in adults typically appear as a succession of four positive or negative deflections at typical latencies: the positive P1 peak around 50 ms from stimulus onset, the negative N1 peak around 100 ms, P2 around 200 ms, and N2 around 250 ms. While the N2 responses are relatively small, N1 is the dominant wave.[213, 215, 222] These responses are recorded near midline over fronto-central scalp regions, and they are generated by the primary auditory cortex and surrounding auditory fields within the superior-temporal plane.[213, 222]

Adult endogenous responses in the oddball paradigm mainly consist of the mismatch negativity (MMN) and the P3, while additional later positive and negative responses may be seen under more specific conditions.[37, 216, 217, 223]

The mismatch negativity

The mismatch negativity (MMN) was first described in adults as a frontocentrally distributed negativity peaking between 100 and 250 ms from the onset of a stimulus change.[221] It has several sources, probably both cortical and subcortical, in the auditory cortex, the frontal lobe, and supratemporally.[224, 225] According to the dominant theory, repeated stimuli or patterns form sound representations (so-called sensory memory traces) in auditory sensory memory, creating expectations. Subsequent sounds are compared with these representations and any difference from what is expected causes cortical processes from which the MMN response arises.[224, 226, 227]. The auditory memory contains both short-term information (as an early memory buffer) and long-term memory traces for patterns that repeatedly occur in the auditory environment, such as language sounds (for example phonemes, syllables, words).[224, 228] Thus, MMN shows plasticity and can be influenced by experience and training.[227, 229]

MMN is an automatic, pre-conscious, pre-attentive response that represents change detection and auditory discrimination.[224, 226, 227] It reveals the distinctiveness of two representations in the auditory sensory cortex, and its elicitation and amplitude correlate with conscious discrimination performance.[212, 224] Numerous sound feature changes can elicit an MMN, such as changes in frequency, intensity, duration, spatial location, rhythmic and melodic patterns, omission of a stimulus from a train of standards, changes in the timing of a standard tone pattern, and also all kinds of changes in speech-related features. Furthermore, MMN is a link between pre-attentive detection of change and subsequent attentive processes, and thus is a prerequisite for orienting in a busy everyday auditory environment and for understanding of speech in noisy environments.[224, 226, 229] The elicitation of MMN does not require conscious detection or awareness of the deviants or attention directed to the sounds.[224, 226] It is therefore a useful tool in research, and has potential in clinical investigations in populations with unavailable or unreliable behavioral responses, or with limited attention and motivation, such as newborns, infants, and small children.[37, 230]

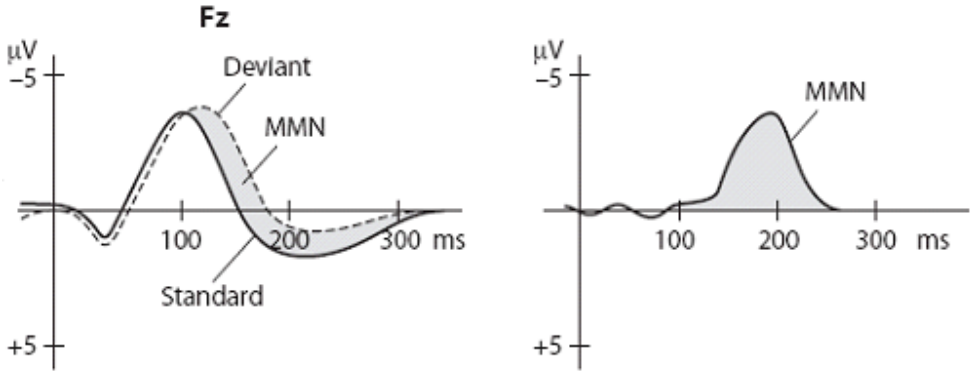

Figure 1. Mismatch negativity (MMN).
The MMN (grey) appears in the difference curve (right) that is derived by subtracting the AERP curve for a standard stimulus (left, solid line) from that of the deviant stimulus (dashed line).

The P3a

For salient sound changes, MMN is followed by a positive deflection called P3a at around 300 ms.[212, 223, 231]. This response is most easily elicited by rare, highly deviant, or novel, attention catching sounds.[37] It has been proposed that it is an electrophysiological marker of the orienting response, and is believed to reflect an involuntary switch of attention, indicating that the stimulus has opened a channel to consciousness.[223, 232, 233] The P3a depends on arousal and is most easily elicited by unattended sounds not belonging to the active task a test person is performing. A prolonged behavioral reaction time and disturbed performance in a simultaneous active task after a stimulus that elicits a P3a shows that it reflects distraction from the primary task.[37, 223, 231, 233] P3a requires a sufficient difference between deviant and standard, but there is still debate whether the elicitation of P3a requires a preceding MMN.[230, 233]

The P3a seems to be generated in the auditory cortex with bilateral association regions prefrontally and temporoparietally.[223] It consists of an early and a late sub-component with different functional equivalents, generators, and scalp distributions, peaking at 200- 300 ms and 300- 350 ms, respectively.[223, 233]

For some stimulus deviances, MMN and P3a may be followed by a late, prolonged negativity at around 400- 800 ms. The functional significance of this response is unclear, but it has been proposed that it represents attentional cognitive processes, such as reorienting to the task after distraction.[37, 216, 234, 235]

AERPs from fetal life till childhood

AERPs are one of the ontogenetically earliest brain responses, and there is neurophysiological evidence from MEG studies for auditory sound detection from as early as 27 GW[46, 236, 237] and

for frequency change detection from 28 GW.[238] A considerable latency decrease of the first prominent peak in long-latency auditory evoked potentials during the last intrauterine and first postnatal months has been shown[236, 237], and about half of fetuses between 33 and 36 GW and two thirds of fetuses between 28 and 39 GW present an MMN-like response to a frequency change.[238, 239]

After birth, AERPs can be registered directly from the scalp, and in the last 20 years there has been an increasing interest in assessing sound discrimination abilities in infants and children.[37] Use of auditory stimuli to study brain function is attractive in these age groups because it is non-invasive, inexpensive, does not require active participation, can be conducted bedside without sedation, and normal hearing as a prerequisite for assessment of cortical auditory processing is easily tested by hearing screening.[36, 37, 49, 50, 52, 216] However, at this stage there is no consensus on whether states of arousal have an important impact on AERPs in this age group. Although some studies have shown significant AERP differences between active and quiet sleep,[219, 240, 241] the majority have not.[219, 228, 242-245]

Traditionally, AERPs are recorded using 8- 16 channels positioned following the international 10- 20 EEG electrode system. However, in the last decade, electrode caps have become available allowing for up to hundreds of channels.[37] Auditory stimulation is performed through loudspeakers or headphones. Slower stimulation rates and larger differences between the standard and deviant stimuli are generally needed than at higher ages.[37, 52, 244]

It is generally difficult to conclude whether infant AERP peaks are analogous to those of children or adults and there is limited evidence about where the neural generators are situated.[56, 238] Neural mechanisms underlying maturational changes in AERPs should be addressed with caution, too. However, early maturational changes during the first half year of life have been related to changes in maturation of the cortical layers and thalamo-cortical connections, in intracortical synaptic organization and synaptic density, and to myelination.[36, 41, 240, 243, 246] The increasing speed of transmission has been associated with myelination and changes in synaptic efficacy.[247, 248]

Exogenous responses

The AERP waveform in newborns and infants does not resemble adult waveforms. Instead of four main peaks, it is mostly biphasic, with a large positive deflection at midline electrodes peaking around 200- 300 ms followed by a slow-wave negativity peaking around 450- 600 ms.[215, 240, 243]. Although it is hard to prove, the early AERP responses are thought to reflect sensory analysis of low-level stimulus features such as intensity and frequency, while longer-lasting activity is supposed to reflect later stimulus processing presumably involving cognitive functions such as memory and attentional processes.[37, 53]

However, before attaining this typical pattern, exogenous responses undergo major changes during the last intrauterine and first postnatal weeks. This typical maturational sequence of early peaks has been described by several study groups, and it has been classified into five maturational levels, depending on the main polarity of the responses between 150-300 ms after stimulus onset on median and lateral electrode sites. The most immature level I-response shows negative deflections over both sites. At level II and III the response becomes undetermined and then positive over midline electrodes. At level IV and V, it becomes undetermined and finally positive over lateral electrode sites as well. This developmental

course is concordant with a 1- 2 months developmental lag of the secondary auditory areas behind the primary ones at term. All levels I-V are seen at term, but levels III-V are the most common.[25, 56, 240, 243]

During infancy, peak amplitudes increase, making the peaks become better defined, and latencies become shorter. The amplitude of the positive peak increases until 3 months of age, while the negative peaks only start to grow thereafter. By 1 year of age, the typical morphology P150-N250-N450 found up to school age is attained.[247, 249] Although the functional correlates of the childhood exogenous responses are poorly understood,[250, 251] it has been suggested that the P150 and N250 responses are precursors of the adult P1 and N2 responses, while the functional significance of the N450 responses is unknown. It has been proposed that it reflects some form of further stimulus processing not occurring in adults under the same conditions, such as building of neural representations and learning.[247] Between the two negative peaks, a positive P350 may be present, however, it decreases as the two negative responses strengthen.[38,247]

Few studies have investigated the development of AERPs in toddlers, while AERPs during later childhood are well understood.[215] In early childhood, the waveform is quite stable including the P1, N2, and N450 peaks,[246, 249, 251] which seem to correspond to the P150, N250, and N450 peaks found at 12 months of age.[249] During early childhood, P1 and N2 are the main exogenous responses on fronto-central electrode sites, both localized in the auditory cortex, mainly the superior temporal gyrus.[222, 252] In response to speech sounds, an additional positive deflection after N2 has been described from 7 months to 7 years of age, disappearing by adulthood.[253] During later childhood, the adult N1 response appears, splitting the positive P1 into two components (P1 and P2). The appearance of N1 between P1 and P2 is strongly dependent on the stimulus presentation rate.[40, 246, 252, 253] For the P1 response, relative peak amplitudes change with time, and latencies decrease, at a mean of 2- 3 ms per month from 3-36 months of age, slowing down with increasing age.[212, 215, 253] While the childhood P1, N1, P2, and N2 evolve into the corresponding adult responses,[246] the infant N450 latency decreases, and the peak fuses with the N250 response between 12- 24 months of age.[247]

After generating a response to a stimulus, a neural population needs time for recovery before being able to produce a new, equally strong response to a new stimulus at the same latency (refractoriness). This can be tested using different inter-stimulus intervals for otherwise equal stimulus paradigms. Newborns and infants need long inter-stimulus intervals to present robust responses. During infancy and early childhood, this long refractoriness successively decreases.[52, 254]

The typical P1–N2 waveform at preschool age using relatively fast stimulus presentation is shown in Figure 3 (in the Results chapter below).

Mismatch responses

An MMN-like response in newborns was first described by Alho et al.[244] It seems to be an ontogenetically early response, already present in the fetus.[238, 239, 255] During infancy, the AERP response to auditory change consists of a negative peak (or negativity) and a positive peak (positivity), or at least one of these.[37, 256, 257] However, infant MMN has a poor signal-to-noise ratio, and its identification in infants and young children is problematic. Recognition memory is very short during infancy, and processes indexed by MMN are immature during the first

years of life.[212, 241, 257-259] Even in newborns and infants this response has been referred to as a precursor of adult MMN, and it is assumed to reflect change-detection mechanisms,[53, 216, 228, 241, 244, 260] although this has been questioned.[212, 227]

MMN has been observed in response to frequency and duration changes of sinusoidal tones, to complex and harmonic tones, speech tones, novel sounds, changes in inter-stimulus interval, and to stimuli breaking a simple or complex rule.[25, 37, 38, 219, 261-264] However, even when newborns and infants are able to discriminate the stimuli behaviorally, only between 50-80% of them show an MMN response.[37, 216, 228, 244, 265]. In some other studies, no MMN has been obtained.[257, 266] And in a follow-up study investigating infants every third month during the first year of life, only one in 12 infants showed an MMN at all ages.[256]

In the last decade, an increasing number of studies in newborns and infants have described the presence of a positive mismatch response (MMR) in a similar time window, present instead of, or in addition to the MMN.[37, 212, 219, 230, 260, 263, 267] As the time windows of these two responses overlap, and the scalp distribution is similar, this response could potentially mask the MMN, and the sum of these responses may be either positive or negative or even at the baseline.[230, 257] This positive MMR (P-MMR) is largest during infancy and decreases thereafter.[61, 256] Its functional nature remains unclear, but suggestions have been made that it is a more immature equivalent of the MMN; a transient detector system and precursor for MMN; an inverted MMN that will flip in polarity with maturation; an index of detection and encoding of acoustic properties of the stimulus, reflecting greater recovery from refractoriness of the first positive exogenous positivity; or it is an analog of the P3a response.[212, 230, 256, 257, 267, 268] Although this question is still under debate, several studies have addressed factors determining the main polarity of the response in the MMN time window. Such factors are technical issues such as placement of the reference electrode, or filtering, and intra-individual factors such as state of arousal, attention, and training. However, age and maturation of the infants and children, and, most importantly, factors directly related to the stimuli (e.g. size of the deviance between the stimuli, complexity, presentation rates, stimulus duration) are the main determinants of response polarity.[37, 53, 61, 219, 267-269]

During infancy and childhood, the latency of the MMR decreases with increasing age from about 200- 450 ms to about 150- 300 ms after sound change onset, showing large inter-subject variability.[256-258] The amplitude is strongly dependent on stimuli, deviance size (a larger deviance usually giving a larger MMR), and stimulus-onset asynchrony (SOA, the interval from start of one stimulus to the start of the following one), while data on the influence of the state of arousal are inconsistent.[212, 219, 242, 245, 270] However, the amplitude of a P-MMR decreases with increasing age, and after 4- 6 years of age, MMR are consistently negative.[61, 212, 250, 267, 271]

P3a

The possible presence of a P-MMR in infants and young children complicates the analysis and interpretation of positive responses elicited by stimulus changes. Thus, some of these P-MMRs may have been misinterpreted as P3a, especially in earlier studies.

A positive response following after a MMN at around 250- 400 ms (in children before school age up to 600 ms) after stimulus change onset has been described in a number of studies from term age through childhood. As with the adult P3a, the amplitude of this

response is the highest to novel sounds, and it is significantly larger when awake than when asleep.[230, 256, 272, 273] From school age, it may be divided into an early and a late subcomponent.[232] As with P3a in adults, it has been proposed that it represents attentive mechanisms, including attention switching.

Late negativities

Late negativities, following an MMN-like or P3a-like response, are observed much more consistently in infants and children than in adults.[38, 216, 240, 274] Many different names have been used for this response, such as negative slow wave, late discriminative negativity, LDN-like negativity, Nc-like negativity, and reorienting negativity.[38, 216, 245, 274, 275] This late negativity is most easily elicited by novel sounds, extreme deviants, and speech sound deviants. It has been proposed that it represents detection of novelty, although it also has been elicited by deviants which were not 'novel'.[36, 240] Its neural origin is unknown.[37, 275]

AERPs in clinical and neuropsychological conditions

Neonatal conditions

Very few studies have investigated the impact of pre-, peri-, and neonatal conditions on AERPs in term-born infants.

Two studies have shown impairments in recognition memory in newborns to diabetic mothers with and without iron deficiency, showing an abnormal response to the mother's voice when compared to a stranger's voice. These abnormal responses were associated with lower scores of the BSID at 1 year of age.[274, 276] In newborns exposed to tobacco smoking during pregnancy, in contrast to newborns to non-smoking parents, physiological hemisphere differences in AERPs to speech stimuli were missing, and neurophysiological signs of speech sound discrimination started later in these infants, suggesting impairments in speech sound processing.[277] Full-term infants with neonatal intracranial hemorrhage showed more negative response amplitudes to both standards and deviants when compared to term controls, and this negative shift was more pronounced at 6 and 12 months of age than at term. The same was true for infants with severe neonatal asphyxia.[278]

Connate conditions

Some studies have investigated AERPs in sensory auditory deprivation and recovery after cochlear implant. Exogenous responses have been shown to be very different from healthy children even after cochlear implant, having a delayed P1 peak and lacking a normal N1 response.[279, 280] Developmental plasticity after cochlear implant has been studied, leading to normalization of these peaks after early (within 3.5 years of auditory deprivation) but not late implantation.[280-282] On the other hand, MMN is present in a group of children who have a good spoken language perception after cochlear implant, but it shows a different scalp distribution and the normal asymmetry is absent.[279] However, deficits in auditory sensory

memory and verbal working memory as measured by MMN and behavioral methods persist at least to school age.[283]

Several studies have shown deficits in AERP responses in children born with a cleft palate, a group that is known to have problems in sound perception and language development later in life. In newborns with a cleft palate, unlike healthy newborns and newborns with an isolated cleft- lip, a frequency deviant did not elicit an MMN.[284, 285] This deficiency in sound discrimination persisted to infancy.[286] Infants 6- 24 months old with non-syndromic cleft lip and/or palate had significantly smaller MMN responses to a frequency deviant than their controls.[287]

Developmental difficulties are also common in craniosynostosis.[288] In infants with plagiocephaly, the exogenous P150 and N250 responses were smaller than in healthy controls, suggesting a central auditory processing disorder in these children.[289] Conversely, in a recent study, infants with deformational plagiocephaly secondary to supine sleep did not show any differences in their cortical auditory responses to speech sounds.[290]

Brain damage and coma

AERPs and MMN have been used to prognosticate outcome on adult comatose patients. While the absence of brainstem auditory-evoked potentials, long latencies, and missing of short-latency AERPs predict adverse outcome, AERPs are useful in predicting recovery. Absence of N100 appears to be a predictor of bad outcome, but the presence of MMN is a very good predictor of recovery, having a positive predictive value for favorable outcome of 89- 100%. However, its sensitivity is quite low, at 33- 56%. Data on the predictive values of the P3 wave are contradictory.[291]

Fischer et al.[292] described a group of 128 severely comatose patients and investigated their N100 and MMN responses. These responses were smaller than in healthy controls. Of the 128 patients, 95 regained consciousness. Of all patients, 33 showed a MMN, and 30 of them regained consciousness, as well as 70 of the 84 patients showing an N100. In a study of 346 comatose patients, the same author compared the predictive value of different clinical and neurophysiological variables on awakening from coma.[293] Again, about 90% of patients with MMN and 87% with N100 awakened. No patient with MMN became permanently vegetative. Likewise, in patients with vegetative state, MMN predicted recovery from the vegetative state, and an increase in MMN amplitudes was seen during recovery to consciousness.[294]

A recent study on patients after traumatic brain injury showed a significantly increased MMN amplitude in a group without macroscopic lesions on MRI when compared to patients with MRI brain lesions and healthy controls.[295]

Dyslexia, language and learning disorders

AERPs have been excessively used in research on dyslexia, language and learning disorders. A complete review of this topic is beyond the scope of this thesis and may be found elsewhere.[227, 296, 297]

Detection, discrimination and effective processing of language-related auditory information are a prerequisite for normal language learning and speech-related

communication.[24, 298, 299] At term birth, the auditory system is genetically tuned to prioritize detection and processing of language-related information over other acoustic stimuli, and during the first year of life, the auditory system is tuned towards linguistic information belonging to the surrounding language (see chapter 'Short summary of early development of the auditory system and speech perception'). Phonological deficits are hallmarks of both language disorders and dyslexia, and they may result from difficulties in distinguishing auditory cues and from cerebral difficulties in processing rapidly presented information. However, the cause of dyslexia and specific language impairments is not confined to defective processing of linguistic stimuli.[227]

AERP studies have shown a relationship between early MMR maturation or MMR anomalies and later language impairment.[300, 301] They have also shown abnormal MMR or MMN in infants and children with, or at risk of, language difficulties,[227, 270, 302] dyslexia[296, 303] or risk for dyslexia,[304, 305] reading disorders,[297, 306] and specific language impairment.[267, 307] These AERP abnormalities were associated with reading, learning, and language outcomes.[297, 301, 308-310]

Auditory or speech processing has also been linked to language and other cognitive abilities in other contexts than these impairments.[300, 311, 312]

Hyperactivity, attention deficit, and distractibility

Over the last decade, an increasing number of AERP studies have been performed on children with attention deficit hyperactivity disorder (ADHD). Several studies have shown a decreased amplitude of the exogenous responses such as P1 in children with ADHD.[313, 314] MMN to a duration deviant was faster and decreased in children with attention deficit.[306, 314] However, another study showed no difference in MMN latency or amplitude to different frequency and duration deviants.[315] Abnormal involuntary attention shifts have been shown in ADHD children with significantly decreased early phase and increased late phase of the P3 response in some,[232, 316, 317] but not all, studies.[314] A late negativity was earlier and smaller in children with ADHD than in controls.[232]

Autism spectrum disorders

Children with autism spectrum disorders are among other signs characterized by deficits in communication and social behavior. They also show abnormalities in various aspects of language and perception.[55] These are reflected in AERP abnormalities.

The results of studies investigating the exogenous components are inconsistent, with prolonged latencies in some studies,[318-320] but not in others,[250, 321], and decreased P1 amplitudes in some studies,[250, 320, 322] but not in others.[318, 319] MMN responses indicate a hyposensitive discrimination of sound duration and a hypersensitive discrimination of sound frequency.[55, 250, 323]. MMN to speech sound changes are mainly reduced.[324, 325] The P3a response is mainly affected by sound quality, being absent or diminished for changes in speech sound, but normal or increased for non-speech sound changes.[55, 250, 323]

For infants at risk, having an older sibling with autism spectrum disorder, an asymmetry of the response to speech sounds, which is present in controls, was missing during the second half year of life.[326]

AERPs in the preterm infant

Although it is more than forty years since the first studies on long-latency auditory evoked potentials in preterm children were published,[327] there is not a great deal of AERP research in preterm infants, with a mean publication rate of about two articles per year over the last decade.

Exogenous responses to non-speech stimuli

Early studies focused on exogenous responses and their maturation around term. Graziani et al.[327] followed a group of 23 premature infants born between 27- 37 GW (BW 1100- 2200 g) every second week from birth to term using relatively loud clicks (90 dB) and a long inter-stimulus interval of 4 s. By visual inspection of midline electrodes, they identified a N1– P2– N2 configuration between 150- 500 ms after stimulus onset, the P2 being small or absent before 32 GW.

Ten years later, Kurtzberg et al.[240] performed the first study in a group restricted to VLBWI. They followed 35 VLBWI and 17 controls every month from term to 3 months of age, using two different consonant-vowel syllables and tone bursts as stimuli. The responses were categorized into five maturational levels according to response polarity between 100- 400 ms on the midline and lateral electrodes as described above for term newborn infants (positive polarity being more mature than negative polarity). At term, VP infants showed significantly more immature patterns for syllables but not for tone bursts, however, there was a considerable overlap between groups. This maturational delay persisted non-significantly to 2 months of age.

In 1987, Rotteveel et al. published a series of studies on follow-up of the maturation of central auditory conduction in 65 preterm infants until 3 months of corrected age, using clicks as stimuli and central electrodes. The infants were divided into 5 groups according to GA and 8 groups according to postmenstrual age at recording. They described a succession of three stages. The premature stage appeared at about 25 GW and consisted of relatively low voltage fast waves (a small positivity at 100 ms, a large negativity at about 250 ms, increasing from 25 GW to 30- 33 GW and decreasing thereafter) and high voltage slow waves (positive slow wave after 500 ms showing a similar maturational course as the 250- ms negative response). The transitional stage started around 36 postmenstrual weeks and showed low voltage noisy records, which were most pronounced at term. A mature stage was achieved by 50- 52 postmenstrual weeks, consisting of a succession of three positive and two negative deflections between about 150- 600 ms after stimulus onset. Maturation was characterized by waveform changes rather than changes in latencies and amplitudes. An increase in the number of responses was seen with increasing maturity.[328]

The same research group reported the detectability rates of individual wave components in low-risk preterm infants born between 25- 34 GW at an age of 30- 41 postmenstrual weeks. They found that components of the preterm waveform show detectability rates that generally are too low to allow for judgments on the integrity of central auditory pathways, but that repeated recordings during the neonatal period can resolve this problem, reaching detectability rates above 85% for the most prominent responses.[329] Compared to full-term infants, at 40 postmenstrual weeks, these preterm infants showed shorter latencies of the

obligatory fast waves (negativity around 130 ms, positivity around 200 ms, negativity around 350 ms), while the latency decline by 3 months of corrected age was decreased, resulting in longer latencies of these same responses by this age. No amplitude differences for the main responses P200 and N350 were found at term or at 3 months of age.[330]

In 39 preterm infants of two GA groups (23- 29 GW and 30- 34 GW), at 35 postmenstrual weeks, Bisiacchi et al.[53] and Mento et al.[44] demonstrated the presence of a positive response between 100- 200 ms (P150) and of a negative response between 150- 300 ms (N200), followed by a sustained late negativity on temporal electrodes. The P150 response to the 1000- Hz standard was not different between the groups, while the N200 response to the 1000- Hz standard and both responses to the 2000- Hz deviant were smaller in the more preterm group. The authors conclude that GA rather than postnatal experience is the main factor explaining cortical processing at this age. No full-term control group was included. Both standard and deviant showed higher AERP deflections on the right than the left between 300- 650 ms (the interval of the late negativity) in response to both the standard and deviant. This hemispheric effect was close to zero in the extremely preterm group but increased after more than 30 GW. This was interpreted as evidence of early functional right lateralization for pitch detection and discrimination arising by 30 GW but not before, and independently of the length of sensorial experience. The authors suggested that maturation of cortical functioning proceeds better inside than outside the uterus.

Using the same paradigm in 18 preterm infants (25- 35 GW) at 35 GW in different sleep stages, no differences in exogenous responses between sleep stages were reported, suggesting equal sensory perception in active and quiet sleep.[52]

In a follow-up study on VLBWI, Fellman et al.[38] compared three groups of infants: a group of 15 VLBWI born small for gestational age (SGA), a group of 20 VP infants born with a BW appropriate for GA (AGA), and 22 healthy, full-term controls. Both preterm groups had AERP recordings at term, 6, and 12 months of age, while the control group had recordings from term and every 3 months up to 15 months of age. Fellman et al. used a harmonic standard tone and a deviant tone with a 50% higher frequency and reported the exogenous responses N250 and P350 as well as endogenous responses (see below). At term, the main exogenous response was a positivity around 250 ms, and it did not show any group differences. By 6 months of age, the N250 response had appeared in full-term and AGA infants but it was still absent in SGA infants. Generally, the response maturation followed postmenstrual age rather than postnatal age.

Using the same frequency-deviant paradigm but adding 10% of environmental noises as novel sounds, Mikkola et al.[234] compared 28 VP infants from the study by Fellman et al. (13 of which SGA) with 13 term controls at 5 years of age. They also added a more challenging paradigm with a short SOA of 300 ms, a short duration deviant and a frequency deviant differing from the standard by only 8%. They demonstrated impaired auditory processing in the preterm infants of both groups, showing smaller P1 amplitudes in both paradigms and larger N2 amplitudes to the frequency deviant in the challenging paradigm. The finding of smaller P1 amplitudes was reproduced in another study on 24 very preterm infants (some of the infants were the same individuals) by the same research group in an active task paradigm.[275]

Lavoie et al.[331] examined 15 healthy children born extremely premature between 25- 28 GW (BW 720- 1320 g) at preschool age and compared them to 15 full-term controls using a passive oddball task using a 20% frequency deviant and a SOA between 550- 950 ms. The preterm group was selected from a larger study by being indistinguishable from the controls in many aspects including IQ, and neurological and psychiatric status. In both groups, two exogenous peaks were identified: a negativity around 100 ms which was largest frontally, and a following positivity, showing a complex topography and waveform on different electrodes and reaching a maximum around 200 ms on temporal electrodes. This pattern is opposite to the usual waveform in this age group. There were no group differences in terms of the latency or amplitude of these two peaks. Around the same age, Dupin et al.[332] reported a significantly larger N2 amplitude at about 200 ms to a 1000- Hz pure tone in an active task, but not in a passive one, in VP children when compared to term-born controls.

In a study by Gomot et al.,[288] 15 preterm infants born between 27- 33 GW having normal IQ, normal reading and writing skills, and normal behavior according to different tests were compared with 15 full-term controls at 9 years of age. A 10% frequency difference and a SOA of 700 ms were used. Both groups showed P150 and N250 responses, as is usual in this age group, with a trend to smaller amplitudes of the P150 response and a significantly smaller N250 in the preterm group on frontocentral and on left-sided temporo-mastoidal electrodes. These group differences could be a sign of impaired auditory processing, and the reduced N250 frontal activity could be related to difficulties in auditory attention in preterm infants, as suggested by the authors.

Lindgren et al.[333] tested 10 healthy VP children born before 29 GW at 10 years of age using a three-tone oddball task and compared them to full-term controls. These VP children had no brain damage on cranial ultrasound and a full-scale IQ above 70. 1000- Hz tones with durations of 50 ms and a SOA between 1400- 1600 ms were presented. A N1- P2- N2 pattern was found on fronto-central electrodes, with larger P2 amplitudes in the VP group, but no group differences for the N1 and N2 amplitudes. VP children had shorter N1 latencies. However, there were topographical differences between groups for the N1 peak, with controls showing the normal pattern of higher amplitudes in the midline, while this was not the case in the VP group.

Exogenous responses to speech sounds

The non-significant trend to somewhat lower maturity scores at term in preterm infants reported by Kurtzberg et al.[240] was replicated by Therien et al.[56] in 35 VP infants (28.4±2.6 GW, BW 1154±374 g) compared with 40 full-term controls, using the consonant-vowel syllables /bi/ and /gi/. There were no differences in the exogenous response latencies to the standard between groups but shorter latencies in the VP infants to the deviant.

At 9 and 12 months of age (corrected), in total 56 healthy VP infants showed frontally positive and occipito-temporally negative responses to a synthetic consonant-vowel stimulus between 90- 190 and 300- 512 ms. No differences with 92 full-term control infants of the same postnatal ages were found.[48]

Jansson-Verkasalo et al.[251] performed a follow-up study on 12 VLBWI and compared them with 12 healthy full-term controls. Most of these infants had changes in cerebral MRI, mainly an increase in CSF. AERP was performed at about 4 and 6 years of age, using semi-

synthetic Finnish syllables. Two deviants differed from the standard in either vowel length or consonant. Exogenous responses (a succession of P1– N2– N4) were compared at 4 years of age and showed no group differences in latencies, amplitudes, or scalp topography.

Endogenous responses to non-speech sound differences

Bisiacchi et al.[53] demonstrated in 39 preterm infants that a MMR to a 1000- Hz vs. 2000- Hz frequency deviance was already present at 35 GW in both children born extremely preterm (23- 29 GW) and moderately preterm (30- 34 GW). It was negative, and larger in the moderately preterm than in the extremely preterm group. Thus, intrauterine rather than extrauterine development seems to provide more suitable conditions for cortical pathway development.

Using the same paradigm in 18 preterm infants between 25- 35 GW, the deviant elicited a frontally negative response between 200- 300 ms on the difference wave in active but not quiet sleep, followed by a sustained positivity. The study suggests that preterm infants at 35 GW show cognitive processing of auditory change detection in active sleep only.[52]

Leipälä et al.[278] compared 9 VP infants with intracranial hemorrhage (five of them with moderately or severely abnormal development at 2 years of age) with 16 VP infants without intracranial hemorrhage and 22 healthy term controls. In these three groups no significant MMR to a 50% frequency contrast was found at term, while a P-MMR was seen at 6 and 12 months of age (corrected). No significant differences were found between the three groups.

In the study by Fellman et al.,[38] a significant MMN to a 50% frequency contrast was present in full-term infants only, both at term and at 1 year of age. Furthermore, only full-term and AGA infants showed a P3a at term, while in later ages the P3a was larger in the preterm groups. It was proposed that these abnormalities in change-detection responses indicated poorer sound discrimination and suggested an increased risk of cognitive, language, and learning problems as well as increased distractibility.

Mikkola et al. reported higher MMN amplitudes in response to a relatively large frequency deviant at preschool age in the same cohort of VP infants (both SGA and AGA) as in Fellman et al.[38] These were compared with term-born controls and it was suggested that they may be due to hypersensitivity to auditory change.[234] The P3a to novel sounds did not significantly differ between groups. No group differences in MMN or P3a were reported when a more challenging paradigm was employed. A partly overlapping group of very preterm infants was subjected to an active AERP task of distinguishing between animal sounds. After exclusion of a subgroup that was not able to complete the task and proved to have lower neuropsychological test results than the children who were included, the research group found no differences in MMN and late negativity in the very preterm group, but significantly weaker positive AERPs in the P3a interval.[275]

In the study of Lavoie et al.[331] at preschool age, a reliable MMN around 200 ms in response to a passive 1000- Hz vs. 1200- Hz frequency change paradigm was found in a small minority of both extremely preterm and term-born children at preschool age, with no significant group differences. Instead, a frontal positive response around 230 ms was seen and described as P3a response. This response was present in all children, but it was smaller in the premature group. A hemispheric effect, the response being larger with tone presentation to the left ear than to the right one, was found in the preterm group only.

Dupin et al.[332] investigated 20 normally developed VP born children (26- 32 GW, mean BW 1455 g) at 5 years of age and compared them with 20 term-born children, matched for IQ, using a passive and an active task. A 30% frequency deviant and a SOA of 550- 750 ms were used. No group differences were found for the MMN response, while the term control group had both higher P3a and P3b responses than the preterm group. Thus, at this age, auditory discrimination seemed intact, but the VP children had more difficulties in detecting targets in a sound stream both at a neurophysiological and a behavioral level, possibly a sign of less accessible attentional strategies.

At 9 years of age, Gomot et al.[288] showed similar MMN to a 10% frequency contrast in preterm infants born between 27- 33 GW and in term-born controls. The later positive deflection (possible P3a) was non-significantly larger in the preterm group.

The study of Lindgren et al.[333] also did not find any difference in MMN between 10 healthy children born below 29 GW and 10 term-born controls at 10 years of age. This study used a 10% frequency contrast and a SOA of 550- 650 ms. In a three-tone paradigm using three different frequencies with a large deviance (one of them as the target for an active task) and a long SOA of 1400- 1600 ms, the same study did not find any group differences in latency, amplitude, or topography of the P300 difference positivity. Thus, no sign of an expected hyperresponsivity could be found in the VP group.

Endogenous responses to speech sound differences

The first study investigating the presence of an adult-like MMN in preterm infants before term was performed by Cheour-Luhtanen et al.,[334] using vowels as stimuli and a SOA of 800 ms. In 11 healthy preterm infants born at 25- 34 GW and recorded at 30- 35 GW in active sleep or awake, they found that the response to the deviant was significantly negatively displaced compared to that to the standard between 300- 400 ms right and 400- 500 ms left frontally. Thus, the response resembled the adult MMN both in terms of morphology and scalp topography, and it was suggested that it was an analogue of the adult MMN.

Therien et al.[56] described a more negative area under the curve to a deviant consonant-vowel syllable as compared to a standard syllable in a study on 35 VP infants as compared to full-term infants at term across all electrodes. These areas were not associated with the results of a recognition memory task. The authors suggested that this alteration of speech sound processing may reflect brain injury, impaired brain growth and development, or be an effect of altered sound environment during the last trimester, or a combination of these factors.

The research group of Key and Maitre et al. tested 57 NICU- infants, not all of them being born preterm (24- 40 GA, median 28 GW), before discharge at a mean GA of 2 months (minimum 32 GW). They used one vowel contrast and two consonant contrasts, in total 4 different consonant-vowel contrasts. Postmenstrual age at examination differed between infants. These contrasts were not presented as an oddball paradigm but equiprobably. They calculated mean amplitudes over pre-defined time windows on the difference curves for frontal and temporal electrodes. The number of trials per syllable was small, on average 15 per infant and trial, but they tried to compensate a resulting poor signal-to-noise ratio by coupling adjacent electrodes and through statistical methods. This group found that a higher GA and a higher postnatal age both were associated with greater AERP differences between syllables. However, only preterm infants born at more than 30 GW profited from postnatal experience,

and the effect of experience accelerated from 2- 3 months after birth. Brain responses to vowels (simpler sound contrast) were less affected than responses to consonants.[49] In addition, hemisphere differences in responses increased with increasing postnatal age, both frontally and temporally. Responses were more positive frontally and more negative temporally in the 250-400 ms time window.[50]

Rago et al.[59] compared 21 moderately preterm infants (BW 1000- 2000 g) with 25 full-term infants of the same postnatal (uncorrected) ages of 6 and 10 months using a standard word and two deviant pseudowords differing by a phoneme or by word stress. The phoneme deviant elicited early and late negative deflections on the difference wave at 250- 350 and 450-550 ms from change onset. The deviant response was more negative at 6 than at 10 months of age. Responses to the phoneme deviant were similar between preterm and full-term groups at both ages. The stress deviant caused a significant P-MMR at 500- 600 ms from change onset. This response did not change between ages, but it was smaller in preterm than term infants.

In 11 VP infants and 13 full-term controls, using a native Finnish and non-native Estonian vowel contrast, Jansson-Verkasalo et al.[60] demonstrated a decreasing MMN amplitude to the non-native contrast in the full-term group from 6 to 12 months of age, while it rather increased in the preterm group of the same corrected age. While the MMN amplitude to this contrast was equal between groups at 6 months of age, it was larger in the preterm than full-term group at 12 months of age. At both ages, the MMN to the native contrast was not different between groups. While the full-term infants, as expected, gradually had decreased their ability to discriminate non-native phonemes between 6- 12 months of age, the preterm infants had kept this ability, and their lower-level processing of acoustic stimulus characteristics was still dominating over language-specific processing at the age of 12 months. Furthermore, the full-term infants had shorter MMN latencies at 6 months, suggesting a faster discrimination of native phonemes.

Comparing VP and full-term infants of the same corrected and uncorrected age (9 and 12 months corrected age) and using different native and non-native phonetic contrasts, Pena et al.[48] showed that maturation rather than experience shapes cortical phonological representations during the first year of life. In all groups, MMRs were found between 170-310 ms that were stronger for native than non-native contrasts, and for phonetic rather than acoustic stimulus differences. Groups of the same corrected age showed equal MMR amplitudes, while at the same postnatal age MMR between groups differed. In both groups, MMR to non-native contrasts disappeared between 9 and 12 months of corrected age.

Using syllable deviants in 12 VLBWI as compared to 12 full-term controls, Jansson-Verkasalo et al.[251, 335] reported smaller MMNs to vowel duration and consonant changes at about 4 years of age in the VLBWI group. Scalp topography did not differ between groups. About 2 years later, decreased MMN amplitudes were restricted to consonant changes and to those VLBWI who had naming difficulties, while VLBWI without naming difficulties did not differ from controls. There were significant correlations between MMN amplitudes at 4 and 6 years of age. The authors conclude that difficulties in pre-attentive auditory discrimination may be implicated in language difficulties in VLBWI.

Recognition memory

A few studies of the same study group have focused on recognition memory after preterm birth in terms of the different responses to the voices of the mother and a stranger. A study by deRegnier et al.[25] compared late preterm and early term infants born at 35- 38 GW and tested within a week of birth with full-term infants tested at two different postnatal ages. During testing, the infants were in active sleep. Brain activity in response to a speech sound alternating with a non-speech sound was recorded. For assessment of recognition memory, trials containing the word 'baby' were used, alternating between the maternal voice and a stranger's voice. In spite of differing postconceptual ages, there were not significant differences in waveform maturity defined according to Novak et al.[243] between preterm and full-term infants at one week of postnatal age. Furthermore, there were no significant maturational differences according to postnatal experience. In the analysis of recognition memory, the preterm infants showed no significant difference in their negative response to the two voices while the full-term infants did. This difference was achieved by a more positive response to the mother's than the stranger's voice in the full-term but not the preterm infants. Postnatal experience did not have a significant effect on the peak amplitudes, while more experienced infants had longer latencies for the maternal than for the stranger's voice. Thus, the development of recognition memory was primarily related to postconceptual and not to postnatal age.[25]

Using the same stimulus paradigm, the study by Black et al.[336] compared a late preterm and an early term group of infants born after IUGR with brain-sparing with a group of the same GA but without IUGR. The IUGR infants had a more localized exogenous positivity around 200 ms, while it was more diffusely distributed in the non-IUGR controls. Furthermore, the amplitude of this response was higher at T4 in the IUGR group suggesting abnormal lateralization of auditory processing. The responses to the maternal and the stranger's voice differed between groups, the IUGR group having significantly larger positive responses to the maternal voice on lateral electrode sites. This finding may correspond to an accelerated though atypical maturation related to the high vulnerability of the hippocampus and other medial temporal lobe structures to IUGR.

A similar paradigm was also used by Therien et al.,[56] again showing the absence of maternal voice recognition in VP born infants at term age, while term controls showed AERP evidence of voice recognition. Use of a 'familiarization period' with 60 presentations of the maternal voice before the recordings did not change the results.

Neonatal factors and AERP in the preterm infant

In the study by Kurtzberg et al. mentioned above, the maturity level of the exogenous AERP responses was not associated with GA, BW, or weight at term, but a trend to more neonatal morbidity was seen in the VLBWI with the most immature patterns.[240] The absence of an association between maturity level and GA was replicated by Rotteveel et al.[328]

Therien et al. reported morbidity in the VP infants included in their study. However, they did not rapport if any associations between neonatal factors and AERPs were investigated.[56]

In the study by Bisiacchi et al.,[53] the amplitude of the N-MMR present at 35 GW to a 1000- Hz vs. 2000- Hz frequency deviance, both in infants born extremely preterm and moderately preterm, was significantly correlated with GA, BW, birth length, and head circumference at birth. GA explained up to 66% of the MMR amplitude variance in regression analysis. Furthermore, GA but not BW and length of NICU stay had an effect on the maturation of hemispheric asymmetry by 35 GW.[44]

The studies by Key et al. and Maitre et al., described above, showed that both GA and postnatal age have an important impact on postnatal phoneme differentiation. A postmenstrual age of at least 30 GW seems necessary to be able to profit from postnatal experience.[49] Gestational age had a significant effect on hemisphere differences only temporally but not frontally.[50]

AERPs in the preterm infant and outcome

Very few studies have tried to elucidate associations between AERPs and outcome.

The first study to look at associations between AERPs and general outcome after the neonatal period was that of Fellman et al.,[38] as described above. They correlated AERPs in preterm infants during the first year of life (corrected) with results of the BSID-II at 2 years of age. At term, positive AERP exogenous response amplitudes on parietal electrodes between 150- 350 ms from stimulus onset correlated with better developmental indices. Furthermore, at 12 months of age (corrected), larger negative voltages in response to the standard between 250-350 ms at frontal electrodes correlated with a better Mental developmental index (MDI), as well as higher positive voltages on the difference wave in the same time window.

Leipälä et al.[278] found no associations between exogenous AERPs or MMR to a 50% frequency deviance at birth, 6, and 12 months of age and normal or abnormal outcome at 2 years of age in VP infants with or without intracranial hemorrhage.

In a study on VP infants elucidating the specialization of auditory processing towards the native language during infancy, Jansson-Verkasalo et al.[60] demonstrated that larger MMN amplitudes to a non-native phoneme contrast at 12 months of age (a sign of decreased specialization towards the native language) were associated with slower language acquisition in terms of lower word production, less developed speech morphology, and shorter length of spoken utterances at 2 years of age.

Using syllable deviants, Jansson-Verkasalo et al. showed that weaker object naming test results were paralleled by diminished MMN amplitudes to both vowel duration and consonant change at 4 years of age after VP birth.[251] Absence of MMN on most electrodes at 4 years of age rather than small MMN amplitudes also predicted naming difficulties at 6 years of age.[335] The authors suggest that pre-attentive auditory processing in VLBWI should be assessed early, along with language development, to identify children at risk of language deficiencies and to initiate timely and disorder-specific rehabilitation.

Mikkola et al.[234] correlated AERP responses at 5 years of age with neuropsychological test results (A Developmental Neuropsychological Assessment– NEPSY, and Wechsler Preschool and Primary Scale of Intelligence-Revised– WPPSI-R) assessed on the same day as AERP recordings. In an easy paradigm including a relatively large frequency contrast and novel sounds, they showed positive associations between the standard P1 and sentence repetition, the novel sound P1 and verbal fluency, and the frequency MMN amplitude and

both verbal fluency and verbal IQ. In a challenging paradigm with a small duration and a small frequency contrast, the frequency N2 amplitude correlated positively with verbal fluency, and the duration P1 with phonological processing and the language domain. They conclude that the decreased P1 amplitudes and enlarged MMN responses may reflect impaired auditory processing that may also affect verbal skills. In an active task in a partly overlapping study group, the same research group found a trend to more erroneous hits in the preterm group and less positive AERPs in the P3a interval. However, AERP components did not correlate with a neuropsychological test of the attention domain.[275]

Recently, Maitre et al.[50, 337] published two studies focusing on prediction of outcome with AERPs after preterm birth. While not all infants included in the studies were premature, the median GA was 28 GW. The authors focused on differences between AERP curves to different consonant and vowel contrasts in the 250- 400 ms time window on frontal and temporal electrodes. More details on the study are described above. AERPs were recorded before discharge, and neurodevelopmental assessment was performed at 6, 12, and 24 months of age. The amplitude of AERP responses contributed to 12-months outcome scores by 21-34%. Different phoneme contrasts correlated with different cognitive and verbal scores of the BSID at 24 months of age. Even after correction for GA and age at AERP, the /du/ vs. /gu/ contrast predicted the cognitive composite score and the /ba/ vs. /ga/ contrast the receptive language score. Greater hemispheric AERP differences temporally were associated with improved communication scores at 6 and 12 months of age and greater differences frontally with improved cognitive scores at 6 months of age (not tested at 2 years of age). Adjustment for GA, gender, antenatal steroids, and maternal socioeconomic score did not alter the associations at 6 months of age, but decreased significance at 12 months of age. The prediction of outcomes persisted after exclusion of 7 infants with brain damage. The authors conclude that AERPs can be used in NICU infants to help identify infants with higher risk for delays during infancy and early childhood and to predict meaningful outcomes, and that it could be complementary to neuroimaging.

Conclusions

It is difficult to draw conclusions on the development of AERPs in preterm infants since the number of studies and the number of infants in each study are small. Furthermore, while the design of stimulus paradigms is an important determinant of both the exogenous and endogenous responses, studies varied widely in the composition of these paradigms. There are great variations in SOA, so there is a potential risk of habituation and refractoriness. The degree of deviance between standard and deviants was very different between studies, posing different degrees of challenge to change detection and discrimination. And use of similar stimuli (mainly speech stimuli) to children from different language environments may be responsible for different AERP responses.[212] Therefore, cautious interpretation of the conclusions drawn from AERP results in the studies published to date is warranted.

During the first postnatal months, preterm infants follow the maturational course of term-born infants, when preterm and term-born infants of equal postmenstrual age are compared. A subtle maturational delay in the most immature preterm infants may be present, but with high degree of overlap at a group level. Postnatal experience does not have a major influence on sound processing. Even during childhood, AERP maturation follows roughly the

same timeline as in children born full-term. However, some AERP components differ after very preterm birth, the most consistent findings being a smaller P1 response. Latencies do not differ between preterm and full-term infants.

Preterm infants and children generally show MMRs to sound changes that resemble those of full-term infants and which are already present before term. During early life, as after term birth, these can be positive or negative, but become negative during childhood. While MMRs during infancy show differences in elicitability and amplitudes in some studies, they do not seem to differ from full-term infants in later childhood. Preterm infants show an impaired recognition memory early in life as shown by an impaired ability to differentiate their mother's voice from a stranger's voice, and they seem to have an impaired or delayed specialization of speech sound processing to the native language during the second half of the first year. Data on P3 responses are inconsistent, but some studies show differences compatible with an increased distractibility in VP infants and children.

Increasing immaturity at birth seems to have a stronger impact on change detection and sound differentiation than on basic sound encoding and processing.

Data on the predictive value of AERP for later outcome are sparse, but several studies suggest that AERP after preterm birth may have potential for prediction of meaningful cognitive and language-related outcomes later in life.

Aims and hypotheses of the thesis

The main aim of this thesis was to investigate the associations of AERPs with outcome in infants and children born very preterm.

I. Our first specific aim was to compare AERP in preschool children born very preterm with children born late preterm and full-term. Our hypothesis was that AERPs in very preterm children are different from the other two groups, and that these AERP abnormalities may resemble those of term-born children with cognitive or behavioral deficits. (Study I)

II. The second aim was to compare AERPs at different times (term-equivalent age and preschool age) with developmental and psychological test results. We hypothesized that cortical function as shown by AERPs after very preterm birth is correlated with neurodevelopmental and cognitive outcome. (Studies II and IV)

III. Our third aim was to investigate if a possible association between AERPs and outcome adds to the information given by other prognostic methods such as MRI. As MRI mainly describes anatomy, we hypothesized that the functional data given by AERPs would provide additional information to the structural findings. (Studies III and IV)

IV. The fourth aim was to investigate the impact of neonatal factors such as immaturity and morbidity on AERPs. Our hypothesis was that different neonatal factors may have different impact on cortical auditory processes, and that these differences would be apparent as different AERP patterns. (Study IV)

Methods

Subjects and study design

The investigations were performed in two prospective longitudinal cohort studies. The second cohort, leading to publications III and IV, was part of a larger study focusing on the IGF-I system after very preterm birth, and several additional papers have been published on this study population.[338, 339]

AERPs and outcome at five years of age (Studies I+II)

The study group consisted of 87 VP infants born before 32 GW and without major congenital malformations. They were recruited prenatally at the NICU in Lund between September 2000 and February 2003. Inclusion criteria were a GA below 32 GW, and an absence of major congenital malformations. All pregnancies had been dated by intrauterine ultrasound at 17- 18 GW. The majority of included children were born before 28 GW (N=55). Neonatal morbidity data including cUS findings were recorded prospectively during the neonatal period.

Of these 87 VP infants, three died during the neonatal period, one moved abroad, one could not be contacted, and the parents of 10 children declined to participate in the study at preschool age. Two children did not cooperate sufficiently for accurate AERP recordings, so 70 VP children were included in the analyses for these two studies at preschool age. The perinatal data of these children are shown in Table 1.

In Study I, we included two control groups. Children in the preterm control group (N=24) were born between 32- 35 GW and recruited in the NICU. They had no major neonatal morbidity. Children in the full-term control group (N=24) were born at ≥37 GW and recruited at the maternity ward of the hospital. At preschool age, the parents of 12 preterm and 9 term controls declined to participate in the study, giving AERP recordings in 12 preterm and 15 term control children. After correction for gestational age, the term control children were significantly younger at follow-up than the other two groups, which is why all further analyses included a correction for age at examination. A comparison of the three study groups is shown in Table 2.

All children investigated at preschool age had passed the neonatal hearing test at 4 years of age.

Table 1. Neonatal characteristics of the very preterm group in studies I and II (N=70).
Values expressed as mean±SD or as numbers (%). Severe intracranial hemorrhage: IVH grade III or PVHI.

Gestational age (weeks)	27.4±1.9
23+0 to 24+6 GW	3 (4)
25+0 to 25+6 GW	17 (24)
26+0 to 26+6 GW	9 (13)
27+0 to 27+6 GW	12 (17)
28+0 to 29+6 GW	18 (26)
30+0 to 31+6 GW	11 (16)
Birth weight (g)	996±288
Birth weight < -2 SD (small for gestational age)	21 (30)
Twins/Triplets	29 (41) / 5 (7)
Antenatal steroids	69 (98)
Days on ventilator	6.7±8.9
Need for inotropics	30 (42)
Blood culture-verified sepsis	19 (27)
Necrotizing enterocolitis	2 (3)
Severe intracranial hemorrhage	15 (21)
PVL	8 (11)
Retinopathy of prematurity grade ≥ 3	7 (10)
Bronchopulmonary dysplasia (oxygen at 36 GW)	35 (50)
Days at the hospital	86±24

Table 2. Characteristics of the three study groups in study I.
Values expressed as mean±SD.

	Very preterm (N=70)	**Preterm controls** (N=12)	**Term controls** (N=15)
GA (weeks)	27.4±1.9	33.8±1.0	40.0±1.3
BW (g)	996±288	2217±500	3725±393
Weight at examination (kg)	18.5±3.1	18.8±2.8	19.3±3.3
Head circumference at examination (cm)	50.6±1.9	51.4±1.6	51.6±1.6
Corrected age at examination (months)	58.6±2.5	57.7±2.3	55.1±3.2

AERPs and MRI at term and outcome at two years of age (Studies III+IV)

Sixty-four VP infants born before 31 GW (dated by intrauterine ultrasound at 17- 18 GW) were recruited at the NICU in Lund between January 2005 and May 2007. Of these, 52 infants were born before 28 GW. The only exclusion criterion was the presence of major congenital anomalies. During the neonatal period, the infants were followed with frequent body measurements and weekly measurements of the concentration of Insulin-like growth factor-I (IGF-I). Protein and energy intake were registered daily. Data on neonatal morbidity as well as administration of steroids and insulin were registered prospectively. Repetitive cUS was performed.

Based on the time when the infants had the lowest weight-standard deviation score (nadir), we defined the period from birth to nadir as the phase of growth restriction, and the period from nadir to 35 GW as the phase of catch-up growth.

Nine of the infants died during the neonatal period, and four chose to leave the study before term. The remaining 51 infants were investigated with MRI. The cerebellar volumes of all these infants were measured, while in 5 infants, measurements of the remaining brain volumes was impossible due to major artifacts.

Because one of the major outcomes of the main study was brain volume, MRI had the priority if any of the infants was too unstable to undergo both MRI and AERP testing. This was the case in four infants. However, their clinical instability was not related to a higher neonatal morbidity but was rather caused by occasional problems such as anemia or upper airway infections. Due to technical problems, the AERP data from another five infants were destroyed at a time when they were too old to repeat the recordings. Thus, we had access to AERP recordings in 42 infants. Their neonatal characteristics are shown in Table 3. Of these 42 infants, 41 were accessible for follow-up at 2 years of age.

At 2-year follow-up, one child had developed cerebral palsy, and none of the children was blind. All but one infant included in the investigations at term and at 2 years of age passed the neonatal hearing screening using otoacoustic emissions. In this child, a bilateral hearing deficiency was diagnosed during infancy, and it finally got a bilateral cochlear implant. As the hearing impairment was diagnosed first after AERP recordings had been performed, the child was not excluded from analysis. It belonged to the subgroup with severe impairment (number 41 in Figures 2 A-C in Publication IV).

AERPs

Recording

At 4- 5.5 years of age, AERPs were recorded in a sound-attenuated room in the Department of Neurophysiology (I+II). During recording, the children watched a silenced movie and were asked not to pay attention on the sounds delivered during the investigation.

Table 3. Neonatal characteristics of the infants with AERP recordings in study IV (N=42).
Values expressed as mean±SD or as numbers (%). Severe intracranial hemorrhage: intraventricular hemorrhage grade III or periventricular hemorrhagic infarction. Brain damage on cerebral ultrasound: any of severe intracranial hemorrhage or periventricular leukomalacia.

Gestational age (weeks)	26.5±1.9
23+0 to 23+6 GW	3 (7)
24+0 to 24+6 GW	7 (17)
25+0 to 25+6 GW	10 (24)
26+0 to 26+6 GW	5 (12)
27+0 to 27+6 GW	7 (17)
28+0 to 30+6 GW	10 (24)
Birth weight (g)	906±289
Birth weight < -2 SD (small for gestational age)	12 (29)
Twins/Triplets	17 (40) / 2 (5)
Antenatal steroids	41 (98)
5-minutes Apgar	7.2±2.0
Days on ventilator	9.8±10.9
Days on additional oxygen	81.5±46.9
Blood culture-verified sepsis	17 (40)
Ibuprofen and/or ligation for patent ductus arteriosus	21 (50)
Necrotizing enterocolitis	1 (2)
Severe IVH/PVHI	3 (7)
PVL	2 (5)
Brain damage on cUS	3 (7)
Retinopathy of prematurity grade ≥ 3	7 (17)
Bronchopulmonary dysplasia (oxygen at 36 GW)	31 (74)

At term age (40.1±0.6 GW), AERPs were recorded on the same day as MRI in the sound-attenuated room in the Department of Neurophysiology. The children were lying on their backs in a crib, fed and swaddled, but no sedation was given.

EEG-electrodes were attached according to the International 10- 20 system on frontal (F3, Fz, F4), central (C3, Cz, C4), and temporal (T3, T4) sites; and in the preschool children also on parietal (P3, Pz, P4) sites. In addition, electro-oculogram electrodes were attached. An EEG (bandpass 0.1-70 Hz, sampling rate 500 Hz) was recorded and referenced to the average of the mastoid electrodes.

Stimuli

Stimuli were delivered binaurally through headsets, at 60 dB Sound pressure level (SPL) at preschool age (I+II), and at 70 dB SPL at term (IV). We used an oddball paradigm, where a succession of repeated, frequent standard sounds is interrupted unpredictably by delivery of a deviant sound (Figure 2). The standard consisted of a 1000- Hz sinusoidal tone with duration of 100 ms including 10 ms rise and fall times. The frequency deviant differed from the standard by a 10% higher pitch (1100 Hz) and the duration deviant by a shorter duration of 50 ms. In the preschool children, we used an additional, third deviant differing from the standard in perceived sound source location. This difference was created by a sound onset difference between the ears of 750 µs, starting with equal probability on the left or the right ear. In both studies, the standard tone had a probability of 70%, while the three deviants at preschool age had a probability of 10% each, and the two deviants at term of 15% each. SOA (from onset of one stimulus to onset of the next one) was 533 ms at preschool age and varied between 760- 820 ms at term.

Stimuli were presented in three blocks of 605- 610 stimuli each, every block containing all deviants. Each block was introduced by a series of at least 5- 10 standard tones. Each deviant was followed by at least one standard tone. Thus, during the recordings, the standard tone was presented 1265- 1290 times. Each of the three deviants at preschool age was presented 180 times, and each of the two deviants at term 270 times.

The total duration of the recordings was about 15- 25 min, including short interruptions between blocks.

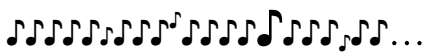

Figure 2. Example of an oddball paradigm.
A succession of standard tones is interrupted by one or several deviant tones.

AERP averaging and analysis

We filtered the continuous EEG offline (bandpass 0.5- 30 Hz, 24 dB attenuation) and divided it into epochs. Each epoch lasted from 100 ms before the onset of a stimulus to 550 ms (I+II) or 800 ms (IV) after onset. The EEG of each epoch was baseline corrected to the 100-ms prestimulus interval. All epochs with amplitudes exceeding ±100 µV (I+II) or ±75 µV (IV) on any electrode were rejected, as well as the first 3- 5 epochs of every block and all epochs following a deviant stimulus epoch. In addition, at preschool age, we performed a visual artifact rejection.

The remaining epochs were averaged, separately for the standard and each deviant, creating standard and deviant AERP curves for each child or infant. To minimize the impact of noise, a minimum of 50 epochs was required for each subject and deviant to be included in further data analysis of this stimulus. This excluded 1- 3 preschool children per deviant from the analysis, but no infants at term.

In order to create grand average curves for the standard and deviants (mean average curves of all infants or children in a group), all included epochs of all the infants or children were averaged together, using the averaged curves of the six frontal and central electrodes. Difference curves for each deviant, both for individuals, and for whole study groups were achieved by subtracting the curve for the standard from the curve for the deviant, again using the averaged curves of the six frontal and central electrodes.

Further analysis differed between studies.

AERPs and outcome at five years of age (Studies I+II)

For both standard and difference curves we calculated mean amplitudes for each 50- ms time window from 0- 550 ms (0- 50 ms, 50- 100 ms, etc.), using the mean of the six frontal and central electrodes.

Based on the grand average standard curve, showing the main positive response P1 at 130 ms and the main negative response N2 at 250 ms, we defined these two responses on the individual standard curves of each child. We defined the P1 latency as the time of the maximum of the most positive peak in the 130±50 ms time interval, and the P1 amplitude as the mean amplitude on the nine frontal, central, and parietal electrodes in the time window latency±30 ms. The N2 latency was defined as the time of the maximum of the most negative peak in the 250±80 ms time interval, and N2 amplitude as the mean amplitude on the same nine electrodes in the time window latency±30 ms.

Based on the expected time window from the literature, in Study I, we defined the time window of the MMR as 150- 350 ms after stimulus change onset (150- 350 ms after stimulus onset for the frequency and direction deviants, 200- 400 ms after stimulus onset for the duration deviant). In this time window, MMR was defined as the peak (positive or negative) with the largest mean amplitude within ±30 ms of the peak maximum on the six frontal and central electrodes. In order to exclude possible P3a-like responses from being identified as MMR, when a negative response preceded a positive one in this MMR time window, we considered the negative response (MMN) as MMR, and the following positive response as 'later positivity'. If several positive peaks were present in the MMR window, the first positive peak was defined as P-MMR and the second as 'later positivity'. For each MMR peak, we defined latency as the time of the maximum amplitude, and amplitude as the mean amplitude over the time window latency±30 ms.

In Study I, we state the number of children showing MMR, MMN, P-MMR, and 'later positivity' in each group. However, as this individual definition of MMR and 'late positivity ' may be noisy and hard to reproduce, in the following Study II, we do not use individual responses but and instead use time windows only.

AERPs and MRI at term and outcome at two years of age (Study IV)

For the standard and difference curves, in individual infants and for the grand average curves, we calculated the mean amplitude and standard deviation of all included epochs for each 10- ms time window from 0 to 800 ms (0- 10 ms, 10- 20 ms, etc.). In addition, we calculated the mean amplitudes for each 100- ms time window from 0 to 800 ms on the standard and difference curves (0- 100 ms, 100- 200 ms, etc.).

The time windows for the exogenous responses were defined based on the peaks of the grand average standard curve. The time window for the first negative response was defined as 50- 200 ms, for the second negative response as 250- 700 ms, and for the positive peak between these negative peaks as 150- 300 ms. For each of these three responses, the presence or absence of a significant peak with the expected polarity in the pre-defined time window was noted. Significance was defined as the presence of one or more amplitude data points with the correct polarity in this time window significantly differing from zero in a two-tailed *t*-test (*t*-value >1.96; $p<0.05$), based on the mean amplitude and standard deviation of all the included epochs. In addition, in order to be able to compare individual amplitudes between infants, irrespective of the presence of a significant response, we identified the largest mean amplitude of the expected polarity in any 50- ms time window within the pre-defined time window for each of the three responses.

Based on the grand average AERP difference curves for the deviants, and based on the individual distribution of significant peaks on individual difference waves (Figures 2B and 2C in Publication IV), the time window of the MMR was defined as 250- 750 ms after stimulus onset for both deviants. For both deviants, the response (positive or negative) with the highest 50- ms mean amplitude in this time window was defined as the MMR, and polarity and 50- ms mean amplitude were noted. For both deviants, we also noted both the positive (P-MMR) and the negative (N-MMR) peak with the highest 50- ms mean amplitude in the 250- 750 ms time window and tested these responses for significant difference from zero as described above ($t>1.96$).

MRI

Fifty-one VP infants underwent MRI imaging (III+IV), which was performed on a 3-Tesla Siemens Magnetom Allegra head scanner. The infants were swaddled in a vacuum fixation pillow, and received a single dose of chloral hydrate as sedation. For volumetric measurements, the protocol consisted of three 3D sequences: a T1-weighted MPRAGE-sequence, a T2-weighted TSE sequence, and a proton density TSE sequence. The voxel size for all sequences was 1 x 1 x 1 mm.

After image acquisition, a sequence of image processing algorithms was applied. We corrected for a consistent signal inhomogeneity of the MRI head coil. The matrix of the three 3D sequences was adapted to the same 160 x 256 pixel matrix, and the sequences were co-registered to create a three-channel data set containing corresponding anatomical structures at equivalent pixels in all three sequences.

Using this data set, brain volumes were measured. Total brain volume (TBV), unmyelinated white matter volume (UMWM), myelinated white matter volume (MWM), total gray matter volume (TGM), and cerebrospinal fluid volume (CSF) were assessed using a template-modified, statistical classification algorithm (κ nearest neighbor) based on signal intensities in the three co-registered data channels.[340] Cerebellar volumes, including cerebellar peduncles, were measured by manual outlining on both T1- and T2-weighted images. One of

the tissue classes or CSF was allocated to every voxel (1 x 1 x 1 mm = 1 µl), and voxels with each tissue class or CSF were summed to calculate tissue volumes.

I performed all the measurements myself, and I was at that time unaware of the clinical data or AERP results. The intra-observer variation was tested by repeating complete segmentations on six randomly chosen infants. The intra-individual correlations were high for TBV, UMWM, TGM, and CSF (*r*-values between 0.91- 0.99) but low for MWM, which is why this small tissue class was excluded from further analysis.

Follow-up

Outcome at five years of age (Study II)

On the same day as AERP recordings were made, the children were tested by one of two psychologists using all subtests of the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R)[341] and the subtests Visual attention, Phonological processing, Narrative memory, and Sentence repetition of A Developmental Neuropsychological Assessment (NEPSY).[342] The two psychologists were trained in these methods and blinded to both the AERP results and neonatal morbidity. In addition, the parents filled in the Strengths and Difficulties Questionnaire (SDQ),[343] in which we analyzed the total score.

For practical reasons, the range of corrected age at examination was as broad as one year (4.3- 5.3 years) and crossed the limit of 5 years for different tests to be performed in the NEPSY protocol. Thus, in order to avoid effects of different test protocols, all the children were tested using the protocols for the age group below 5 years. We used percentiles for 4-year-olds even in the children who were 5- 5.3 years old when no percentiles for 5-year-olds were available. In order to elucidate different aspects of the NEPSY Visual attention subtest, we analyzed the number of correct markings (VAco) and the time to complete this test (VAt) separately.

Limits for abnormal test results were put at <85 in WPPSI-R, ≤25th percentile in NEPSY, and >16 on the SDQ. To exclude the effect of severe cognitive impairment on NEPSY test results, children with WPPSI Full-scale IQ≤70 (*N*=4) were not included in NEPSY analysis.

Outcome at two years of age (Study IV)

Outcome was assessed in 41 VP children with neonatal AERP and MRI data by a psychologist blinded to AERP and MRI results. The Bayley Scales of Infant Development, 2nd Edition[344] were used. A suboptimal development was defined as index scores <85 (corresponding to more than 1 SD below the normative mean) for the Mental developmental index (MDI) or Psychomotor developmental index (PDI). If MDI or PDI scores were below 50, a score of 50 was assigned, according to the manual.

After the BSID, we (co-author I H-P and myself) performed a standardized neurological examination using the protocol for the Neurological optimality score (NOS, Hammersmith)[345], were a NOS <74 was defined as suboptimal.

Three outcome groups were defined. Children having any of MDI <70, PDI <70, CP, blindness, or deafness at follow-up were categorized as having severe impairment. Children performing with all of MDI ≥85, PDI ≥85, and NOS ≥74 and who showed no history or signs of CP, or impairment to their hearing or vision, were categorized as having no impairment. All other children were assigned to the outcome group with moderate impairment.

Statistical analyses

Relationships between categorical variables were assessed using χ^2 or Fisher's exact test.

We used an unpaired, two-tailed *t*-test for group comparisons of continuous variables when two groups were compared, and Mann-Whitney *U*-test if the continuous variables did not have a normal distribution. The two-tailed *t*-test was also used to test the presence of significant AERP responses. When more than two groups were compared, ANOVA was performed and Bonferroni-correction was used in post-hoc analysis.

For relationships between continuous variables, we used Pearson's correlation coefficient, or Spearman's rank correlation coefficient where any of the continuous variables did not have a normal distribution.

If any of the comparisons above needed correction for other variables, we employed regression analysis, using logistic regression analysis for comparison of categorical variables and linear regression analysis for correlation of continuous variables. These regression analyses were also used for multiple regression models, correcting the impact of single factors on variables of interest for other factors (for example for testing the associations of morbidity variables with AERP, and for comparing the associations of AERPs and MRI with outcome).

When group differences in AERP scalp topography were investigated, ANOVA for multiple measurements was used, with Greenhouse- Geisser correction where the assumption of sphericity was violated. Where further correction for clinical data such as age at examination was necessary, we used univariate ANCOVA.

Intra-observer variation for repeated brain volume measurements (test-retest) was tested using a paired-samples *t*-test.

Because the groups tested were relatively small, a general use of Bonferroni-correction for multiple comparisons would have erased most or all of the significant associations found in this work. Therefore, in order to avoid reporting accidental associations caused by multiple comparisons, only results that were consistent across different tests, adjacent AERP time windows, or between several deviants were presented.

A *p*-value of <0.05 was considered as significant.

Ethical considerations

All studies were approved by the Regional Ethics Review Board, Lund, Sweden. Whenever possible, written and oral information was given prior to delivery and parental informed consent was obtained after birth from both parents. In addition, written informed parental consent was obtained before follow-up.

Many children and families did not directly benefit from participation. However, we believe that the neurological and psychological testing as well as AERP recordings at preschool age, performed in a playful environment and atmosphere, did not impose a significant burden on the children. In some children we detected abnormal development in global or circumscribed neurological, cognitive or behavioral functioning during the psychological or neurological follow-up, and these children were referred to a medical or developmental specialist for further diagnostics and early intervention. The follow-up testing in the studies was more extensive than that performed on other very preterm born children at our unit at the time. However, national follow-up routines recently have been introduced and local follow-up routines have been extended, introducing several of the tests which were used in these studies.

MRI and AERPs during the neonatal period were performed at term and thus at a time when the vast majority of infants were stable, and transfer to the MRI unit could be performed easily. The calmness of the infants was mainly assured through feeding immediately prior to the examination, by positioning them in a comfortably enclosing vacuum pillar, and through the use of ear protection. Thus, only a mild sedative (chloral hydrate) was needed for MRI. In addition to the study-related analyses, anatomical MRI sequences were reviewed by a neuroradiologist experienced in neonatal MRI, thus allowing for detection of anatomical brain abnormalities that had not been obvious on earlier cUS. This allowed for a more intense clinical follow-up, independently of study-related testing, in infants with abnormalities carrying a high risk of adverse development.

Because infant AERPs were recorded irrespective of the degree of activity, and because recordings could be interrupted when they moved or fussed, no sedation was needed and it was only during attachment and detachment of the electrodes that the infants were disturbed. During recordings at preschool age, the children watched a self-chosen, silenced cartoon which easily motivated them to accomplish the recordings. A few children who we were not able to convince to accept the EEG electrodes had to be excluded from the analyses.

Results and comments

AERPs at five years of age (Study I)

Standard curves of the three study groups and the obligatory responses P1 and N2 are shown in Figure 3. The P1 amplitude was significantly lower in the VP group than in both control groups (p=0.031 and p=0.012 for comparison with the preterm and term control group, respectively), and the P1 latency was shorter in the VP and term control group than in the preterm control group (p=0.001 for comparison VP vs. preterm controls). In accordance with this, mean amplitudes in 50-ms time windows were lower (less positive) in the VP group than in both control groups between 100- 200 ms (p=0.003- 0.033 for the four comparisons) and lower than in the term control group even at 200- 250 ms (p=0.019). Differences between the control groups were not significant.

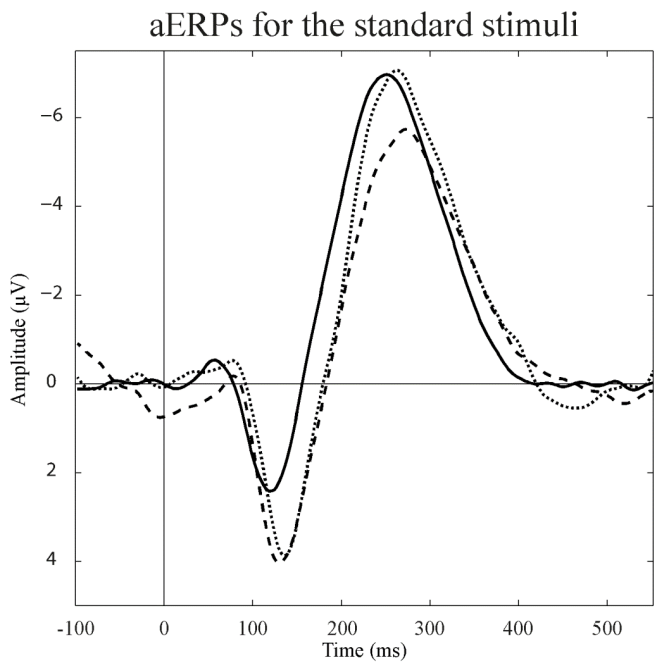

Figure 3. AERPs for the very preterm group (thick line) and the late preterm (dotted line), and term (dashed line) control groups. Observe that positive polarity is downwards and negative polarity upwards, in accordance with the traditional way of presenting AERP data. The main obligatory responses are the positive response P1 around 120 ms and the negative response N2 around 250 ms.

We interpret this finding as caused by a decreased activity of the cortical P1 generator. Possible explanations are impairment in basic auditory encoding and local or general brain atrophy, both associated with an increased risk of cognitive dysfunction. Several MRI studies have shown general and local decreases in GM after VP birth.[111, 133, 346] Decreased P1 amplitudes have been reported in children with ADHD, autism spectrum disorders, and those at risk of language problems,[305, 320, 347] all of which have an increased incidence in VP infants. Furthermore, our results are consistent with an earlier finding by Mikkola et al. in the same age group of VP born children. In their study, lower P1 amplitudes were associated with low performance in verbal subtests of NEPSY.[234]

Examination at a higher corrected age was correlated with significantly shorter P1 and N2 latencies (r=-0.490 and -0.426, respectively, p<0.001. Figure 4), and these correlations were significant for both peaks, in the VP (r=-0.451, p<0.001 and r=-0.305; p=0.01) and in the term control group (r=-0.566, p=0.028 and r=-0.674; p=0.006), but not in the preterm control group. The latency decrease was as rapid as approximately 3 ms per month, which is considerably faster than has been described earlier[215, 246] and questions the presumption of a slow, continuous latency decrease over time. Instead, there seems to be a phase of very fast maturation at preschool age that has not been described before. This novel finding needs to be confirmed in longitudinal studies focusing on this age group.

Age at examination was not associated with the amplitudes of P1 or N2.

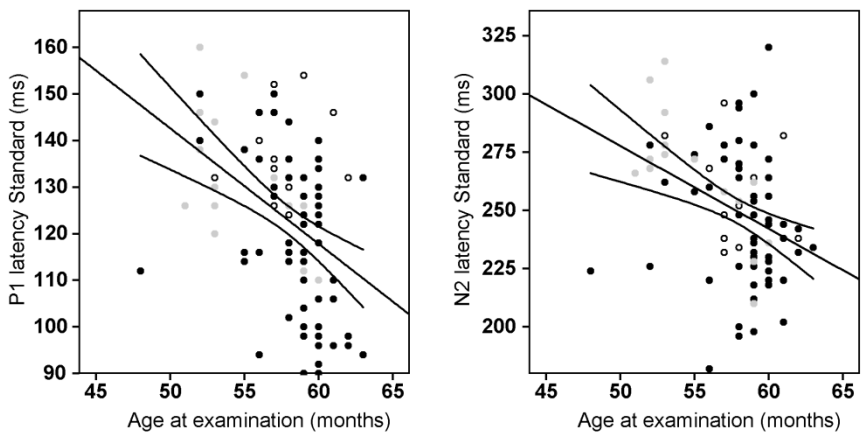

Figure 4. Correlations between age at examination and the latencies of the P1 and N2 peaks in the three groups combined. Black symbols represent VP children, circles the preterm controls, and grey points the term control children. Curved graphs mark the 95% confidence interval of the fit line.

The presence or absence of MMR was not different between VP and control children for any of the deviants, and neither were the mean amplitudes in any of the difference wave time windows. Sound change detection seems not to be different between groups for the deviant stimuli used in this study.

AERPs and outcome at five years of age (Study II)

Cognitive test results of the 70 VP children and of those with brain damage (here defined as the presence of any of IVH grade III, PVHI, or PVL in neonatal cUS) are shown in Table 4. As expected, children with brain damage scored significantly lower in several psychological tests.

Table 4. Cognitive test results and SDQ-scores for all children and for the children with neonatal brain damage.
*p<0.05; **p<0.01 for comparison of VP children with and without neonatal brain damage.
VIQ- Verbal IQ, PIQ- Performance IQ, PSQ- Processing speed quotient, FSIQ- Full-scale IQ, VAco- Visual attention correct markings, VAt- Visual attention time to complete, PP- Phonological processing, NM- Narrative memory, SR- Sentence repetition, Tot- Total score.

Test	Score	All children (N=70)			Brain damage (N=10)
		N	Mean±SD	Abnormal (%)	Mean±SD
WPPSI	VIQ	69	97.5±12.0	9 (13)	92.0±12.6
	PIQ	70	97.1±14.8	13 (19)	91.5±20.7
	PSQ	67	85.0±11.6	30 (45)	74.8±15.0**
	FSIQ	69	94.2±13.4	13 (19)	86.8±16.4
NEPSY	VAco	67	33.5±9.1	11 (16)	26.7±18.8*
	VAt	67	208±67	12 (18)	253±71*
	PP	69	11.8±2.3	10 (14)	11.2±2.6
	NM	69	10.0±4.8	18 (26)	7.5±3.7
	SR	68	17.3±4.3	9 (13)	16.7±6.0
SDQ	Tot	70	9.1±4.6	3 (4)	12.8±5.3**

Cognitive test results were related to AERPs. Better cognitive test results (except for VAt) showed a consistent association with more positive AERP amplitudes on the duration difference curve starting at 150 ms after change onset (Table 5). These associations were confirmed when children with abnormal and normal cognitive test results were compared. Children with abnormal results in all nine subtests had lower mean amplitudes after 150 ms than those with normal results. Furthermore, children with abnormal Processing speed quotients had more negative amplitudes in all seven time windows between 150- 500 ms on the frequency difference curve than children performing normally (significant for the 350- 400 ms time window; p=0.011), and children with abnormal VAco scores had lower mean amplitudes to the direction deviant in all seven time windows, reaching significance in the 200- 250 ms (p=0.044) and 300- 350 ms time windows (p=0.014).

Correlations of better cognitive test results with higher mean amplitudes on difference curves reached significance mostly in time windows after 300 ms. This is reasonable as the

more advanced auditory cortical processing associated with cognition (as represented by MMN and P3a responses) appears in these later time windows.

Faster completion of the Visual attention test correlated with shorter P1 (r=0.249; p=0.048) and N2 latencies (r=0.319; p=0.010). However, cognitive test results did not correlate with the amplitudes of these responses or with mean amplitudes in time windows on the standard curve. Factors causing a decrease in P1 and N2 latencies during childhood are continued myelination, synaptic differentiation, and synaptic specialization.[246, 348] Shorter P1 and N2 latencies in children with better test results may thus be associated either with reduced prematurity-associated impairment or with faster maturation of these processes. MRI studies have shown delayed microanatomical differentiation and myelination in WM tracts after preterm birth[159] and smaller local volumes in cortical auditory areas[133]. Higher ADC values and lower anisotropy implying impaired maturation and myelination in the pons and the inferior colliculus have been shown to correlate with longer latencies of auditory-evoked potentials in infants born VP[160,209]. Thus, both delayed or impaired myelination and impaired cortical differentiation may explain the significantly increased latencies in children with decreased GA, sepsis, and lower Apgar scores in our study (see below).

Table 5. Correlation coefficients between mean amplitudes in 50-ms time windows for the duration difference curve and cognitive test results.
#p<0.1; *p<0.05; **p<0.01.

VIQ- Verbal IQ, PIQ- Performance IQ, PSQ- Processing speed quotient, FSIQ- Full-scale IQ, VAco- Visual attention correct markings, VAt- Visual attention time to complete, PP- Phonological processing, NM- Narrative memory, SR- Sentence repetition, Tot- Total score.

Test	Score	N	150- 200 ms	200- 250 ms	250- 300 ms	300- 350 ms	350- 400 ms	400- 450 ms
WPPSI	VIQ	69	0.069	0.156	0.148	0.229#	0.138	0.092
	PIQ	70	0.048	0.124	0.039	0.203#	0.211#	0.151
	PSQ	67	0.157	0.151	0.191	**0.355****	**0.354****	**0.274***
	FSIQ	69	0.071	0.152	0.108	**0.255***	0.197	0.145
NEPSY	VAco	67	0.151	0.067	0.022	0.221#	**0.340****	0.235#
	VAt	67	0.192	-0.030	0.025	0.006	-0.067	-0.254#
	PP	69	**0.267***	**0.255***	0.166	0.207#	0.099	0.106
	NM	69	0.166	0.151	0.109	0.193	0.150	0.116
	SR	68	0.140	0.116	0.070	**0.252***	0.132	0.175

AERP curves for children with and without brain damage as diagnosed on neonatal cUS are shown in Figure 5. Children with brain injuries had AERP difference curves that were negatively displaced in the 100- 450 ms time windows for all three deviants when compared to children with no brain injury. Thus, negative responses in the MMN time windows were larger and positive responses in the P3a time windows were smaller in children with brain injuries. The association of brain damage with abnormal AERP amplitudes over such a long

time window supports that brain damage seems to have an impact on both early and later cortical auditory processes.

ERP amplitudes and polarities depend on the magnitude of synaptic activation; the localization and orientation of the cortical or subcortical generators; the excitatory or inhibitory nature of the input; and reception via synapses distal or proximal to the cell bodies.[349] The negative AERP displacement is, therefore, an indicator of altered brain development after neonatal brain damage and immaturity at birth.

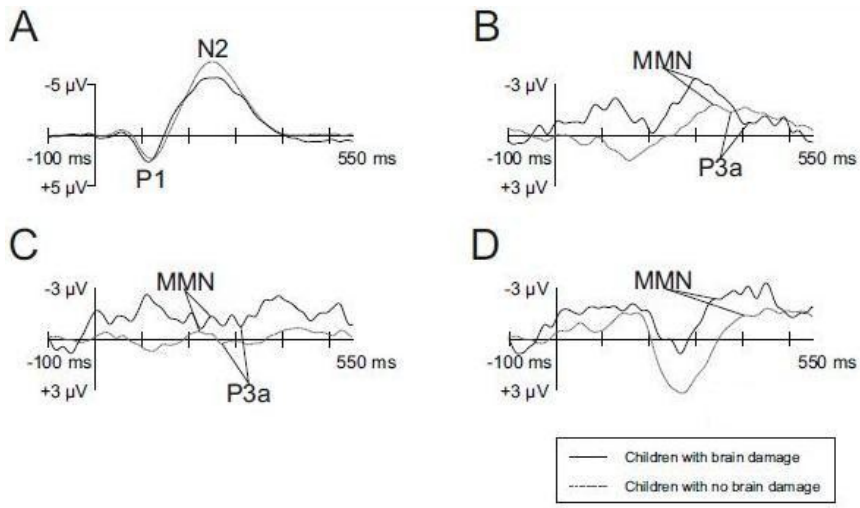

Figure 5. Grand average AERP standard curve (A) and difference curves to the frequency (B), direction (C), and duration deviants (D) of children with and without brain damage. The main responses are marked on each curve. No P3a can be observed on the average curve of the duration deviant.

Neonatal morbidity was also associated with AERP changes, as shown in Table 6. Neonatal morbidity correlated with amplitudes in early time windows only, while decreasing GA correlated with more negative amplitudes in both early and late time windows. Thus, early AERP time windows reflecting early cortical processes such as encoding and early processing were affected by GA, neonatal brain damage, and perinatal morbidity. Conversely, later time windows representing more advanced cognitive processes such as change detection, auditory discrimination, and attentional switch, which are for the most part correlated with outcome, were associated with GA and neonatal brain damage only. Thus, as expected, different neonatal risk factors seem to have different influences on central auditory processing later in life.

Lower GA tended to be associated with smaller P1 amplitudes, even after correction for neonatal morbidity (β=0.335; p=0.063), and neonatal morbidity and brain damage were not

associated with P1 amplitudes. Lower P1 amplitudes in children born VP have been described earlier,[234] and in this study we also found significantly lower P1 amplitudes in VP infants. Thus, environmental factors common to all VP infants rather than morbidity related to prematurity or major perinatal brain damage seem to determine the development of early cortical auditory encoding, at least up to preschool age. The auditory environment during the last trimester is different for VP and term-born infants. One possible explanation for this finding is that later auditory processing may be affected by both the absence of favorable intrauterine influences (mainly in the low-frequency spectrum), and the presence of the unfavorable effects of the NICU environment, such as increased sound exposure, high-frequency overstimulation (noisy ventilators and support devices, disturbance from alarms), repeated painful interventions, and neurotoxic and ototoxic medications.[50, 51]

Table 6. Correlation coefficients between neonatal morbidity and mean amplitudes in 50-ms time windows after stimulus change onset in multiple regression analysis
Only data with $p<0.1$ are shown. *$p<0.05$; **$p<0.01$

N=number of children with this characteristic. Vent – days on ventilator, F – frequency deviant, L – direction deviant, D – duration deviant

	N	100- 150 ms	150- 200 ms	200- 250 ms	250- 300 ms	300- 350 ms	350- 400 ms	400- 450 ms
Male	35	L 0.222			L -0.203			
GA			**D 0.273***				L 0.237	**L 0.274*** D 0.206
SGA	21	L -0.238						
5-min Apgar		**F 0.309*** L 0.278	**L 0.331***					
Vent		**D -0.478***	**D -0.617****	**D -0.630****	**D -0.651****			
ROP	6							
BPD	35	**D 0.299***						
Sepsis	18	**D 0.298***		**L 0.356*** D 0.255	D 0.272			

MRI at term and the IGF-I system (Study III)

We found significant positive correlations between GA at birth and TBV, UMWM, TGM, and CBV at term (r=0.46- 0.60, $p\leq0.001$). Brain volumes did not differ according to gender, and we found no significant differences in brain volumes between infants with and without neonatal brain damage as defined by cUS. However, in two of the five infants where semiautomated brain segmentations could not be performed, this was due to ventriculo-peritoneal shunts after major neonatal IVH, which may have affected the results. After

correction for GA, brain volumes did not correlate with doses of steroids or insulin administrated from birth to 35 GW.

As expected, SGA infants had significantly lower brain volumes (p=0.001- 0.013 for the five volumes) than the other preterm infants. They also had lower mean IGF-I concentrations from birth to 35 GW (19.2±6.0 vs. 25.3±7.0 µg/L). Mean IGF-I concentrations from birth to 35 GW, but not at 40 GW, correlated positively with all brain tissue volumes at term (r=0.44-0.58; p<0.001- 0.002; Figure 6), but not with CSF volume. Our study is the first to show such a correlation between postnatal IGF-I concentrations and brain volumes after VP birth. The association between IGF-I concentrations and CBV at term was most evident from 30 GW. Around this time, growth in most very preterm infants is changing from growth restriction (further loss of weight-SDS compared with intrauterine growth) to catch-up growth (increase in weight-SDS).[338] As no differences in protein or caloric intake were found in the 25% of infants with the smallest CBV at term, neither before or after 30 GW, our results suggest that improved protein and caloric intake may not be sufficient to counteract postnatal restriction in brain growth in these infants. After disruption of placental IGF-I supply at birth followed by low levels for several weeks,[338, 350, 351] an increasing endogenous production of IGF-I from around 30 GW, as shown in an earlier study by our group,[338] may be a prerequisite for improved brain growth.

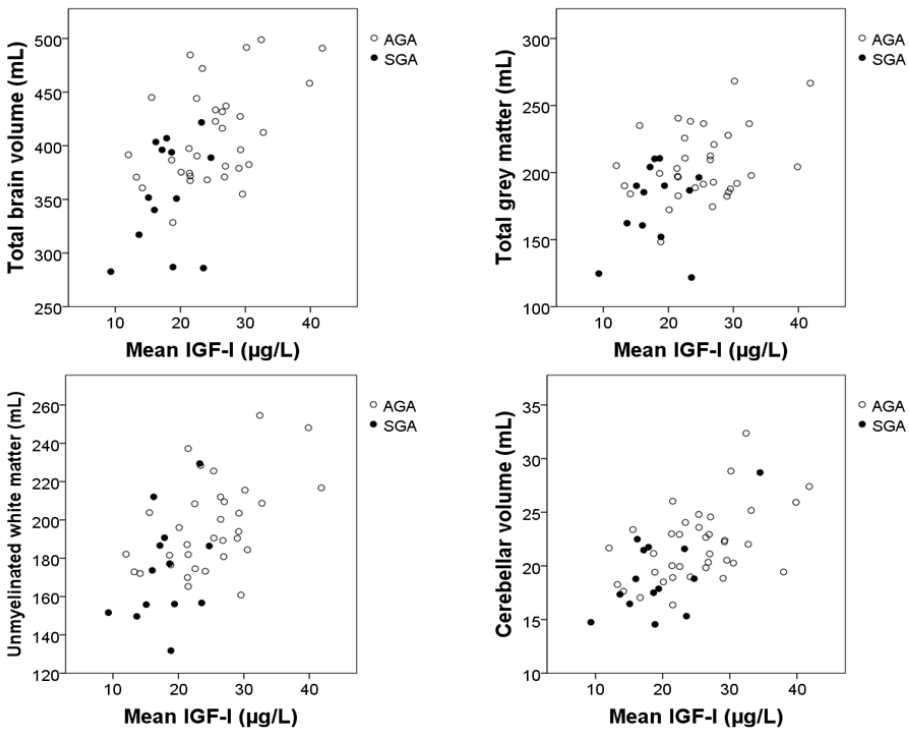

Figure 6. Correlations between mean IGF-I from birth to 35 GW and brain volumes at term.

IGF-I has been shown to be involved in many aspects of normal brain development, such as proliferation, differentiation, maturation, myelination, and apoptosis, and affects both neuron and oligodendrocyte populations[352-355]. The impact if IGF-I on both GM and WM volumes shown in this study is consistent with these effects.

Correlations between brain volumes and mean IGF-I concentrations, except for TGM, remained significant after adjustment for GA, gender, severe brain damage on cUS, mean protein and energy intake, and administered doses of steroids and insulin. However, after adjustment for SGA, only CBV remained significantly associated with IGF-I.

AERP and MRI at term and outcome at two years of age (Study IV)

Grand average AERP curves to the standard and deviants are shown in Figure 7.

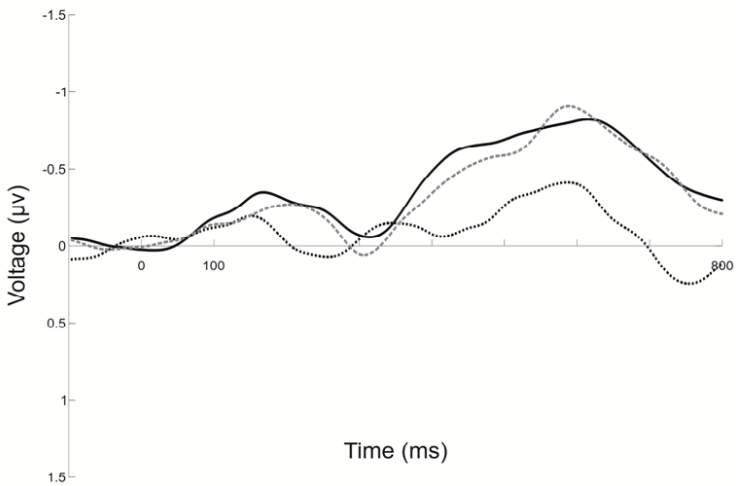

Figure 7. Grand average AERP curves to standard, duration, and frequency deviant. Positive deflections are downwards, negative upwards. Standard: thick black line. Duration deviant: black dotted line. Frequency deviant: grey dashed line.

Responses to the standard and to both deviants show a negative deflection between 50-200 ms and a negative slow-wave between 250- 700 ms from stimulus onset. Around 200 ms, instead of the major positivity earlier described in newborn and preterm infants at term,[38, 56, 215, 247], the curve returned to zero without displaying a positive response. However, looking at individual curves, we found significant positive responses in 11 of the 42 infants (Figure 2A in Publication IV).

Both in univariate and multiple regression analysis, neither amplitudes nor the presence or absence of significant exogenous responses correlated with perinatal factors such as GA, SGA, sex, or birth as a twin or triplet. Brain volumes and the IGF-I system were not associated with exogenous responses either. On the other hand, neonatal morbidity had a strong impact on exogenous responses at term, as is shown in Table 7. Increased neonatal morbidity was associated with the presence of a significant early negativity, the absence of a significant positivity, and higher amplitudes of the sustained late negativity (N450). Furthermore, more negative amplitudes in the time windows up to 300 ms and between 700- 800 ms were also associated with morbidity. However, not all morbidity was uniformly associated with exogenous responses. While the associations described above were significant for Apgar scores <7, use of both hydrocortisone and betamethasone, BPD, and longer requirement for additional oxygen, we found no associations with sepsis, PDA in need of treatment, insulin, or severe ROP.

Kurtzberg et al and Novak et al described a typical maturational pattern of early obligatory AERP responses up to 400 ms in VP and full-term infants during the final gestational and early postnatal weeks, as described in the Background chapter.[240, 243] During these weeks, the responses switch from negative polarity over both median and lateral sites (level I) to positive responses over both sites (level V), starting at the midline electrodes. Around term, the majority of full-term and preterm infants have positive responses over midline electrodes (level III-V). And although the number of full-term infants reaching higher maturity levels by term was higher, most VP infants in earlier studies had positive midline responses.[56, 240] However, the VP infants in our study were born at earlier GA than those in previous studies, and the presence of an early negative and the absence of a following positive response on the grand average difference curves may be a sign of delayed maturation in the most immature infants. In fact, infants having a larger positive response around 250 ms were less sick than the others. Having a significant early negativity and no significant positivity was associated with neonatal morbidity. We did not find any correlations between maturity levels and GA or outcome. However, higher doses of betamethasone and the presence of BPD were associated with lower maturity levels at term (F 5.38; p=0.009 and F 3.11; p=0.028, respectively). Our data support the conjecture that morbidity and/or postnatal steroid administration may delay cortical maturation. However, this delay may be time limited or too small to be associated with 2-years outcome.

Of the 42 infants, 37 had a significant response in the N450 time window, and even the remaining 5 infants showed a non-significant negative deflection in this time window reaching t-values >1. A major sustained, negative standard response peaking around 450 ms has been described earlier in this age group.[37, 56, 215, 240] In univariate analysis, a higher N450 was associated with MDI ≥85 (p=0.024), and there was a positive association between more negative amplitudes to the standard between 300- 500 ms (the main time window of the N450 response) and both higher MDI and MDI≥85.

Interestingly, although the infants with the highest morbidity would be expected to have the biggest problems in achieving an adequate early nutrition, and although increased morbidity was associated with higher N450 amplitudes, a higher protein but not caloric intake

Table 7. Significance of relationships between AERPs to the standard and neonatal morbidity.

*p<0.05, **p<0.01, ***p<0.001, p≥0.1 marked as NS.

p-values represent positive relationships between the given variables. For example the presence of a significant N50- 200 peak is positively associated with presence of a 5- min Apgar score <7. Decreasing amplitudes of the P150- 300 peak have a positive correlation with higher total accumulated dose exposure to steroids (doses of betamethasone transformed to hydrocortisone equivalents using a multiplication factor of 40). Only AERP time windows with significant associations with morbidity are included.

	5- min Apgar <7 (Y/N)	Days on ventilator	Steroids (mg/kg/d)	Hydrocortisone (mg/kg/d)	Betamethasone (mg/kg/d)	BPD (Y/N)	Days on O2
N50- 200 present	**.021** *	**.012** *	**.001** **	**.028** *	**.002** **	NS	**.007** **
N50- 200 increasing amplitude (µV)	.065	.099	**.004** **	**.020** *	**.003** **	NS	**.024** *
P150- 300 absent	NS	NS	.051	NS	.058	**.013** *	**.028** *
P150- 300 decreasing amplitude (µV)	NS	NS	**.002** **	.058	**.002** **	**.038** *	**.008** **
N250- 700 increasing amplitude (µV)	NS	.061	**.038** *	NS	**.011** *	NS	NS
Standard curve increasing negative amplitude (µV)							
0-100 ms	**.035** *	NS	**.013** *	**.024** *	**.033** *	NS	**.039** *
100- 200 ms	.057	NS	**.003** **	**.041** *	**.004** **	NS	**.006** **
200- 300 ms	NS	NS	**.007** **	.057	**.005** **	NS	.077
300- 400 ms	NS	NS	.065	NS	**.024** *	NS	NS
700- 800 ms	**.007** **	NS	**.047** *	NS	.091	NS	NS

during the phase of growth restriction was associated with higher N450 amplitudes (r=-0.346; p=0.027). Nutrition during the phase of catch-up growth did not have such an effect. Thus, both higher early protein intake and higher MDI were associated with larger N450 responses. In our study, a higher early protein intake was not significantly associated with MDI.

However, early protein intake may have a positive impact on brain development in several brain areas1[46,356] including those involved in the N450 response.

After correction for neonatal factors and morbidity, a higher N450 amplitude and more negative amplitudes to the standard in time windows 200- 700 ms after stimulus onset were associated with better outcome measures in all areas except for PDI, see Table 8.

Table 8. Relationships between exogenous AERP responses and time windows to the standard and outcome at two years of age after correction for neonatal factors and morbidity.
NS $p \geq 0.1$, *$p<0.05$, **$p<0.01$, ***$p<0.001$. 95%-confidence interval for odds ratios (OR).

	MDI	PDI	NOS	Normal outcome (Y/N)	Severe impairment (Y/N)
N250- 700 amplitude (µV)	**β -0.680** ***	NS	**β -0.638** **	NS	NS
Standard curve mean amplitude (µV)					
200- 300 ms	**β -0.519** **	NS	NS	NS	**OR 1.44-373** *
300- 400 ms	**β -0.520** **	NS	NS	NS	**OR 2.71-23409** *
400- 500 ms	**β -0.585** ***	NS	**β -0.568** **	NS	NS
500- 600 ms	**β -0.494** **	NS	**β -0.499** *	**OR 0.00-1.00** *	NS
600- 700 ms	NS	NS	NS	OR 0.00-1.39	OR 0.59-999435

The functional significance and exact origin of the N450 response is not known, but it has been proposed that it reflects further stimulus processing which is absent in adults. For example, it may represent building of neural representations and learning.[247] Its strong correlations with outcome at 2 years of age suggests that it may represent higher cortical functions involved in cognitive processes. The response becomes even more prominent during infancy, but it successively fuses with the growing N250 response during childhood.[246, 247, 288] More research on the origin and significance of this response is needed. Furthermore, as there is no data showing whether the neonatal N450 response is associated with later cognitive outcome even in children born at term or in other newborns at- risk for adverse outcome, further research is needed to address this question. Whatever the case may be, our data from this study support the idea that neonatal events impairing the normal development of the cortical processes underlying this response may also have long-lasting impacts on other cortical functions which determine later neurocognitive function. Our study suggests that such adverse events would be something other than premature birth itself, neonatal morbidity, nutrition, or the IGF-I system.

Grand average deviant-minus-standard difference curves for the duration and frequency deviants for the 42 VP infants are shown in Figure 1B and 1C in Publication IV.

Responses on the grand average difference curves to both deviants had mainly positive deflections (MMR) between 250- 750 ms after stimulus change onset. These deflections were highly significant on the group level (p<0.000001 for the duration deviant and <0.0001 for the frequency deviant). However, responses showed a high inter-individual variability. While a majority of the infants showed mainly positive deflections in these time windows (P-MMR), a considerable number (15 and 16 of 42 infants for the two deviants, respectively) had a main negative deflection (N-MMR), and a few showed successive responses with both polarities (see Figures 2B and 2C in Publication IV). Because of its association with maturation,[268] we focused on the polarity of the MMR rather than its amplitude in further analyses.

Infants with a significant N-MMR to the frequency deviant had a higher GA and a higher BW than infants without a significant N-MMR (GA 191±13 vs. 181±13 postmenstrual days; p=0.020, BW 1013±330 g vs. 833±237 g; p=0.045). Birth as a multiple was associated with elicitation of positive MMR (χ^2 7.32; p=0.007) to the frequency deviant. No associations with gender were seen. Brain volumes were not associated with any MMR, even after adjustment for perinatal factors. Children with significant N-MMR to the duration deviant had higher mean IGF-I plasma concentrations during the phase of catch-up growth (p=0.029) and a faster increase of weekly IGF-I concentrations over time from birth to 35 GW (p=0.043) than infants without a significant N-MMR. The impact of nutrition was contradictory. Increasing protein intake during the phase of growth restriction was associated with a positive polarity of the duration MMR (p=0.045) and with a trend to absence of N-MMR to the frequency deviant (p=0.082). On the other hand, a higher energy intake from birth to 35 GW was associated with a trend to negative polarity of the duration MMR (p=0.079), the absence of a significant duration P-MMR (p=0.027), a trend to absence of a significant frequency P-MMR (p=0.097), and a lower amplitude of this response (p=0.023).

MMR to the duration deviant was not consistently associated with neonatal morbidity. Associations between the frequency MMR and morbidity are shown in Table 9.

There was a strong association between morbidity and a positive polarity of the MMR, the presence of a significant P-MMR and absence of a significant N-MMR, as well as more positive amplitudes in frequency difference curve time windows between 200- 500 ms. In univariate analysis, similar associations were found between MMR and outcome. A negative polarity of the frequency MMR, smaller P-MMR, larger N-MMR, and more negative amplitudes in the 100- 500 ms and 700- 800 ms time windows were associated with a higher PDI, NOS, and normal outcome, as are shown in Table 10.

Correction for perinatal factors (GA, BW-SDS, gender, birth as a twin or triplet) alone had no major impact on these associations with MMR. However, after correction for both neonatal factors and morbidity, the only remaining significant association between frequency MMR or time windows and outcome was a positive association between the presence of a significant P-MMR to the frequency deviant and a PDI<85 (OR 57.3, 95% CI 1.15- 2843; p=0.042). Days on a ventilator were the only morbidity factor that was independently associated with outcome in multiple regression analysis.

Table 9. Significance of relationships between frequency MMR / frequency difference wave time windows and neonatal morbidity.
p-values representing the degree of significance of positive relationships between given variables. For example, positive polarity of the largest MMR was associated with higher total accumulated steroid doses from birth to 35 GW (betamethasone doses transformed to hydrocortisone equivalents using a multiplication factor of 40). Decreasing amplitude of the N-MMR is associated with a 5- min Apgar score <7.
Relationships with *p*-values ≥0.1 are marked as NS.

	5- min Apgar <7 (Y/N)	Days on ventilator	Sepsis (Y/N)	Steroids (mg/kg/d)	Hydrocortisone (mg/kg/d)	Betamethasone (mg/kg/d)	BPD (Y/N)	Days on O2	Later discharge
MMR pos polarity	**.007**	NS	NS	**.034**	.059	.085	NS	NS	.052
Significant P-MMR present	NS	.093	**.044**	.084	NS	**.019**	NS	NS	NS
P-MMR increasing amp (µV)	NS	**.019**	**.022**	**.015**	.073	**.008**	NS	NS	**.006**
Significant N-MMR absent	**.004**	**.001**	.071	**<.001**	**.004**	**.001**	**.029**	**.001**	**.014**
N-MMR decreasing amp (µV)	**.002**	.068	.749	**.009**	**.027**	**.017**	**.006**	**.023**	**.014**
Frequency difference curve increasing amp (µV)									
200-300 ms	.062	.055	NS	**.027**	NS	**.044**	.082	**.047**	**.030**
300-400 ms	**.039**	**.030**	NS	**.004**	**.031**	**.006**	**.004**	**.001**	**.012**
400-500 ms	.057	**.034**	NS	**.015**	**.033**	**.009**	**.009**	**.016**	**.005**
500-600 ms	NS	.088	.072	NS	.069	NS	NS	NS	**.002**
600-700 ms	NS	NS	NS	NS	NS	NS	NS	NS	**.042**
700-800 ms	**.031**	NS	NS	NS	**.047**	NS	NS	NS	NS

Several different factors have been shown to influence the polarity of the MMR. These are in part technical factors such as placement of the reference electrode, filters, and stimulus-related factors. However, maturity is another important factor determining the polarity of this response,[268] and during infancy and childhood, with increasing maturity, a negative polarity becomes more and more prevalent.[37, 228, 257] A source in deeper cortical layers III to IV, where the thalamo-cortical pathway terminates, has been suggested as the origin of the P-MMR,[246] while the superficial layers of the cortex are not fully developed by term age.[42] Whereas the functional nature of the P-MMR remains unclear,[59, 230] the N-MMR in newborns and infants has been proposed to be a precursor of adult MMN.[212, 242, 260] However, this remains to be confirmed.[212]

Table 10. Relationships between frequency MMR / frequency difference wave time windows and outcome at two years of age.
NS $p \geq 0.1$, *$p<0.05$, **$p<0.01$. p-values for positive associations. NS $p \geq 0.1$, #$p<0.1$, *$p<0.05$, **$p<0.01$.

	MDI	PDI	NOS	Normal outcome (Y/N)
MMR polarity (negative/positive)	NS	**95±16/ 81±17** *	**75±5/ 70±7** *	χ^2 **7.03** **
N-MMR peak present (Y/N)	NS	NS	**74±5/ 70±7** *	χ^2 2.93
N-MMR amplitude (µV)	NS	*r* -0.289	***r* -0.318** *	-1.3±1.2/ -0.7±1.0
Frequency difference curve mean amplitude (µV)				
100-200 ms	*r* -0.265	NS	***r* -0.370** *	NS
200-300 ms	NS	*r* -0.263	***r* -0.393** *	NS
300-400 ms	NS	***r* -0.355** *	***r* -0.385** *	NS
400-500 ms	NS	***r* -0.330** *	NS	NS
700-800 ms	NS	*r* -0.265	***r* -0.324** *	**-0.3±1.1/ 0.6±1.0** *

In our study, VP infants who were more preterm, had a lower BW, and a higher morbidity, showed a neurophysiological pattern corresponding to less mature cortical frequency change detection, which is associated with worse outcome at 2 years of age. These data are in agreement with a cortical maturational delay in very preterm infants that may be further impaired by morbidity, as is shown in studies with advanced MRI.[43,113] However, MMR was not an independent predictor of outcome, as it was no longer associated with outcome other than a subnormal PDI after correction for morbidity (but not after correction for GA alone). This suggests that morbidity rather than prematurity in itself is associated with the delay in cortical and AERP maturation.

To compare whether 2-years outcome showed a stronger association with AERP or global brain volumes as measured by MRI, we created a regression model, with outcome being the dependent variable and AERP and brain volumes the independent variables. The five brain volumes were included in this model one by one, while we chose the AERP measure with the strongest association (lowest p-value) in univariate analysis for each outcome measure. These were the mean amplitude on the standard curve between 400- 500 ms (main time window for the N450 response) for MDI and absence of severe impairment, and negative polarity of the frequency MMR for the remaining outcomes. The results are shown in Table 6 in Publication IV. For each of the 25 comparisons, AERP showed lower p-values than brain volumes, and after correction for brain volume, AERP was still significantly associated with outcome in all the 25 comparisons. Brain volumes were (after correction for AERP) significantly associated with outcome in 4 out of 25 comparisons. In 17 out of 25 comparisons, the combination of

AERP and brain volume showed a better association with outcome than any single one of these factors.

In recent decades, conventional and advanced MRI techniques have been increasingly used to predict outcome after preterm birth[131,159,180] (see Background). While to date, diffusion-related techniques may prove difficult to use for the assessment of the integrity of the WM tracts necessary for cortical auditory processes because of the small size of the structures involved, fMRI has already shown potential for this task.[180] Volumetric MRI methods have shown volume decrements in cortical areas involved in auditory processing, and linked it to later outcome.[131, 133] It is probable that the use of such modern MRI methods would have increased the association of MRI with outcome in this study. However, we show that the prognostic value of AERPs after VP birth may be better than has been believed, and more research should be directed to this.

General discussion and future perspectives

Early prognostication of later outcome after VP birth is important for many reasons. In addition to end-of-life decisions during the first days and weeks, psychological aspects for parents and families, and early initiation of individual disorder-specific rehabilitation to prevent and reduce future difficulties in multiple domains are crucial for the infant and parents. Further, early prognostic measures are needed for planning and distribution of resources in society and for faster development and optimization of pre-, peri-, and postnatal care in the most immature infants. Previously, follow-up studies of innovations or interventions in neonatal care have mostly included follow-up for up to two years of age, but no assessment of long-term outcome. In the last two decades, the detection and description of less severe problems after VP birth, which often occur in the cognitive, behavioral, educational, and social domains, and thus are not reliably detected by two years of age, has promoted prolonged follow-up, to preschool age, school age, and beyond. At the same time, as more extremely preterm infants survive and advances leading to major improvements in survival free of severe impairment have become uncommon, the issue of improving cognitive and behavioral outcomes has become increasingly important. Improvements in perinatal care are continual, and so waiting for follow-up data from school-aged ex-preterm children to evaluate the effect of these improvements leads to a considerable delay in the development of care. Therefore, robust early prognostic methods, preferably which provide assessment at term equivalent or even earlier, are of utmost importance.

There is an abundance of methods which have been proposed for prognostication of later outcome. Perinatal risk scores, clinical variables, biomarkers, structural assessments with cUS and MRI, and functional methods using fMRI, aEEG, near-infrared spectroscopy, evoked potentials in different sensory domains, VERPs, and AERPs are only some examples. All of them have shown more or less potential for this purpose. However, the degree to which resources have been allocated to research into these methods has been uneven, with much focus on anatomical methods, mainly MRI, over the last 10- 15 years.

The use of AERPs has some advantages compared with MRI, such as lower cost, requirement of fewer staff, easier recording outside tertiary centers, no need to move the patient from the ward, and easy use even in unstable patients. However, very little clinical research has been directed towards this method. Because of their automatic and pre-attentive character, AERPs including MMR are an excellent tool for assessing auditory processing and discrimination in newborns and infants with limited attention or motivation.[38, 60, 219, 230] Other than our work, we found fewer than ten studies investigating AERPs in preterm infants and their correlation with outcome, and none that had investigated the impact of neonatal factors other than GA on AERPs.

This thesis shows that AERPs after VP differ from those of full-term and late preterm infants. The amplitude of the P1 response was decreased, which is an abnormality that has

also been described in children with cognitive and behavioral problems (reading problems, attention deficit, and autism). These problems have an increased incidence after VP birth. A small P1 amplitude is interpreted as the effect of decreased electrical generator activity representing cortical auditory encoding in VP infants, and it may be caused by local or general brain atrophy or impaired synaptogenesis or synaptic specialization. In a previous study, lower P1 amplitudes in VP were associated with low performance in verbal subtests of neurocognitive tests,[234] a result that we have not been able to reproduce with a different paradigm and different psychological test methods. Changes in amplitudes in the time windows of MMN and P3a are also in agreement with abnormalities seen in children with learning disabilities, reading and language-related disorders, autism spectrum disorders, distractibility, and attention deficit disorder.

In addition, we found that AERPs in VP infants at two different ages are associated with meaningful outcomes. We showed how various morbidities which are common after VP birth are associated with changes in auditory processing, having an impact on sound detection, auditory encoding, change detection, and possibly attentional processes. Some of these changes seem to be related to delayed maturation, and later catch-up or compensation by brain plasticity may be possible. Signs of delayed MMR maturation at term equivalent age (Study IV) could no longer be found at preschool age (Study I). Whether the normalization may be ascribed to brain plasticity is unclear. The two cohorts are, however, not fully comparable since the first cohort was born five years earlier than the second, which contained more infants at the limit of viability and had the advantage of NICU care development during those years. Other changes seem to be more permanent and related to outcome years later. We also showed that some changes in auditory processing present at term and several years after the neonatal period do not seem to be related to prematurity in itself or morbidity, suggesting that other factors during the neonatal period or later may have long-lasting effects on cortical sound processing and may be related to cognitive problems. Some possible factors could be an adverse acoustic environment in the NICU, sensory overstimulation, sleep deprivation, repetitive painful procedures, and neurotoxic or ototoxic medications. More research is needed to investigate a possible role of these factors.

This work has not been designed to determine whether MRI or AERP have a better potential for prognostication of cognitive outcome after VP birth. This is partly because there are many influences following discharge that will have an impact, irrespective of brain development and damage during the neonatal period. It is unlikely that any single examination can be found which could reliably predict future development in every preterm infant. On the contrary, it is reasonable to believe that a combination of methods, for example anatomical, metabolic (such as H-MRS), and functional assessments, will improve prognostication of outcome. AERP mostly measures cortical inter-neuronal synaptic activity. Cortical function is not necessarily associated with cortical GM volume. Generally, in volumetric MRI studies, stronger associations have been found between WM and outcome than GM volumes. An intact connectivity is a prerequisite for normal cerebral processing in brain functions involving several different brain areas. WM connectivity, as assessed by DTI, has shown associations with cognitive and motor outcomes in many studies (see 'Background'). To investigate both intact local cortical activity based on normal cortical microanatomy and intact WM connectivity should give additional information compared to

each of these measures alone. We showed that AERP may be a functional investigation of cortical function with the potential to improve prognostication of outcome, in concert with other methods. We have recorded DTI sequences at term on most of our infants who had AERP recordings at term and plan to perform measurements of WM diffusivity and anisotropy in relevant WM areas. We also plan to link AERP results in our study at term age to local brain volumes as analyzed by voxel-based morphometry in brain areas connected to auditory information processing.

As discussed above, extended follow-up is needed to achieve reliable prognostication of cognitive and behavioral outcome. The BSID are an established neuropsychological test battery carried out at 2 years of age, and they are correlated with cognitive performance at 5 years of age.[357] However, the test scores are not sensitive predictors of cognitive and behavioral problems at school age.[17] To our knowledge, no study has as yet investigated the predictive value of neonatal AERPs for outcome after 2 years of age in VP infants. To investigate the associations between AERPs at term and cognitive and behavioral outcome, we aim at follow-up of these study groups to school age or above.

Although our studies belong to the largest AERP studies on preterm infants, and the study at preschool age to our knowledge includes the largest number of very immature born children published so far, they did not have enough power to establish meaningful cut-offs usable in clinical settings to define special risk groups within the VP group. Thus, additional work is needed to confirm our results and to define such cut-offs. Data analysis programs need to be created which in a semi-automated or automated way analyze AERP recordings and provide measures usable for outcome prognostication in the individual infant.

A majority of AERP studies in recent years in VP infants and children used speech-related stimuli. We used a simple tone paradigm which tests basic cortical auditory processes which are a prerequisite for analysis of speech sounds, and which is language-independent and independent of earlier sound experience. However, we do not know if our paradigm has the best potential for prognostication of meaningful outcomes. It is probable that different paradigms have to be used to predict different cognitive functions and outcomes. Due to maturation and development of auditory functions, the same paradigm will not be usable for all age groups. Future research will have to compare different stimulus types including, for example, speech-related stimuli (for example vowel and consonant contrasts, syllables, words), simple tones, complex tones, and complex environmental sounds, both for prognostication of general outcome, but also for specific questions to be answered for different age groups. The age and condition of the infants and children do not permit recordings which take too long, which limits the number of stimuli that can be tested in a clinical setting. Modern paradigms allow for a larger number of stimuli, differing in various sound qualities, to be tested within the same time frame, and may thus reduce the number of studies required to determine which paradigms are the most effective.[218, 220]

Interestingly, MMRs to different kinds of deviants were associated with outcome at different ages. Frequency and duration are processed differently in the ear and the brain, with frequency showing a hardwired encoding already at the level of the inner ear, which is absent for duration. Thus, factors affecting brain development may have different impacts on processing of these different sound qualities. Furthermore, duration and frequency affect different characteristics of speech, and impaired encoding will disturb different aspects of

language learning and thus of cognitive development.[54, 58, 59] Another aspect is that equal deviances of sounds place different challenges on auditory processing in different ages. Using deviants which are too difficult will cause MMR to be absent in all children, and using deviants which are too easy may elicit responses even in children with abnormal brain function. One challenge of AERP research is to find paradigms which present the appropriate level of challenge to auditory processing for the tested children. Apart from faster stimulus succession and one additional deviant in the older age group, we used identical paradigms in all of the studies. Thus we can suggest that the duration paradigm was too difficult for the newborn group, but appropriate for the preschool group, and that the frequency paradigm may have been too easy for the preschool group to allow differentiation between normal and abnormal cortical processing in individual children. Further studies will be needed to establish optimal standard-deviant differences for different stimulus types and ages. Again, the use of modern multi-feature paradigms will allow for the testing of a higher number of different deviance types within the same paradigm. Further, comparison of scalp-recorded AERPs with auditory-evoked magnetic fields would shed light on localization of cortical generators for different AERP responses.[196, 358]

The role of the IGF-I system for brain growth and development was not the main focus of this thesis. However, we showed correlations between neonatal IGF-I concentrations and brain volumes at term. Furthermore, higher mean IGF-I concentrations during the phase of catch-up growth and a faster postnatal weekly increase in IGF-I concentrations [IGF-I(β)] were associated with the presence of a significant N-MMR to the duration deviant, possibly representing a more mature auditory discrimination pattern. At follow-up, both increasing IGF-I(β), UMWM, and CBV were associated with MDI ≥85, and in multivariate analysis, higher IGF-I(β) and UMWM combined with female gender were the models with the highest predictive value for normal MDI scores.[359] Thus, normal plasma concentrations of IGF-I and its binding proteins are important for normal brain growth and maturation. As theses are usually decreased after VP birth, early substitution to intrauterine physiological levels might improve brain development. This hypothesis has to be tested in randomized controlled trials.

Another important result of this thesis is the accidental discovery of a phase of very fast maturation in early cortical sound processing between 4- 5 years of age, represented by a very fast decrease in the P1 and N2 latencies. This finding is contradictory to the usual description of a successive, slow latency decrease over time during early childhood. As no earlier work has focused on the age group investigated in our study, this phenomenon has not been described previously. If confirmed, all future AERP studies on children at preschool age would need to include corrections for age at examination. However, a longitudinal study at preschool age with frequently repeated AERP recordings in the same children would have to be performed to elucidate this question. As most myelination processes in auditory tracts have been completed before preschool age, such a fast maturation would have to be caused by synaptic reorganization and specialization.

In conclusion, this thesis shows that AERPs have the potential to become a tool for prediction of cognitive outcome in infants and children born very preterm, and as such may become a complement to other methods such as MRI. The studies included have highlighted the associations of AERP measures at different ages with developmental and cognitive test results. We have shed more light on the impact of prematurity, perinatal factors, and neonatal morbidity on cortical auditory processing, and on how this processing is associated with cognitive outcome. However, further research is needed in this promising field.

Sammanfattning på svenska

Barn födda före 32 gestationsveckor, även de utan svåra neurologiska avvikelser, har en hög förekomst av neuropsykologiska problem såsom läs-, inlärnings-, språk-, minnes- och beteendeproblem. Det är ännu inte klarlagt vilka funktionella och strukturella förändringar i hjärnan som orsakar dessa problem. Möjligheten till tidig diagnos behövs men saknas ännu.

Auditiva händelserelaterade potential (AERP) är neurofysiologiska mått på hjärnans reaktion på hörselstimuli och registreras med elektroencefalografi (EEG). I mer än 50 år har AERP använts i stor utsträckning i neuropsykologisk och utvecklingsforskning. De är uttryck för olika kortikala processer och representerar upptäckt av ljudet, dess analysering, jämförelse med andra och tidigare ljud och ljudrelaterad uppmärksamhet. Dessa processer är avgörande för omedveten orientering i en krävande ljudmiljö och för kognitiva processer som att lära sig språk. Hos fullgångna barn och vuxna har onormala AERP satts i samband med sådana kognitiva och beteendeproblem som ofta förekommer efter mycket för tidig födsel. Hittills har forskning om AERP hos prematura barn varit mycket begränsad. Därför var syftet med detta doktorsarbete att undersöka om AERP hos mycket prematurfödda förskolebarn skiljer sig från mognare prematura och fullgångna barn och om dessa skillnader korrelerar med kognitiv utveckling. Dessutom avsåg vi att utforska om AERP vid fullgången tid (40 graviditetsveckor) är av värde för att förutsäga utvecklingen i barnaåldern och hur AERP är relaterade till hjärnvolymer uppmätta med magnetresonanstomografi (MRT).

Vi undersökte 70 mycket prematurfödda barn i 4-5-års ålder och jämförde dem med mognare prematurfödda och fullgångna barn av samma ålder. Alla dessa barn genomgick AERP och psykologiska testmetoder. Dessutom utförde vi AERP-registrering och MRT hos ytterligare 42 mycket prematurfödda barn vid fullgången tid och följde upp barnen med psykologiska och neurologiska test vid 2-års ålder.

Våra resultat visade att mycket prematurfödda barn i förskoleåldern skiljer sig från barn födda senare i graviditeten avseende AERP och att deras AERP-avvikelser liknar dem man tidigare påvisat hos fullgångna barn med kognitiva och beteendeproblem. Framför allt har de lägre amplituder i tidiga AERP-vågor. Däremot hittade vi i denna ålder inga skillnader i deras förmåga att skilja åt olika ljud. Vi visade också att snabbare tidig ljudbearbetning inom den mycket prematurfödda gruppen var förenad med bättre psykologiska testresultat och att förmågan att skilja åt ljud skiljde sig mellan barnen med normala och abnorma testresultat. Sjukligheten i neonatalperioden påverkade bearbetningen av hörselintryck ännu i 5-års åldern och den påverkade andra kortikala processer än för tidig födsel eller hjärnskada diagnostiserad med ultraljud.

Hos spädbarnen som undersöktes med AERP vid fullgången tid visade vi att senare ljudbearbetningsprocesser (efter 250 ms) och åtskillnad av ljud har en stark korrelation med såväl kognitiv som neurologisk utveckling vid 2-års ålder. Dessutom var det snarare neonatal sjuklighet än prematuritet i sig som förändrade förmågan att skilja mellan ljud. AERP visade

starkare koppling till utvecklingen vid denna ålder än hjärnvolymer. Hjärnvolymerna korrelerade dock med koncentrationerna av tillväxtfaktorn Insulin-like growth factor-I i neonatalperioden till skillnad från AERP.

Vi drar slutsatsen att AERP bör kunna utvecklas till en lovande metod för att förutsäga den senare utvecklingen hos mycket prematura barn och att denna metod kan ge viktig information utöver den som erhålls med anatomiska metoder som MRT. Ytterligare forskning behövs dock innan AERP kan bli användbart i klinisk praxis.

Deutsche Zusammenfassung

Kinder, die vor 32 Schwangerschaftswochen (SSW) geboren werden, haben, auch ohne schwere Hirnschäden, ein hohes Vorkommen neuropsychologischer Probleme wie Lese-, Lern-, Gedächtnisschwächen, Sprach- und Verhaltensprobleme. Welche Struktur- und Funktionsveränderungen des Gehirns diese Probleme hervorrufen ist nicht ausreichend untersucht, und frühe diagnostische Methoden fehlen bisher.

Auditory event-related potentials (AERP) werden als Gehirnrindenaktivität von Höreindrücken ausgelöst und sind im Elektroenzephalogramm (EEG) nachweisbar. Seit über 50 Jahren sind sie in neuropsychologischer und Entwicklungsforschung verbreitet. Sie spiegeln verschiedene Hirnrindenprozesse wie Entdeckung, Bearbeitung, Unterscheidung von Lauten und Veränderungen in der Aufmerksamkeit wider. Solche Prozesse sind von entscheidender Bedeutung sowohl zur Orientierung in einer Umgebung voll von Geräuschen als auch z.B. für den Spracherwerb. Bei Kindern und Erwachsenen wurden abweichende AERP mit solchen kognitiven und Verhaltensstörungen in Verbindung gebracht, die bei sehr Frühgeborenen besonders häufig vorkommen. Dennoch gibt es bisher nur sehr wenig AERP-Forschung an Frühgeborenen. Aus diesem Grunde war das Ziel dieser Doktorarbeit zu untersuchen, ob AERP bei sehr frühgeborenen Vorschulkindern sich von reiferen Früh- und Reifgeborenen unterscheidet, und ob eventuelle Unterschiede mit der kognitiven Entwicklung korrelieren. Darüber hinaus wollten wir den Voraussagewert von AERP zum normalen Geburtstermin (40 SSW) für die spätere Entwicklung in der Kindheit untersuchen und mit dem von Gehirnvolumina, gemessen mit Magnetresonanztomographie (MRT), vergleichen.

Zu diesem Zwecke untersuchten wir 70 sehr Frühgeborene im Alter von 4-5 Jahren und verglichen sie mit reiferen Früh- und Reifgeborenen des gleichen Alters. Diese Kinder wurden mit AERP und psychologischen Testverfahren untersucht. Darüber hinaus führten wir bei weiteren 42 sehr Frühgeborenen AERP und MRT zum normalen Geburtstermin und Entwicklungstests im Altern von 2 Jahren durch.

Unsere Resultate zeigen, dass das AERP bei sehr Frühgeborenen im Vorschulalter von dem reifer geborener Kinder abweicht. Die Abweichungen ähneln denen von Reifgeborenen mit kognitiven und Verhaltensproblemen. Wir fanden aber hier keine Gruppenunterschiede im Unterscheidungsvermögen von Lauten. Wir zeigten, dass in der frühgeborenen Gruppe eine schnellere frühe Lautverarbeitung mit besseren psychologischen Testergebnissen verknüpft war, und dass die Tondifferenzierung sich zwischen Kindern mit normalen und abweichenden Testergebnissen unterschied. Verschiedene Komplikationen in der Neugeborenenperiode beeinflussten die Lautverarbeitung noch im Alter von 5 Jahren. Dabei wurden andere Prozesse von Komplikationen beeinflusst von Frühgeburtlichkeit und eventuellen Hirnschäden.

Bei den zum normalen Geburtstermin mit AERP untersuchten Frühgeborenen zeigten wir, dass spätere Prozesse sowohl der Lautverarbeitung (nach mehr als 250 ms) als auch der

Lautunterscheidung in hohem Ausmaß mit sowohl kognitiver als auch neurologischer Entwicklung im Alter von 2 Jahren korrelieren. Neonatale Komplikationen beeinflussten die Lautunterscheidung stärker als eigentliche Frühgeburtlichkeit. AERP stand in stärkerem Zusammenhang mit späterer Entwicklung als Gehirnvolumina. Hingegen korrelierten Gehirnvolumina, aber nicht AERP, mit dem Wachstumsfaktor IGF-I in der Neonatalperiode.

Unsere Schlussfolgerung ist, dass AERP zur Voraussage der späteren Entwicklung bei sehr Frühgeborenen vielversprechend ist und einen Beitrag über das MRT hinaus leisten kann. Mehr Forschung ist jedoch vonnöten, bevor AERP im klinischen Alltag anwendbar wird.

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