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Elina Niemitalo-Haapola

DEVELOPMENT- AND NOISE-INDUCED CHANGES IN CENTRAL AUDITORY PROCESSING AT THE AGES OF 2 AND 4 YEARS

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UNIVERSITY OF OULU,
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Academic dissertation to be presented with the assent of the Doctoral Training Committee of Human Sciences of the University of Oulu for public defence in Keckmaninsali (HU106), Linnanmaa, on 2 June 2017, at 12 noon

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Abstract

To be able to acquire, produce, and comprehend language, precise central auditory processing (CAP), neural processes utilized for managing auditory input, is essential. However, the auditory environments are not always optimal for CAP because noise levels in children's daily environments can be surprisingly high. In young children, CAP and its developmental trajectory as well as the influence of noise on it have scarcely been investigated. Event-related potentials (ERPs) offer promising means to study different stages of CAP in small children. Sound processing, preattentive auditory discrimination, and attention shifting processes can be addressed with obligatory responses, mismatch negativity (MMN), and novelty P3 of ERPs, respectively.

In this thesis the developmental trajectory of CAP from 2 to 4 years of age as well as noise-induced changes on it, were investigated. In addition, the feasibility of the multi-feature paradigm with syllable stimuli and novel sounds in children was evaluated. To this end, obligatory responses (P1, N2, and N4) and MMNs for consonant, frequency, intensity, vowel, and vowel duration changes, as well as novelty P3 responses, were recorded in a silent condition and with babble noise using the multi-feature paradigm. The participants were voluntary, typically developing children.

Significant P1, N2, N4, and MMN responses were elicited at both ages. Also a significant novelty P3, studied at the age of 2 years, was found. From 2 to 4 years, the P1 and N2 latencies shortened. The amplitudes of N2, N4, and MMNs increased and the increment was the largest at frontal electrode locations. During noise, P1 decreased, N2 increased, and the latency of N4 diminished as well as MMNs degraded. The noise-induced changes were largely similar at both ages.

In conclusion, the multi-feature paradigm with five syllable deviant types and novel sounds was found to be an appropriate measure of CAP in toddlers. The changes in ERP morphology from 2 to 4 years of age suggest maturational changes in CAP. Noise degraded sound encoding, representation forming, and auditory discrimination. The children were similarly vulnerable to hampering effects of noise at both ages. Thus, noise might potentially harmfully influence language processing and thereby its acquisition in childhood.

Keywords: attention, auditory discrimination, central auditory processing, children, mismatch negativity (MMN), multi-feature paradigm, noise, novelty P3, obligatory responses, toddlers

Niemitalo-Haapola, Elina, Kehitykselliset ja melun aiheuttamat muutokset keskushermostollisessa kuulotiedon käsittelyssä kahden ja neljän vuoden iässä.
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Tiivistelmä

Kielen omaksumiselle, tuottamiselle sekä ymmärtämiselle on tärkeää tarkka keskushermostollinen kuulotiedon käsittely eli ne hermostolliset prosessit, joita käytetään kuullun aineksen käsittelyyn. Kuunteluympäristöt eivät kuitenkaan aina ole optimaalisia kuulotiedon käsittelylle, sillä melutasot lasten elinympäristöissä voivat olla hyvinkin korkeita. Pienten lasten kuulotiedon käsittelyä, sen kehittymistä ja melun vaikutusta siihen on tutkittu vähän. Kuuloherätevasteet ovat toimiva tapa tarkastella pienten lasten kuulotiedon käsittelyä eri näkökulmista. Äänen käsittelyä, esitietoista kuuloerottelua ja tarkkaavuuden siirtymistä voidaan tarkastella obligatoristen vasteiden, poikkeavuusnegatiivisuuden ja novelty P3 -vasteiden avulla.

Tässä väitöskirjassa tarkastellaan kuulotiedon käsittelyn kehittymistä kahden vuoden iästä neljän vuoden ikään sekä melun vaikutusta siihen. Lisäksi arvioidaan tavuärsykkeitä ja poikkeavia ääniä sisältävän monipiirreparadigman soveltuvuutta lapsitutkimuksiin. Tutkimuksissa rekisteröitiin monipiirreparadigman avulla obligatorisia vasteita (P1, N2 ja N4); konsonantin, taajuuden, intensiteetin, vokaalin ja vokaalin keston muutokselle syntyneitä MMN-vasteita sekä novelty P3 -vasteita hiljaisuudessa ja taustamelussa. Tutkimuksen osallistujat olivat vapaaehtoisia tyypillisesti kehittyviä lapsia.

Molemmilla tutkimuskerroilla P1, N2, N4 ja MMN poikkesivat merkitsevästi nollatasosta samoin kuin kaksivuotiailta tutkittu novelty P3. Kahden vuoden iästä neljään vuoteen P1- ja N2-vasteiden latenssi lyheni sekä N2, N4 ja MMN vahvistuivat, muutoksen ollessa suurinta frontaalisilla elektrodeilla. Melun aikana P1 heikkeni, N2 vahvistui ja N4-vasteen latenssi lyhentyi. Lisäksi MMN-vaste heikkeni. Melun aiheuttamat muutokset olivat samankaltaisia sekä kahden että neljän vuoden iässä.

Johtopäätöksenä voidaan todeta viittä eri tavuärsyketyyppiä ja yllättäviä ääniä sisältävän monipiirreparadigman olevan toimiva menetelmä taaperoiden kuulotiedon käsittelyn tutkimiseen. Kahden ja neljän ikävuoden välillä tapahtuvat muutokset vasteissa kuvastavat kehityksellisiä muutoksia kuulotiedon käsittelyssä. Melu heikentää äänitiedon peruskäsittelyä, edustumien muodostumista ja esitietoista kuuloerottelua. Lapset olivat lähes yhtä alttiita melun vaikutuksille sekä kahden että neljän vuoden iässä. Melu voi siis haitata kielen prosessointia ja sen omaksumista.

Asiasanat: keskushermostollinen kuulotiedon käsittely, kuuloerottelu, lapset, melu, monipiirreparadigma, novelty P3 -vaste, poikkeavuusnegatiivisuus, taaperoikäiset, tarkkaavaisuus

To my family

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This thesis would not have been possible without participation of many people, who I want to gratefully acknowledge. First, the participants and their families: your time and efforts were invaluable. I warmly acknowledge your commitment for this work.

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In April 2017 Elina Niemitalo-Haapola

Abbreviations

ANOVA	Analysis of variance
AP	Anterior-posterior electrode location
CAP	Central auditory processing
CON	Condition of listening
DEV	Deviant type
EEG	Electroencephalography
ERP	Event-related potential
F0	Fundamental frequency
MMN	Mismatch negativity
MMR	Mismatch response
mMMN	Magnetic mismatch negativity
RL	Right-left electrode location
SD	Standard deviation
SLI	Specific language impairment
SLT	Speech and language therapist
SNR	Signal to noise ratio
SOA	Stimulus onset asynchrony
SPL	Sound pressure level

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Niemitalo-Haapola, E., Lapinlampi, S., Kujala, T., Alku, P., Kujala, T., Suominen, K., & Jansson-Verkasalo, E. (2013). Linguistic multi-feature paradigm as an eligible measure of central auditory processing and novelty detection in 2-year-old children. Cognitive Neuroscience, 4, 99–106.

II Niemitalo-Haapola, E., Haapala, S., Jansson-Verkasalo, E., & Kujala, T. (2015). Background noise degrades central auditory processing in toddlers. Ear & Hearing, 36, 342–351.

III Niemitalo-Haapola, E., Haapala, S., Kujala, T., Raappana, A., Kujala., T., & Jansson-Verkasalo, E. (2017). Noise equally degrades central auditory processing in 2- and 4-year-old children. Accepted for publication in Speech, Language, and Hearing Research. https://doi.org/10.1044/2017_JSLHR-H-16-0267

The original idea of this thesis was from the author. The final data collection procedure was designed together with the supervisors and the other co-authors. The author recruited all participants, except two children, when they were at the age of 2 years. The author evaluated the language skills of the children at the age of 2 years and SLT Henna Häkli, MA at the age of 4 years. The author collected EEG-data together with SLT Sini Haapala, PhD (at the age of 2 years), Henna Häkli (at the age of 4 years), and an EEG-technician. The author made all EEG-analyses in the guidance of the supervisors and with consultation from Sini Haapala. The author made also all statistical analyses with consultation of supervisors and statisticians Hanna Heikkinen, MA, and Päivi Laukkanen-Nevala, PhD. The author wrote the first drafts of all article manuscripts which were then revised by the supervisors and other co-authors. All articles were finalized by the author, based on comments and suggestions of supervisors and other co-authors. The author made all figures and tables in the articles.

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1 Introduction

Central auditory processing (CAP) is fundamental for language acquisition (Kuhl *et al.* 2008). In order to construct neural representations of speech sounds, child must be able to perceive, recognize, and discriminate small and rapid spatial-temporal variations and cues from the speech stream (Benasich *et al.* 2016). Those variations provide also means to recognize words and prosodic features from continuous speech, which is an essential prerequisite for lexical development as well as for understanding of syntactic and pragmatic elements (Ingram 2007, Newman *et al.* 2006). However, the auditory environments are not always optimal for CAP because noise levels in children's daily environments can be surprisingly high (MacAllister *et al.* 2009). This thesis was inspired by clinical observations and considerations addressing young children's acoustical environments. The main concern was what are the effects of background noise on toddler's CAP at the time of intensive linguistic development?

Young children, infants and toddlers, are a challenging participant group to study. Event-related potentials (ERPs) extracted from electroencephalography (EEG) provide means to examine CAP (Luck 2005). ERPs are non-invasive, temporally exact, and suitable to study participants with limited co-operation skills. By using obligatory responses, the mismatch negativity (MMN), and the novelty P3 of ERPs, the different stages of CAP can be addressed in order to understand developmental trajectories of CAP as well as the effects of noise on it. Even though ERPs are widely used in child studies, there is a lack of information from maturational changes from 2 to 4 years of age (Wunderlich & Cone-Wesson *et al.* 2006).

Noise has several detrimental effects on hearing, physiology, and cognitive skills (for a review, see Evans 2006). In adults with a mature neural system and language skills, the deteriorating effects of noise on CAP were evident (Shtyrov *et al.* 1998, 1999) and had long-term consequences (Brattico *et al.* 2005, Kujala *et al.* 2004). Also in school-aged children, noise interferes with CAP (Anderson *et al.* 2010). However, to our knowledge, the effects of noise on cortical level of CAP in toddlers have not previously been studied. In addition, it needs to be determined whether CAP of younger children is more vulnerable to the effects of noise than in older children.

Studies I, II, and III were carried out during years 2009–2016. To justify the ERP recording approach used in this thesis, the feasibility of the multi-feature paradigm with syllable stimuli and novel sounds in toddler studies was investigated in Study I. To our knowledge, this was evaluated for the first time for syllable stimuli together with novel sounds in toddlers and it formed a solid base for Study II and Study III. In addition to investigating the feasibility of the paradigm, the auditory discrimination profiles for the five speech sound features, as well as for attention capture, were reported at the age of 2 years in Study I. In a follow-up, Study III, the developmental trajectories of ERPs in typically developing children at the ages of 2 and 4 years were determined. Furthermore, the effects of noise on CAP were investigated in Study II and Study III.

This thesis provides new information on the means to study CAP efficiently in young children, on developmental trajectories of CAP, and the effects of noise on CAP. From the clinical point of view, the results emphasize the role of the assessment of the auditory environment as an essential part of clinical intervention made by the speech and language therapists. In addition, the results promote the need to enhance the awareness of children’s auditory environments among the professionals working with children as well as the professionals responsible for planning and maintenance of those environments.

2 Literature review

2.1 Central auditory processing

CAP involves the neural mechanisms used in processing the acoustic input received by the ears. From the functional and behavioral point of views, central auditory processes are fundamental for localization of the sound source, discrimination and recognition of auditory signals and patterns, utilization of the temporal aspects of audition, and coping with degraded acoustic signals or with competing acoustic signals (American Speech-Language-Hearing Association 2005). CAP also includes the efficiency and effectiveness of neural networks while processing auditory input (Geffner 2013). A more popular way of describing CAP is accomplished by Katz, who stated that CAP is "what we do with what we hear". The functional CAP in the early childhood forms the basis for later language skills (Jansson-Verkasalo *et al.* 2004a, 2004b, 2010, Lyytinen *et al.* 2015).

Anatomically, CAP takes place at the central auditory nervous system after the acoustic signal has passed the outer, middle, and inner ear and it is transformed to action potentials including information on frequency, intensity, and temporal aspects of the sound (Webster 1999). The central auditory pathway begins from the cochlea, where the **cochlear nerve originates** (cochlear division of VIII cranial nerve). It transmits the neural signal to the **cochlear nuclear complex**; tonotopically arranged to the anterior ventral, posterior ventral, and dorsal cochlear nucleus of the brain stem (Paulsen & Waschke 2011, Purves *et al.* 2012, Webster 1999). Next, at the lateral and medial **superior olivary nucleus** of the pons the origins of sound sources are processed by measuring the sound intensity differences (the lateral superior olivary nucleus) and sound timing differences (the medial superior olivary nucleus) and yielding binaural interaction. Thereafter the lateral lemniscus transforms the information to the central nucleus of the inferior colliculus in the midbrain, which is the largest brainstem auditory nucleus. There the divergent auditory information is uniformed again. Next, axons go through the brachium of the **inferior colliculus** to the **medial geniculate body** of the thalamus which is also tonotopically organized and utilizes information of sound source, location, onset, offset, frequency, and intensity. The dorsal division of the medial geniculate body has a role in maintaining and directing auditory attention. The auditory pathway via the sublenticular portion of the internal capsule ends at **the primary auditory area** at the **cerebral cortex** (superior temporal gyrus). The primary auditory areas are surrounded by and co-operate with **the auditory association cortex** and **the secondary auditory areas** at the frontal lobe, thus enabling integration of neural data.

CAP includes bottom-up and top-down processes (Bellis 2011, Webster 1999), both needed for functional auditory perception. The bottom-up processing, sensory encoding, involves neural coding from cochlea to cortex and at the cortex. Top-down high-order processing, in turn, utilizes previous experiences and memories in order to process auditory information. Even though the core of CAP is based on bottom-up processing, the interaction of these processes together with allocation of attention is warranted for functional CAP (Davis & Johnstrude 2007).

In addition, CAP is characterized by high plasticity (Benasich *et al.* 2014; Giannakopoulou *et al.* 2013; for a review see Kujala & Näätänen 2010), meaning experience-based changes in neural function and/or structure. Plasticity enables a child to take advantage of varying auditory environments and languages (Kujala & Näätänen 2010). Positive plasticity is involved, for example, while an individual adopts a new speech sound system during exposure to new language (Giannokopoulou *et al.* 2013) or retains hearing after cochlear implantation (Sharma *et al.* 1997). However, some auditory experiences might lead to harmful consequences instead of positive plasticity. These harmful effects might occur, for example, when a long-term exposure of noise has long-lasting effects on CAP (Brattico *et al.* 2005; Kujala *et al.* 2004). Similarly in children, recurrent otitis media causing fluctuating hearing loss yields alterations in CAP even though the otitis media was no longer present (Haapala *et al.* 2014).

Exact and right-timed CAP is essential for language acquisition. A child has to be able to perceive, recognize, and discriminate acoustic signal to detect components used for phonemic, lexical, syntactic, and pragmatic processing (Ingram 2007, Newman *et al.* 2006; more details in chapter 2.1.2). Problems in CAP in children are associated with several diagnostic groups, e.g., Asperger syndrome (Jansson-Verkasalo *et al.* 2003), autism (Dunn *et al.* 2008), dyslexia (Guttorm *et al.* 2005), learning problems (Kraus *et al.* 1996), schizophrenia (Umbricht & Krljes 2005), specific language impairment (SLI; Rinker *et al.* 2007), and stuttering (Jansson-Verkasalo *et al.* 2014).

2.1.1 Development of central auditory processing

The development of CAP begins already in the uterus (Partanen *et al.* 2013a), as the fetus is able to hear low frequency tones at the gestational age of 27 weeks (Hepper & Shahidullah 1994). At the mean gestational age of 37 week, the fetuses are able to discriminate frequency changes (Huotilainen *et al.* 2005). The learning-induced changes, based on sound discrimination and memory representation forming, also take place in fetal CAP (Partanen *et al.* 2013b).

After birth, the infants are exposed to a new auditory environment, dominated by their native language or languages. Also the structural and functional changes in the central auditory system continue during the first years of life. The results of both of these major changes are seen in the development of CAP, while the neural representations get sharper (Jansson-Verkasalo *et al.* 2010; Ortiz-Mantilla *et al.* 2016) and the advantage of phoneme inventory of the mother language is evident at the end of the first year of life (for a review, see Kuhl 2010). Also the first signs of deviant CAP are detected during the first year (Guttorm *et al.* 2005).

In children, ranging toddlers to school-aged, CAP is still characterized with major alterations as the central nervous system continues to mature. The speed of sound processing increases developmentally (Sharma *et al.* 1997) and the speech sound representations are finalized (Kuhl & Rivera-Gaxiola 2008). Sharma *et al.* (2002) have suggested that during the first 3.5 years of life, the capacity of CAP to change is maximal. Thus, the positive and negative auditory experiences may have a strong influence on CAP during those years. Also, the predicting signs of future linguistic and literacy skills can be detected in CAP already in early childhood (Jansson-Verkasalo *et al.* 2004a, 2004b, 2010, Kuhl & Rivera-Gaxiola 2008, Lyytinen *et al.* 2004).

During adolescence, CAP becomes more stable (Ponton *et al.* 2000). Even though the plasticity of CAP decreases in adulthood, it sustains its capability to change and the alterations in the daily listening condition modify CAP. In elderly people peripheral hearing sensitivity and neural plasticity decreases (for a review, see Martin & Jerger 2005).

2.1.2 Central auditory processing and language acquisition

Functional CAP is essential for language acquisition (Kuhl *et al.* 2008). In order to decode continuous speech sound stream to smaller units, child has to be able to perceive, recognize, and discriminate spatial-temporal variation in it (Benasich *et al.* 2010).

Largely accepted theories of language acquisition, statistical language learning (Saffran 2003) and the magnet theory (Kuhl *et al.* 2008), are both based on the assumption that a child has to be able to recognize and discriminate phonemes from sound-streams (Burns 2013) in order to construct neural representations, “maps”, of the speech sound system (Kuhl *et al.* 2008). However, without exactly and precisely functioning CAP that perceptual segmentation is not possible. Benasich *et al.* (2010) has suggested that those “maps” are also needed for literacy-skill development.

Based on prosodic features, child segments word shapes from sound-streams (Ingram 2007). In Finnish, for example, stress is on the first syllable of word. Thus, by discriminating alterations in frequency and intensity, markers for stressed syllable, child can segment speech sound stream to words, which is prerequisite for lexical development (Newman *et al.* 2006). Prosodic features are also utilized for decoding of syntactical as well as pragmatic elements, also essential for language acquisition and comprehension (Ingram 2007).

The correlation between CAP and language skills is evident in children. Studies showed that infants with more matured auditory discrimination, as indexed by MMN, had later in life larger vocabulary, opposite to children with diminished or missing MMN (Jansson-Verkasalo *et al.* 2004a, 2004b). Also the N2 elicited by frequency deviant at the age of 6 months predicted later language skills at the age of four years (Choudhury & Benasich 2011). Furthermore, toddlers with a history of recurrent otitis media showed differences in MMNs and co-occurring decrement in their consonant inventories after recovery from otitis media (Haapala *et al.* 2014, 2015). Thus, even transient difficulties in CAP might cause detectable changes in language skills.

Alterations in CAP are also connected to problems in literacy skill in school-aged children (Lyytinen *et al.* 2015). Also in pre-literal children CAP predicts future literacy skill (White-Schwoch *et al.* 2015). Especially the connection between neural processing of consonants in noise was essential for future literacy-skill.

2.2 Auditory event-related potentials

A non-invasive and temporally accurate means to study CAP is to record event-related potentials (ERPs), brain responses which reflect postsynaptic potentials triggered by sensory stimuli, cognitive processes, and movements (Luck 2005). Anatomically, the electrical activity giving rise to ERPs occurs mainly at the cortex in the cortical pyramidal cells and can be recorded from the surface of the scalp with EEG. ERPs are a useful way to study neural activity connected to specific events and to obtain stimulus specific information with a high temporal resolution (Luck, 2005). The main pitfall of ERPs is the weak spatial accuracy with respect to neural generators.

One group of ERPs is auditory ERPs, neural responses to acoustic stimuli. Physiologically, auditory ERPs are generated at the thalamo-cortical pathway and at the auditory cortex (Luck, 2005). Auditory ERPs are an objective and useful means to investigate the neural basis and different phases of CAP even in young children (Friedrich & Friederici 2010, Jansson-Verkasalo *et al.* 2010, Partanen *et al.* 2013a, Partanen *et al.* 2013b) and its impairments in clinical groups (for a review, e.g. Jeste & Nelson 2009; Näätänen *et al.* 2012).

The auditory ERPs are studied by presenting stimuli with selected characteristics in a specific design or research composition, called a paradigm, related to the research question (Luck 2005). From the recorded EEG data the ERPs are extracted by averaging EEG segments time locked to specific auditory events. The characteristics of auditory ERPs change as humans transition from newborns to adults. In children, the commonly studied auditory ERPs are obligatory P1, N2, and N4 responses together with change- elicited responses, MMN and novelty P3. In this thesis only those auditory ERPs of children are addressed.

2.2.1 The multi-feature paradigm

In order to elicit ERPs, different research paradigms can be used. Previously, the oddball paradigm with repetitive stimuli, standards and only one or two stimulus types at a time, were widely used. In order to enable the presentation of several sound-feature changes in a time-efficient manner (Näätänen *et al.* 2004), to resemble more natural speech (Kujala *et al.* 2007, Lovio *et al.* 2009, Pakarinen *et al.* 2009, Sorokin *et al.* 2010), and to partially overcome the neural refractoriness effects (Kujala *et al.* 2007, Putkinen et at. 2012) the multi-feature paradigm (also known as “Optimum-1”; Näätänen *et al.* 2004, Pakarinen *et al.* 2009) was invented.

The multi-feature paradigm consists of repetitive standard stimuli (for example, syllable /ke:/) and several different deviants (Näätänen *et al.* 2004, Pakarinen *et al.* 2009). In each deviant, one auditory feature is changed while the rest of the features are shared with the standard stimulus. For example, the fundamental frequency (F0) is increased or speech sound changed from /k/ to /p/. Standards and different deviants are presented in a sequence, so that every other stimulus is a standard and every other is one of the deviants (Figure 1). The standard stimulus and the remaining stimulus features of the deviants strengthen the memory trace for the standard sound features (Näätänen *et al.* 2004).

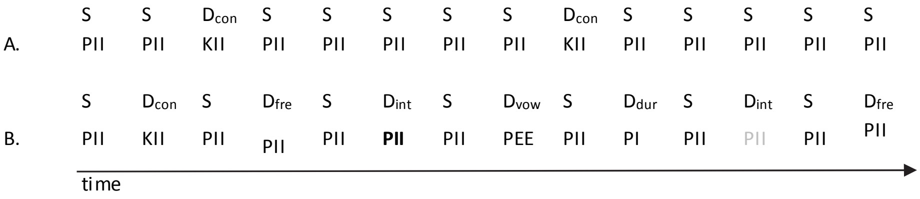

Fig. 1. Schematic presentation of the syllable stimuli embedded to A. the oddball paradigm and B. the multi-feature paradigm. S denotes standard syllable, D_{XXX} deviant syllable, super/subscript frequency change, and bolded/fainted intensity change

With the multi-feature paradigm, fairly similar responses have been obtained as with the oddball paradigm (e.g. Lovio *et al.* 2009, Näätänen *et al.* 2004). The multi-feature paradigm with syllable stimuli has proven to be a suitable method for investigating CAP in school-aged children (Lovio *et al.* 2009) and in adults (Kujala *et al.* 2006) as well as in clinical subgroups (Kujala *et al.* 2010, Lovio *et al.* 2010). In addition, the multi-feature paradigm with tone stimuli was found to be suitable for child studies at the age of 2 -years (Putkinen *et al.* 2012). However, studies published before Study I of this thesis did not test the feasibility of the multi-feature paradigm with syllable stimuli and novel sounds for investigating CAP in toddlers.

2.2.2 Obligatory responses

The obligatory responses are stimulus-elicited neural responses suggested to reflect early phases of sound encoding (Čeponienė *et al.* 2002, 2005). They are also called exogenous responses (Luck 2005), which means that they are arisen based on characteristics of a stimulus, not based on the internal aspects of the listener. Physiologically, the obligatory responses are generated at the thalamo-cortical pathway (Ponton *et al.* 2000). In children, the obligatory responses form the P1-N2-N4 complex (Choudhury & Benasich 2011), which is usually determined from the response to standard stimuli (Figure 2).

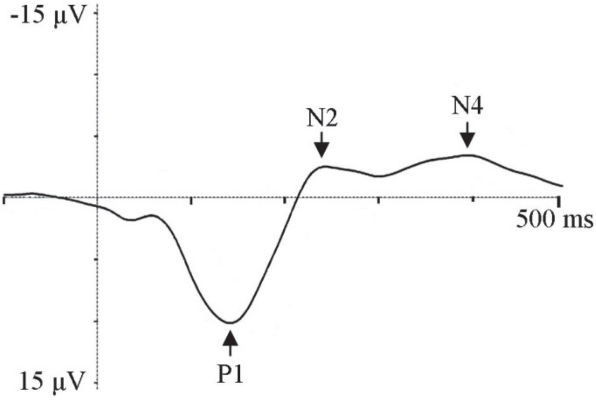

Fig. 2. An example of the average standard waveform. The P1, N2, and N4 responses are marked with arrows. Negativity is plotted upwards.

P1

Fronto-centrally maximal P1 response is a robust positive deflection, which was suggested to reflect automatic basic processing of auditory sound features (Čeponienė *et al.* 2002, 2005; Figure 2). The maximum of P1 is around 100 ms after stimulus onset (Čeponienė *et al.* 2002, 2005).

The latency of P1 is used as a biomarker of the maturation of the central auditory pathway (Sharma *et al.* 1997, 2002), because it decreases developmentally towards adulthood (Jing & Benasich, 2006, Paquette *et al.* 2015, Ponton *et al.* 2000). The developmental changes of the P1 amplitude are not that uniform. During the early years, it was reported to be stable (Čeponienė *et al.* 2002, Choudhury & Benasich 2011; Paquette *et al.* 2015) or first maximal at the age of 10–11 months (Jing & Benasich 2006) and then diminishing by 24 months (Jing & Benasich 2006). It continues to diminish from 5 years to adulthood (Ponton *et al.* 2000). However, changes in the P1 during the years from 2 to 4 are scarcely studied (Wunderlich & Cone-Wesson 2006).

N2

In children N2 is a negative response following P1 response (Čeponienė *et al.* 2003, Figure 2). It was proposed to index the high-order sound processing (Čeponienė *et al.* 2005) and forming of sensory representations (Anderson *et al.* 2010, Choudhury & Benasich 2011). N2 has its maximum at around 250 ms after stimulus onset. N2 has a similar fronto-central amplitude distribution as P1 response. In addition to N2 detected from standard response, N2* can be detected from deviant wave as response to deviant tone (e.g. Choudhury & Benasich 2011). However, N2 and N2* might reflect different neural processes. In this thesis, only N2 is addressed.

The latency of N2 diminishes developmentally towards adulthood (Choudhury & Benasich 2011, Jing & Benasich 2006, Sharma *et al.* 1997) similarly to the P1 latency. Also the amplitude of N2 diminishes developmentally from 9 months to 24 months (Jing & Benasich 2006) and from 4 years to adulthood (Čeponienė *et al.* 2002).

N4

N4 is a negative response following the N2 in children (Čeponienė *et al.* 2005, Figure 2). It was suggested to reflect high-order sound processing together with the N2 (Čeponienė *et al.* 2005) and sensory representations of repetitive sounds (Choudhury & Benasich 2011). It has the maximum around 350–400 ms after stimulus onset. Like P1 and N2, N4 has fronto-central amplitude distribution.

The developmental trajectories of N4 elicited by syllable stimuli are scarcely studied. For the tone stimuli, the N4 latency decreases from 3 to 48 months (Choudhury & Benasich 2011). The amplitude increases from 3 to 16 months, and then decreases by 24 months (Jing & Benasich 2006).

2.2.3 Change-elicited responses

The change-elicited responses, i.e. MMN and novelty P3, are evoked when change (a deviant) occurs in the sound stream (Näätänen *et al.* 1978, Polich 2007). The change-elicited responses are part of automatic perceptual-cognitive processing (for a review Näätänen *et al.* 2010, Polich 2007), depending on the internal factors of the listener and reflecting different phases of CAP than the obligatory responses. The change-elicited responses are determined from the standard minus deviant difference wave or from average deviant wave (Luck 2005).

MMN

MMN (Näätänen *et al.* 1978, for a review see Näätänen *et al.* 2011, Figure 3) is elicited by a violation of regularity in repetitive aspects of sound streams. MMN response is quantified from the deviant minus standard difference waveform. It reflects pre-attentive auditory discrimination and sensory memory (Näätänen *et al.* 1978, for a review see Näätänen *et al.* 2011) as well as sensory representations of the native language (Kuuluvainen *et al.* 2014, Näätänen *et al.* 2007, Winkler *et al.* 1999). In some studies, MMN is called mismatch response (MMR) due to positive polarity in babies (Choudhury & Benasich 2011, Kushnerenko *et al.* 2002, Leppänen *et al.* 2004, Trainor *et al.* 2003).

The MMN amplitude was reported to correlate also with behavioral discrimination skills and diminished MMN amplitudes are associated with poor discrimination (Amenedo & Escera 2000, Choudhury & Benasich 2011, Kujala & Näätänen 2010, Kujala *et al.* 2007, Pakarinen *et al.* 2007, Weber *et al.* 2005). Recently, Paquette *et al.* (2015) suggested that the MMN latency reflects language skills, since young children at ages of 3 months, 12 months, and 36 months with smaller expressive language scores had longer MMN latencies than children with better scores.

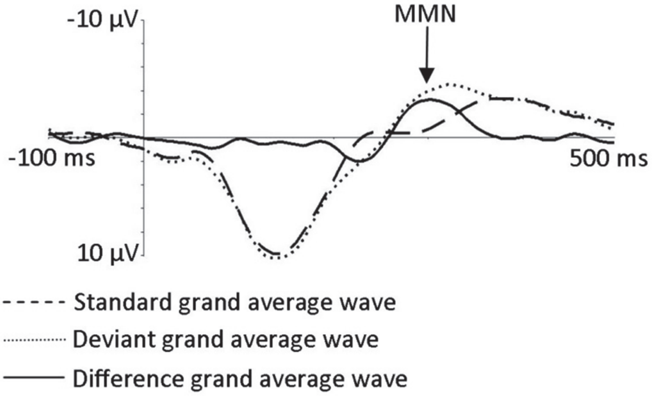

Fig. 3. An example of the grand average waveforms for standard and deviant stimuli, and grand average difference waveform. MMN is marked with an arrow and the negativity is plotted upwards.

MMN is primarily generated at the bilateral supra-temporal cortices and at the right frontal lobe (for a review, see Näätänen *et al.* 2007, Näätänen & Kreegipuu 2012). In young children, the auditory MMN has a fronto-central amplitude distribution having its maximum at 200–300 ms after stimulus change onset (Kushnerenko *et al.* 2002, Putkinen *et al.* 2012).

Developmentally, MMN morphology is altered substantially. In some studies, MMN in infants has a positive polarity which changes to a negative response during the early years (Choudhury & Benasich 2011, Kushnerenko *et al.* 2002, Leppänen *et al.* 2004, Trainor *et al.* 2003). The latency of MMN shortens and the MMN amplitude was suggested to follow an inverted-U-shaped trajectory first increasing and then decreasing until adulthood (Cheour *et al.* 2000). From 3 to 24 months, the MMN scalp distribution shifts towards more anterior areas (Jing & Benasich 2011).

Novelty P3

Fronto-centrally maximal novelty P3 is one of the P3 responses which were proposed to reflect attention shifting processes (for a review see Polich 2007; Figure 4). It is elicited by a rare and unexpected sound, a novel sound, in a stream of repetitive sounds (e.g. a bang in the middle of the syllable stream; SanMiguel *et al.* 2010, Sorokin *et al.* 2010). In some studies, also term P3a, with subcomponents ‘early P3a’ and ‘late P3a’ were used for a novelty triggered response (Haapala *et al.* 2016, Polich & Criado 2009). The novelty P3 was suggested to index attentional orienting and frontal and hippocampal activity (Parmentier *et al.* 2011, Sorokin *et al.* 2010). In addition, the latency of P3 responses was suggested to reflect timing of attentional processes (Polich, 2007). Prominent novelty P3 response has its maximum at 200–300 ms after sound-change onset (Sorokin *et al.* 2010).

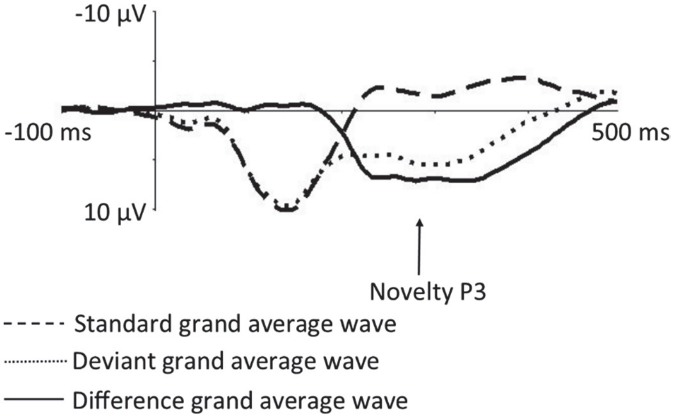

Fig. 4. An example of novelty P3 response. Response is marked with an arrow and the negativity is plotted upwards.

Novelty P3 is an effective tool to investigate the development of attentional orienting and its deficits in children (Gumenyuk *et al.* 2005). However, it has scarcely been studied in young children and its developmental trajectories are unknown.

2.3 Noise

Noise, as unwanted sound (WHO, 1999), interfere with auditory perception, attention, and ERPs (Kujala & Brattico 2009). In everyday life noise is a combination of sounds of different origins (WHO, 1999). The common hypernym ‘background noise’ can be divided to ambient noise and activity noise (Rantala *et al.* 2015, Sala & Rantala 2016). Activity noise originates from the activities happening in the current space. It may include audible speech from a single or multiple talkers, unclear babble, coughs, or sounds from e.g. toys, furniture, or dishes. One type of activity noises is cafeteria or cocktail party noise including a combination of babble and sounds from dishes. Ambient noise refers to external and internal noise not originating from direct activity in the current space. External ambient noise sources may include traffic and industry nearby. Internal ambient noise sources may include humming, originating from e.g. air condition systems and machinery (computers, data projectors). However, in some studies term internal noise refers to neural noise, occurring in the central nervous system and associated to autism spectrum disorders (Simmons *et al.* 2009, Weinger *et al.* 2014).

Noise, like all the other sounds, is a physical phenomenon and it can be addressed regarding the rules of acoustics. The intensity of noise, the magnitude of air vibrations, is indicated with logarithmic decibel (dB) units reflecting sound pressure level and experience of sound loudness (Benson, 1996, Speaks, 1999). An increment of 3 dB in sound pressure is judged to double the loudness of sound. Another essential dimension of sound is frequency, the number of oscillations per second, reflecting the sound pitch and measured with Hertz (Hz) units. In addition, the reverberation time indexes the time needed for the original sound to attenuate by 60 dB. The higher the reverberation time, the more echoic the room is.

Noise levels can be measured by using sound level meters at one time point or as an equivalent over a time window (db $L_{eq,}$ Speaks 1999, Krokstad & Laukli 2008). However, the numeric value from the sound level meter does not reflect the audible sound as it is processed in the human auditory system. Thus, the weighting of specific frequency ranges is used to provide more specific information (Krokstad & Laukli 2008). Commonly the A-weighting is used to simulate the frequency range of the human auditory system and thus provide naturalistic sound level results.

One element related to the distractibility of noise, in addition to the intensity and frequency of noise, is the relation between the target signal and noise. This relation can be described by calculating the SNR (Speaks, 1999). The bigger the ratio, the more audible the target signal is compared to noise. For children, at least 0 dB SNR is required for speech comprehension at school settings (Crandell & Smaldino 2000, Neuman *et al.* 2010). In adults, the SNR for correct speech perception is lower than in children and the SPL of noise can be even greater than the target signal yielding negative SNR. However, distractibility of noise differs between individuals, thus the SNR one person finds suitable might be annoying for someone else. In addition, varying intermittent noise seems to annoy listener more than monotonous constant noise (Astolfi & Pellerey 2008).

2.3.1 Noise in children's environments

Noise in children's environments has mainly three origins: traffic or industry noise from the outside, music, and activity noise including, for example, babble, yells, or sounds from toys, dishes, or furniture (Evans 2006). The noise levels vary according to the time, place (Sjödin *et al.* 2012), activity, and number of children present (Shield & Dockrell 2004).

The WHO guideline for the maximum level of ambient noise during teaching is 35 dB (WHO 1999), but the activity noise during the day is much higher. Previously, at school the mean noise exposure of personnel was found to be around 71 dB LA_{eq} (Sjödin *et al.* 2012) and children from 66.3 dB LA_{eq} to 74.3 dB LA_{eq} (Shied & Dockrell 2008). However, the mean noise level during the active hours at day-care centers, measured next to the child's ear, were as high as 82.6 dBA L_{eq} (from 81.5 to 83.6 dBA L_{eq}; McAllister *et al.* 2009).

2.3.2 The effects of noise on children

The most evident and best-known effects of noise are hearing problems. Transient high-energy noise or long-term exposure to high-level noise can produce acoustic trauma to the inner ear, thus causing hearing problems or tinnitus (Langguth *et al.* 2013). Besides hearing problems, noise has effects on typical bodily functions in children, as chronic exposure to loud noise increases systolic blood-pressure and alters stress-hormone levels (For a review, see Hohmann *et al.* 2013).

In children, noise also influences cognitive skills (for a review, see Evans 2006, Shield & Dockrell 2003). In noisy conditions, learning outcomes are weaker than in acoustically optimal conditions (Shield & Dockrell 2008). In addition, noise interferes with attention functions (Hygge *et al.* 2003) as a sudden sound signal captures attention. Also motor reaction times and number of errors increase during noise (Barutchu *et al.* 2010), reflecting the difficulties to concentrate during noise. In school-aged children, episodic memory is impaired during noise (Boman 2004, Hygge *et al.* 2003, Söderlund *et al.* 2010). However, unlike in typically developing children, in some cases moderate noise levels might even facilitate cognitive performance in children with ADHD (Söderlund *et al.* 2007).

Noise affects also language skills at various levels. First, speech comprehension is impaired during noise as noise hampers speech perception (Prodi *et al.* 2013) and reduces word recognition accuracy (Stuart *et al.* 2006). Auditory memory is impaired during noise (Hygge *et al.* 2003) having a negative impact on language processing. At the semantic level, word learning performance is restricted during noise (McMillan & Saffran 2016, Riley & McGregor 2012). In addition, pronunciation of new words is harder for toddlers to learn during noise compared to silence (Riley & McGregor 2012). Furthermore, noise was suggested to interfere in reading skills acquisition (for a review, see Evans 2006).

Younger children are more sensitive to the influence of noise on language skills than older children (Bradley & Sato 2008, Newman *et al.* 2011, Prodi *et al.* 2013, Stuart 2005, Wilson *et al.* 2010). In addition, children with language problems are more affected by noise than typically developing peers (Vance & Martindale 2012, Ziegler *et al.* 2011). For example, high-functioning children with autism or Asperger syndrome performed more poorly in speech comprehension tasks during background sounds with temporal dips than children developing typically (Alcantara *et al.* 2004). Also children with dyslexia were inferior in consonant discrimination task (Hazan *et al.* 2013) and speech comprehension tasks (Ziegler *et al.* 2009) during noise compared to typically developing children. Similarly, children with hearing impairments are vulnerable to the negative effects of noise than their typically hearing peers (Caldwell & Nittrouer 2013, Crandell & Smaldino 2000). Interestingly, children speaking their second language (Nelson *et al.* 2005) and bi- and trilingual children are also more vulnerable to the hampering effects of noise than monolingual children (Tabri *et al.* 2011).

2.3.3 The effects of noise on central auditory processing

The effects of noise on different phases of CAP can be addressed by investigating auditory brainstem responses as well as auditory ERPs. At the brainstem level, the hampering effect of noise is well established (for a review, see Anderson & Kraus 2010). Also the connection between speech-in-noise perception skills and early brainstem responses is evident in children and in adults (Anderson & Kraus 2010). At the cortical level, the ERPs provide information on the effects of noise on CAP, even though there are scarcely studies in young children.

In school-aged children, the amplitude of P1, suggested to index sound encoding, was smaller during noise than in the silent condition (Anderson *et al.*

2010). Also the latency of P1’ was delayed during noise (Russo *et al.* 2009). The amplitude of N2, proposed to reflect sound encoding and memory representation forming, was increased during noise in school-aged children with the weakest speech-in-noise perception skills (Anderson *et al.* 2010). However, in school-aged children with the best speech-in-noise perception skills, there was no such effect. Additionally, the latency of N2 in typically developing children was increased during noise (Warrier *et al.* 2004). In adults, noise with zero or negative SNR decreases the amplitudes of obligatory responses while the latency increases as the SNR decreases (Whiting *et al.* 1998). However, there are no previous studies on the effects of noise on the obligatory responses on toddlers and preschoolers.

The MMN, indexing pre-attentive auditory discrimination, is also altered by noise. In adults, the amplitude of MMN diminishes during noise (Kozou *et al.* 2005). Increasing noise levels were found to increasingly diminish the MMN amplitude (Martin *et al.* 1999, Muller-Gass *et al.* 2001). The lateralization of MMN also changes during noise in adults (for a review, Kujala & Brattico 2009). As indexed by the magnetic counterpart of MMN (MMNm), consonant change-elicited stronger MMNm at the right hemisphere during noise, while it was stronger at the left hemisphere in silent condition (Shtyrov *et al.* 1998, 1999). The effects of noise on the MMN latency in adults are diverse. MMN latencies during noise having been reported to decrease (Kozou *et al.* 2005), remain stable (Kozou *et al.* 2005) or increase (Martin *et al.* 1999, Muller-Gass *et al.* 2001). The difference might depend on the noise types (Kozou *et al.* 2005) or noise levels (Muller-Gass *et al.* 2001) used. However, there are no previous studies on this issue in children.

Long-term effects of noise on adult CAP have also been reported. Kujala *et al.* (2004) found that even in a silent condition workers exposed to occupational noise for 2 to 15 years (mean 6 years) had a decreased MMN for consonant change over the left hemisphere compared to adults with no noise exposure, the groups having no differences in hearing thresholds. Furthermore, the onset of MMN was found to be delayed and the magnitude of MMN altered even in a silent condition in a group of occupationally noise-exposed (over 10 years) workers (Brattico *et al.* 2005).

To conclude, noise has detrimental effects on CAP. The hampering effects are evident in both in children and adults. However, there are no previous studies investigating the effects of noise on young children at the neural level.

3 The aim of the study

The purpose of this thesis was to investigate developmental trajectories as well as noise-induced changes in ERPs reflecting sound encoding, memory representation forming, and auditory discrimination of five speech sound features in a follow-up study. In addition, the feasibility of the multi-feature paradigm for child studies was evaluated. To this end, ERPs were recorded with the multi-feature paradigm including syllable stimuli and novel sounds in silent and noisy conditions at the age of 2 years and again in the same children at the age of 4 years.

In Study I, the aim was to evaluate the feasibility of the multi-feature paradigm with syllable stimuli and novel sounds for investigating CAP in toddlers. The paradigm included standard stimulus syllables, five different deviant syllable types (consonant, frequency, intensity, vowel, and vowel duration changes), and novel sounds. It was hypothesized that the standards, deviants, and novel sounds embedded in the multi-feature paradigm elicit significant obligatory responses (P1, N2, and N4), deviant specific MMNs, and novelty P3 responses, respectively, in toddlers.

Study III aimed to investigate developmental changes in CAP. We assumed that from 2 to 4 years of age, P1 and N2 latencies and amplitudes decrease, MMN amplitudes increase, and the amplitude distribution of all of them changes.

Noise-induced changes in CAP were determined in Study II and Study III. In Study II, the effects of noise in typically developing 2-year-old children were studied. Study III was a follow-up and aimed to address effects of noise on CAP and the differences between the ages of 2 and 4 years in typically developing children. Noise was expected to interfere with speech sound encoding and pre-attentive auditory discrimination. It was hypothesized that noise decreases P1 and MMN amplitudes, increases N2 and N4 amplitudes, and alters ERP latencies and amplitude distributions. In addition, it was hypothesized that younger children are more vulnerable to the effects of noise than older children because at the age of 2 years the language system is less mature and neural representations might be less stable than at the age of 4 years.

4 Methods

4.1 Participants

The volunteers were recruited via internet mailing lists, public advertisements, and in parent–child meetings. In the beginning, 22 children participated in the study at the age of 22–26 months. The number of participants was based on approximations made with power-analysis and the tradition of previous ERP-studies conducted at our EEG-laboratory. The participants were typically developing monolingual children from Finnish-speaking families. In the questionnaire the parents reported no cases of linguistic problems, dyslexia, or severe mental illness in their families. The development of the participants was followed in healthcare centers in accordance with the health care system in Finland, and no developmental concerns were reported. Before the first EEG-registration, they had had a maximum of two episodes of otitis media.

At the age of 2 years, the typical linguistic status was ensured with the Finnish version of the Comprehension Scale of the Reynell Developmental Language Scales III (Kortesmaa *et al.* 2001) and the Finnish version of the MacArthur Developmental Inventory (Lyytinen 1999). In addition, speech production was evaluated from a speech sample recorded in a semi-structured play situation with the parent. Clinically healthy ears at the time of the EEG recordings were confirmed by the otologists. At this point, one participant had an acute otitis media and was withdrawn from the study (Figure 5). Transient otoacoustic emissions screening result was acquired from 12 children. In addition, six children with insufficient co-operation to otoacoustic emissions screening had passed the neonatal otoacoustic emissions screening at the maternity ward.

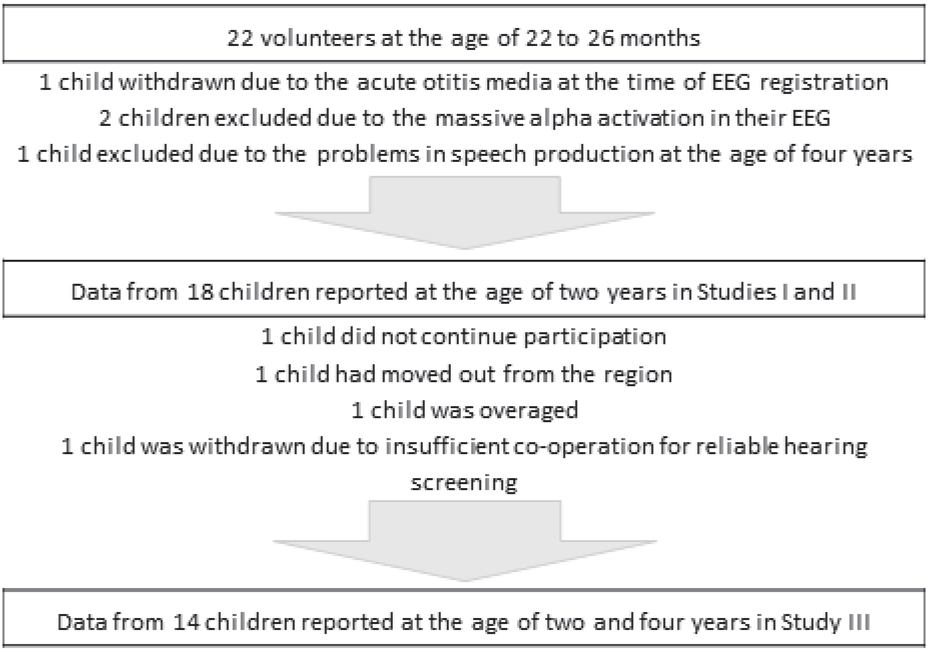

Fig. 5. A schematic illustration of the number of participants and the reasons for withdraws and exclusions.

During the EEG recordings at the age of 2 years, two children had massive alpha activation in their EEG-data and they had to be excluded from the study (Figure 5). Finally, in a follow-up at the age of 4 years one child showed problems with speech production as shown by a clinical assessment of a speech sample and was excluded from the whole study. Thus, the data from 18 children (8 girls, 10 boys) was analyzed and reported at the age of 2 years in Study I and Study II.

In the follow-up at the age of 4, 14 children from those 18 children continued their participation (Figure 5). One family refused to continue, one child turned out to be over-aged, one family had moved to another city, and one child did not co-operate in the hearing status screening and was excluded from the 4-years-old sample. The typical language status was ensured with the Finnish version of the Reynell Developmental Language Scales III (Kortesmaa *et al.* 2001), the Auditory Sequential Memory tasks of the Finnish version of the Illinois Test of

Psycholinguistic Abilities (Kuusinen & Blåfield 1974), the Finnish version of the Boston Naming Test (Laine *et al.* 1997), and by a clinical assessment of a speech sample recorded during a semi-structured play-situation with a researcher. All children passed the otoacoustic emissions screening at the age of 4 years. In addition, their hearing level was screened. In order to participate, the child had to hear 15 dB sound at 0.5, 1, 2, and 4 kHz separately with both ears.

This study was carried out in accordance with the Declaration of Helsinki and it was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District. Participants were volunteers and had the possibility to discontinue their participation at any time without further consequences. Written informed consent was given by the parents before the EEG-registrations at the age of 2 years. For the traveling costs associated with EEG recordings, 15 euros compensation was paid to the families. In the follow-up, the parents again gave a written informed consent and the children gave an oral informed assent. A small toy was given to the children as compensation for the time used for the EEG recordings at the age of 4 years.

4.2 ERP recording and analysis

4.2.1 Stimuli and multi-feature paradigm

In these studies, semisynthetic consonant-vowel syllable stimuli and novel sounds were used. The syllable stimuli were generated by using the Semisynthetic Speech Generation method (Alku *et al.* 1999, Sorokin *et al.* 2010) which uses vowels produced by humans and modifies them with an artificial vocal tract model. With this method, it is possible to manipulate stimulus-features and the outcome has a realistic jitter in the periodic structure of waveform, typical of speech. After vowel duration, fundamental frequency (F0), and intensity of the vowels were adjusted, the consonant /k/ or/ p/ was attached to the modified vowel in order to form a plosive-vowel syllable with suitable characteristics.

The standard syllable (50 % of the stimuli used) was /ke:/ or /pi:/ with a duration of 170 ms (consonant 12 ms and vowel 158 ms) and 101 Hz F0 (Figure 6). Deviant syllables included five speech sound feature changes relevant in Finnish:

1. consonant change from/k/ to /p/ and /p/ to /k/ (/ke:/ => /pe:/, /pe:/ =>/ke:/)
2. F0 change ±8% from 101 Hz to 93 Hz and to 109 Hz

3. intensity ± 7dB increment/decrement
4. vowel change from /e:/ to /i:/ and from /i:/ to /e:/ (/ke:/=>/ki:/, /pe:/ => /pi:/)
5. vowel duration increment from 158 ms to 108 ms

Each deviant type had 8 % probability. Bi-directional changes were chosen to regulate phoneme specificity (Lovio *et al.* 2009, 2010) and neural refractoriness effects (Kujala *et al.* 2007) as well as to evade increment/decrement distortion (Lovio *et al.* 2009, 2010). However, the vowel duration change was only a mono-directional decrement due to the challenges in interpretation of the MMN elicited by a duration increment (Jacobsen & Schröger 2003, Putkinen *et al.* 2012).

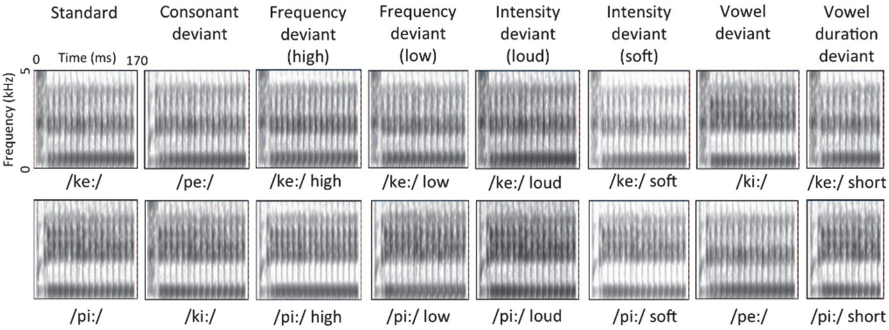

Fig. 6. Spectrograms of standard stimuli (/ke:/ and /pi:/) and consonant, frequency, intensity, vowel and vowel duration deviants.

Besides standards and deviants, non-speech novel sounds were presented in the sequences with the same 8 % probability as the deviants. They were natural daily human and non-human sounds with 200 ms duration (Sorokin *et al.* 2010).

The stimuli were presented with a multi-feature paradigm (Lovio *et al.* 2009, Näätänen *et al.* 2004, Pakarinen *et al.* 2009, Sorokin *et al.* 2010). In the multi-feature paradigm every other stimulus is standard and every other one of the deviants or a novel sound (Figure 7). The order of the deviants and novel sounds was pseudo-randomized so that similar deviant types were never presented successively. The multi-feature paradigm was chosen because it enables the presentation of several sound-feature changes in time-efficient manner (Näätänen *et al.* 2004), partially overcomes the neural refractoriness effects (Kujala *et al.* 2007, Putkinen *et al.* 2012), and a varying syllable stimulus stream resembles natural speech more than previously used oddball paradigm (Kujala *et al.* 2007, Lovio *et al.* 2009, Pakarinen *et al.* 2009, Sorokin *et al.* 2010).

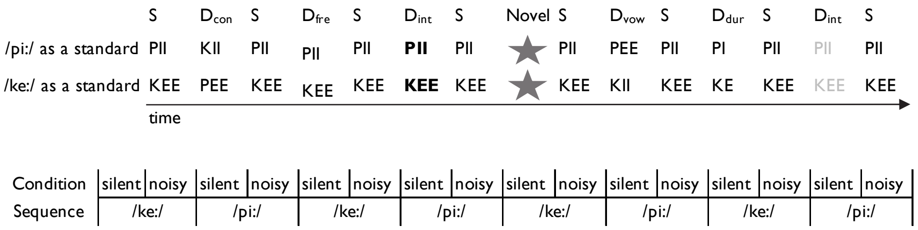

Fig. 7. Schematic presentation of five different deviant types and novel sounds embedded in the multi-feature paradigm and presented with two alternating listening conditions. S denotes standard syllable, D deviant syllable, super/subscript frequency change, bold/faint intensity change, and star denotes novel deviant.

4.2.2 EEG recordings

EEG was recorded by a professional EEG-technician together with two SLTs. During the recording, the participant sat in an electrically shielded and sound-dampened room on a chair beside the parent or on the parent's lap. The ambient noise level in the room was 43 dB and the reverberation time 0.3 seconds. To keep the participant calm and satisfied during the recording, they watched either muted cartoons, books, or played with quiet toys, stickers, pens, and papers. The parents were told to avoid speaking with the child, to sit still, and to maintain the child's attention in the activities. The participant and the parent were video-monitored during the EEG recording to ensure a high- quality data.

The EEG was recorded with 32 ActiCAP 002 active electrodes (Ag-AgCl sintered) with an active shielding and impedance converter. They were attached to an electro-cap in accordance with a 10–20 system. During the EEG recording, an electrode at the FCz location was used as an online reference. Additional disposable bipolar electrodes were applied for recording eye movements. They were located below the outer cantus of the left eye and above the outer cantus of the right eye. The Brain Vision amplifier with a bandpass filter 0.16–1000 Hz and sampling rate 5000 Hz was used for online amplification and the Brain Vision Recorder 1.10 for EEG recording. The quality of the EEG was constantly monitored during the recording.

The stimuli were presented with the Presentation 13.0 software via two loudspeakers (Genelec 6010A) at 75 db sound pressure level (SPL).

Loudspeakers were located at 40 degrees angles to the left and right and 130 cm in front of the child. A free sound field was chosen to avoid the use of headphones that potentially would be intolerable for 2-year-old year participants. The presentation was divided into six minute sequences each including 540 stimuli. Each stimulus sequence began with ten standard syllables and continued with alternating standards, deviants, and novel sounds. The stimulus onset asynchrony was 670 ms. If necessary, there were breaks between the stimulus sequences and refreshments were served. The electrode contacts were secured when necessary and after the breaks. From six to eight stimulus sequences were presented, depending on co-operation of the child.

4.2.3 Background noise

The stimulus sequences were presented alternating between silence and noise (Figure 7) including mostly modified babble of several speakers but also non-speech activity sounds like clings, and coughs (Figure 8). The babble noise was used because it was shown to interfere with CAP in adults more than traffic or white noise (Kozou *et al.* 2005) and it resembles children's daily auditory scene. The babble noise was continuous and it was presented with 55 dB SPL and 20 dB (SPL) signal to noise ratio (SNR).

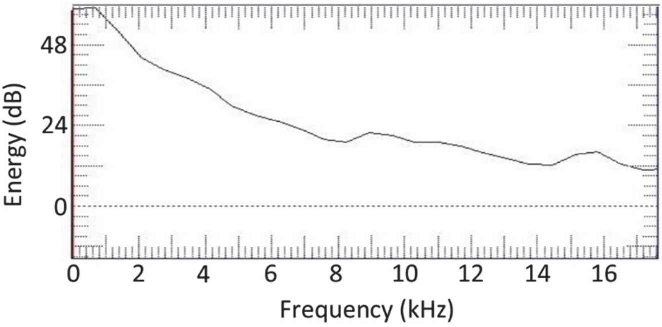

Fig. 8. The long-term average spectra of the babble noise.

4.2.4 EEG analysis

The EEG data were off-line analyzed with the Brain Vision Analyzer 2.0. In the beginning, the EEG sequences of each of the participants were combined based on the recording condition. The electrodes Fp1, Fp2, PO9, PO10, O1, Oz, and O2 were excluded due to massive artefacts from face and neck muscles which was present thorough the EEG data. The data from the final 25 electrodes were further analyzed. Next, the data sampling rate reduced to 250 Hz and the digital 0.5–45 Hz, 24dB/octave band-pass filter with zero-phase sift filters were applied in order to avoid aliasing and artefacts not originating from the brain (Luck 2005). The reason for using digital zero-phase filters was their capability to filter data without phase distortion. Then the data were off-line referenced to the mathematical average of the mastoids to enable inspection of hemispheric differences (Luck 2005) and to render a good MMN SNR (Kujala *et al.* 2007).

The artefact correction was made in two phases. First, an ocular correction was made with independent component analysis. Then, the data were inspected and all the epochs with over ±150µV voltage, exceptionally low amplitude of 1.5 µV in 100 ms time window, or 50 µV/msec voltage gradient were excluded. Finally, the data were digitally 1–20 Hz, 48 dB/octave band-pass filtered with zero-phase sift filter. Preliminary inspection revealed no distinct effects between the slopes of 48-dB/octave and 24-dB/octave on timing or magnitude of the responses. The 48-db/octave slope was selected for the final analysis because near band-pass boundaries it filters out noise more exactly than the 24-dB/octave slope and with short stimulus onset asynchrony its use is justified (Luck 2005).

For the peak detection, the data were divided into 600 ms epochs, starting 100 ms before stimulus onset and ending 500 ms after stimulus onset. The epochs including the ten standards at the beginning of each stimulus sequence and standards following novel sound were rejected. Next, the epochs were clustered based on stimulus type. The epochs for standards, each deviant type, and novel sounds were separately combined. The number of accepted trials varied between the participants, ages and conditions (Table 1). Thereafter, the baseline correction calculated as the mean voltage in the -100 ms to 0 ms time window was applied and each epoch cluster was averaged.

Table 1. The representative electrodes, time windows for peak detection, and number of accepted trials at the ages of 2 and 4 years (N = 14) in silent and noisy conditions (Study III).

Response	Representative electrodes		Time-window for peak detection	Mean number of accepted trials			
				At the age of 2 years		At the age of 4 years	
	2 years	4 years		Silent	Noisy	Silent	Noisy
P1	C3	F4	70–180	727	678	835	814
N2	C4	C3	190–290				
N4	Cz	F4	320–440				
Consonant MMN	C3	Cz	180–290	144	135	166	163
Frequency MMN	C4	F4	160–270	146	137	166	163
Intensity MMN	Cz	F4	180–300	144	135	167	162
Vowel MMN	C3	Fz	160–260	146	136	167	163
Vowel duration MMN	Cz	F4	250–360	146	136	166	163

All remaining 25 channels analyzed were used for visualization of data by amplitude distribution maps. In addition, nine channels were selected for peak detection. Commonly used channels F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 were chosen because the responses studied have the best SNR in these channels (Kujala *et al.* 2007). The obligatory P1, N2, and N4 responses were determined from grand average standard waves separately in both ages and conditions. The MMNs for five deviant types were determined from the deviant minus standard difference wave in both ages and listening conditions. The novelty P3 response was determined from novelty minus standard differences waves in 2-year-old children in the silent condition. Time windows for peak detection were separately selected for each response type at both ages in the silent condition and then applied to the noisy condition also (Table 1). Latency of each response was determined from the representative electrode selected together with the time window. The latency of the MMN elicited by the vowel duration change was corrected to begin from the time of the stimulus difference onset. The mean amplitude of each response was calculated based on ±20 ms integration window centered at the selected time point at the representative electrodes. Numerical latency and amplitude information were used for statistical analysis of the results.

4.3 Statistical analysis

Numeric information exported from the Brain Vision Analyzer –program was statistically analyzed with Statistica 10. The analysis began by determining the existence of the responses in different ages and conditions. A t-test was carried out in order to compare amplitudes at the representative electrodes to zero.

Repeated-measures analyses of variance (ANOVA) with within subjects factors age, condition (CON), anterior-posterior electrode location (AP), right-left electrode location (RL), and deviant type (DEV) was run to analyze ERP amplitudes and voltage distributions. Repeated-measures ANOVA with within subject factors age and condition was run to analyze ERP latencies. Based on sphericity, Huynh-Felt (Study I) or Greenhouse-Geisser (Study II and Study III) correction was used if necessary. Fisher's least significant difference post hoc test was used for source detection and partial eta squared (η_p^2) for effect size determination.

5 Results

5.1 Multi-feature paradigm as a research tool of toddlers (Study I)

The multi-feature paradigm with syllable stimuli elicited P1, N2, and N4 responses significantly differing from zero at the age of 2 years (Figure 9, Table 2; Study I). All of them had fronto-centrally maximal amplitude distribution (for P1, the main effect for AP F = 108, $p = 0.000$, $\eta_p^2 = 0.86$, post hoc $p = 0.000$; for N2, the main effect for AP F = 5, $p = 0.012$, $\eta_p^2 = 0.23$, post hoc $p \leq 0.02$; for N4, the main effect for AP F = 15, $p = 0.000$, $\eta_p^2 = 0.47$, post hoc $p \leq 0.001$). Robust P1 together with evident N2 and N4, elicited by standard syllable stimuli with 50% presentation rate, indicate the feasibility of the multi-feature paradigm for investigating these responses.

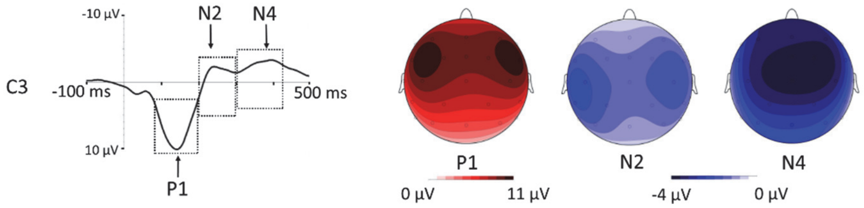

Fig. 9. The grand average wave for standard stimuli and the amplitude distributions at the age of 2 years (N = 18) in typically developing children studied with the multi-feature paradigm with syllable stimulus. The time windows for the peak detection are marked with squares and the negativity is plotted upwards.

Table 2. The characteristics of the obligatory responses at the age of 2 years in typically developing children (N = 18, Study I) studied with syllable stimulus embedded to the multi-feature paradigm. The mean of accepted trials was 722 trials ranging from 534 trials to 859 trials.

Response	Amplitude (µV)		Latency (ms)	
	Mean	SD	Mean	SD
P1	9.9[1]	3.4	140	10
N2	-2.3[1]	2.1	247	20
N4	-3.6[1]	2.4	380	28

[1] $p < 0.01$ for the statistical difference from 0 at the C3 electrode

Each deviant type (consonant, frequency, intensity, vowel, and vowel duration change) elicited a MMN response significantly differing from zero at the representative electrode at the age of 2 years (Figure 10, Table 3, Study I). Each deviant type also yielded MMN with unique characteristics (the main effect for DEV F = 6, $p \leq 0.007$, $\eta_p^2 = 0.27$). MMN to the vowel duration change had the shortest latency (the main effect for DEV F = 10, $p \leq 0.001$, post hoc $p \leq 0.007$) and that of the intensity change the longest (post hoc $p \leq 0.006$). The vowel duration change elicited the most robust MMN (post hoc $p \leq 0.007$). Overall, MMNs had a central distribution (the main effect for AP F = 10, $p \leq 0.001$, $\eta_p^2 = 0.37$, post hoc $p \leq 0.04$) but the hemispheric voltage distribution varied (the RL x DEV interaction F = 4, $p \leq 0.001$, $\eta_p^2 = 0.\ 19$, post hoc $p \leq 0.027$; the AP x RL x DEV interaction F = 3, $p \leq 0.001$, $\eta_p^2 = 0.14$). The MMN elicited by the consonant change was the strongest at the left hemisphere C3 (post hoc $p = 0.3$ in comparison to F3, post hoc $p \leq 0.05$ to other electrodes) whereas the MMN to the frequency change had its maximum at the right hemisphere C4 (post hoc $p \leq 0.001$). The MMN elicited by intensity change was the strongest in the midline at Cz (post hoc $p \leq 0.05$). The MMN for the vowel change, in turn, had a bilateral distribution with no significant difference between left and right electrode locations. For the vowel duration change, the MMN was strongest at the midline Cz, even though the statistical difference between electrode locations Cz and C3 was marginal (post hoc $p = 0.06$, post hoc $p \leq 0.001$ in comparison to other electrode locations).

Taken together, significant MMNs with unique characteristics indicated that toddlers were able to pre-attentively discriminate several speech sound features presented in the same stimulus sequences with the multi-feature paradigm, supporting the feasibility of the paradigm.

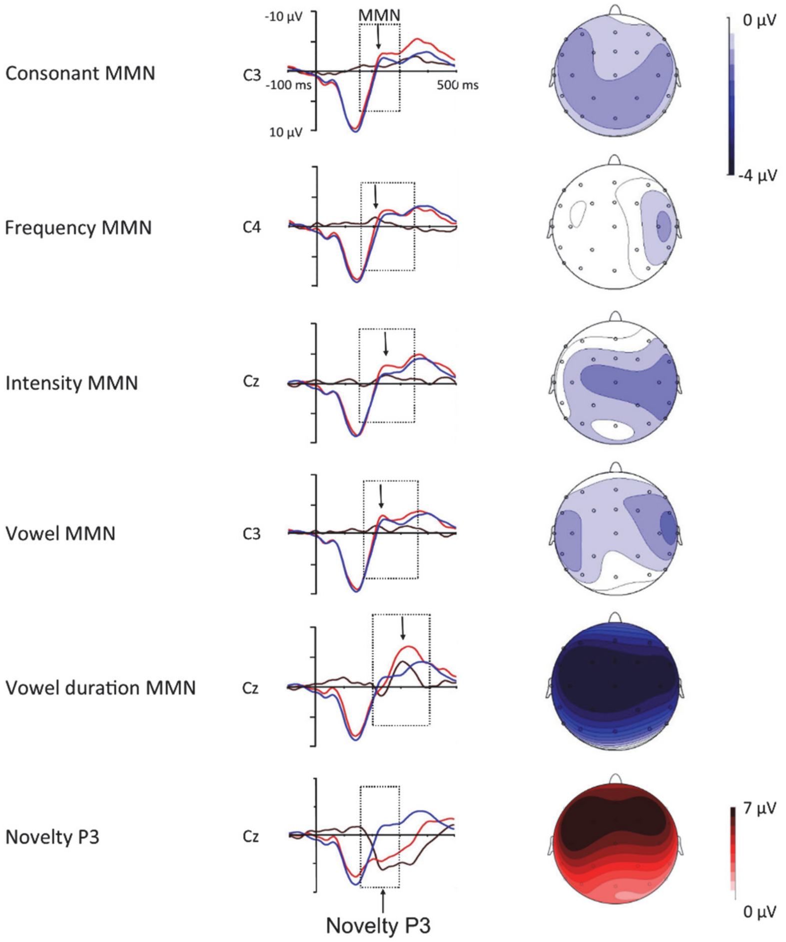

Fig. 10. The grand average waves for standard (blue line) and deviant (red line) stimuli, the difference waves (brown line), and amplitude distributions for the MMN and novelty P3 response at the age of 2 years in typically developing children (N = 18, Study I). The time windows for the MMN and novelty P3 peak detection are marked with squares and the negativity is plotted upwards.

Table 3. The characteristics of MMN and novelty P3 responses in 2-year-old typically developing children (N = 18, Study I). MMNs were elicited by five different speech sound changes presented with the multi-feature paradigm. The latency of MMN to vowel duration decrement is corrected with regard to the onset of the deviation. The mean of accepted trials was 145 trials ranging from 100 trials to 171 trials.

Response	Representative electrode	Amplitude (µV)		Latency (ms)	
		Mean	SD	Mean	SD
Consonant MMN	C3	-2.5[1]	2.0	220	48
Frequency MMN	C4	-2.1[1]	2.7	231	42
Intensity MMN	Cz	-2.7[1]	2.2	265	50
Vowel MMN	C3	-1.2[1]	2.3	225	18
Vowel duration MMN	Cz	-4.4[1]	2.7	185	25
Novelty P3	Cz	7.7[1]	3.6	260	41

[1] $p < 0.01$ for the statistical difference from 0 at the representative electrode

The embedded novel sounds elicited novelty P3 responses significantly differing from zero at the age of 2 years (Figure 10, Table 3, Study I). The novelty P3 had fronto-central amplitude distribution (the main effect for AP F = 29, $p \leq 0.001$, $\eta_p^2 = 0.63$, post hoc $p \leq 0.001$). The present results suggest that the multi-feature paradigm with novel sounds is feasible for studying attentional processes simultaneously with speech sound processing and auditory discrimination in toddlers.

5.2 Developmental changes in event-related potentials (Study III)

Developmental changes of obligatory responses (P1, N2, and N4) and MMNs were studied by investigating the same children at the ages of 2 and 4 years. All of the responses significantly differed from zero at both ages at the representative electrodes.

5.2.1 Obligatory responses

Developmentally, the P1 latency significantly decreased from 139 ms to 117 ms (the main effect F(1,13) = 103, $p \leq 0.001$, $\eta_p^2 = 0.\ 89$, post hoc $p \leq 0.001$, Figure 11, Study III). At the same time, the P1 amplitude increased from 10.6 µV to 11.2 µV, but the change was not statistically significant. The P1 amplitude distribution changed during the development (Age x AP interaction F(1,18) = 52, $p = 0.038$, $\eta_p^2 = 0.26$). At the age of 2 years, the P1 distribution was fronto-centrally maximal (post hoc $p \leq 0.001$) and at the age of 4 years frontally maximal (post hoc $p \leq 0.001$).

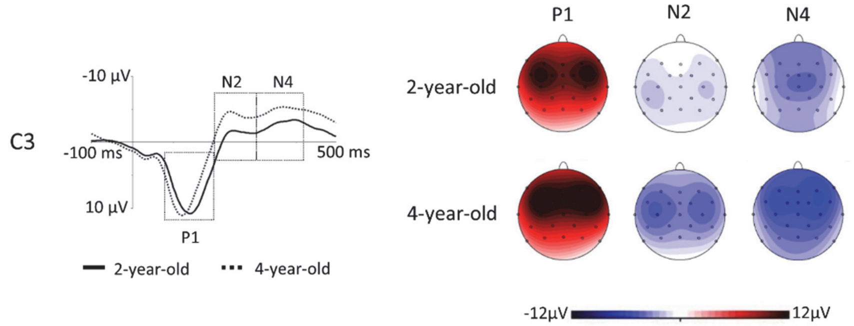

Fig. 11. The grand average waves for standard stimuli and amplitude distributions of P1, N2, and N4 responses in typically developing children at the ages of 2 and 4 years (N = 14). The time windows for the peak detection are marked with squares and the negativity is plotted upwards.

From 2 to 4 years of age, the N2 latency significantly decreased from 249 ms to 243 ms (the main effect for Age F(1,13) = 5, $p = 0.05$, $\eta_p^2 = 0.26$, post hoc $p = 0.053$, Figure 11) and the N2 amplitude significantly increased from -2.0 µV to -4.7 µV (the main effect for Age F(1,13) = 12, $p = 0.005$, $\eta_p^2 = 0.47$, post hoc $p = 0.005$). In addition, the N2 amplitude distribution changed from 2 to 4 years (Age x AP interaction F(1,15) = 18, $p = 0.001$, $\eta_p^2 = 0.\ 58$; Age x LR interaction F(2,26) = 4, $p = 0.03$; $\eta_p^2 = 0.23$). At the age of 2 years, N2 was centrally maximal (post hoc $p \leq 0.001$) and stronger laterally than at the midline (post hoc $p = 0{,}048$). At the age of 4 years, N2 was maximal fronto-centrally and over the left hemisphere (post hoc $p \leq 0.001$).

The N4 latency increased from 375 ms to 393 ms developmentally, but the change was not statistically significant (Figure 11). From 2 to 4 years, the N4 amplitude increased significantly from -4.9 µV to -6.5 µV (the main effect for Age F(1,13) = 21, $p = 0.001$, $\eta_p^2 = 0.61$) and the amplitude distribution changed (Age x AP interaction F(1,17) = 13.08, $p = 0.001$, $\eta_p^2 = 0.50$). At the age of 2 years, N4 was fronto-centrally maximal (post hoc $p \leq 0.001$), whereas at the age of 4 years, N4 was frontally maximal (post hoc $p \leq 0.002$).

5.2.2 Mismatch negativity

From 2 to 4 years of age, the MMN latencies diminished, but the change was not statistically significant (Figure 12, Table 4). Overall, the MMN amplitudes increased developmentally (the main effect for Age F(1,13) = 5, $p = 0.04$, $\eta_p^2 = 0.28$, post hoc $p = 0.04$). There was no significant Age x DEV interaction, suggesting that the developmental MMN amplitude increment was similar for the deviant types.

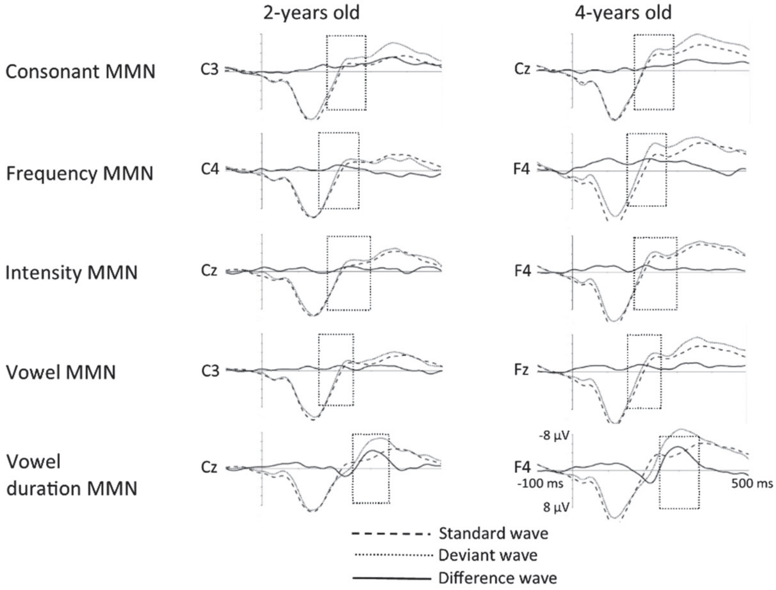

Fig. 12. The grand average waves for standard stimuli, for the five deviant types, and the difference waves in typically developing 2- and 4-year-old children (N = 14). The time windows for the MMN peak detection are marked with squares and the negativity is plotted upwards.

Table 4. The characteristics of MMN responses in typically developing children at the ages of 2 and 4 years (N = 14, Study III). The latency of MMN to the vowel duration decrement is corrected with regard to the onset of deviance.

Response	Amplitude (µV)		Latency (ms)	
	At the age of 2 years	At the age of 4 years	At the age of 2 years	At the age of 4 years
Consonant MMN	-2.2 (2,5)^2	-1.9 (1.8)^2	237 (32)	234 (31)
Frequency MMN	-1.7 (2.9)^3	-3.5 (3.2)^2	214 (26)	224 (27)
Intensity MMN	-1.7 (3.0)^3	-1.9 (2.5)^3	238 (26)	233 (28)
Vowel MMN	-1.5 (2.3)^3	-2.0 (1.8)^1	213 (22)	201 (24)
Vowel duration MMN	-4.2 (2.5)^1	-5.6 (3.0)^1	189 (21)	177 (18)

$^1p < 0.001$, $^2p < 0.01$, $^3p < 0.05$, ^{ns}non- significant for the statistical difference from 0 at the representative electrode. Standard deviation in the brackets.

The MMN amplitude distribution changed from 2 to 4 years of age (Age x AP interaction F(2,16) = 8, $p = 0.002$, $\eta_p^2 = 0.39$; Age x RL interaction F(2,26) = 4, $p = 0.03$, $\eta_p^2 = 0.23$, Figure 13). At the age of 2 years, the MMNs were centrally maximal (post hoc $p = 0.007$) and evenly distributed in the left-right dimension. At the age of 4 years, the MMNs were frontally maximal (post hoc $p \leq 0.027$) and strongest at the midline and right hemisphere (post hoc $p = 0.03$).

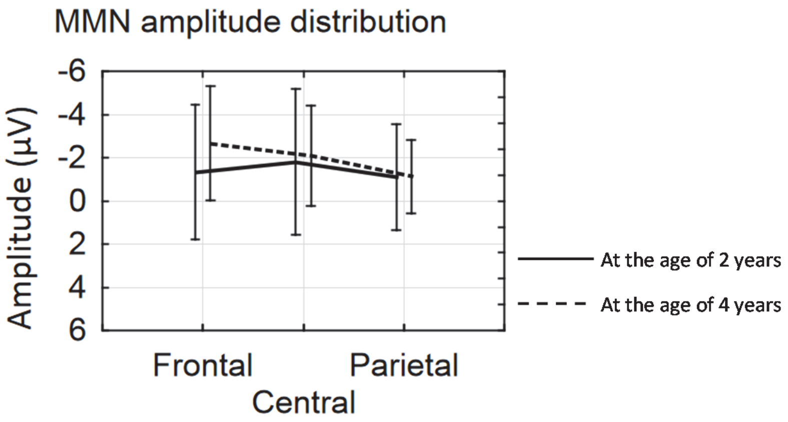

Fig. 13. The anterior-posterior distribution of MMNs averaged over the five deviant types at the ages of 2 and 4 years in the silent condition (N = 14, Study III). At the age of 2 years, MMNs were centrally maximal. At the age of 4 years, MMNs were frontally maximal. The negativity is plotted upwards.

5.3 The effects of background noise on event-related potentials (Study II and Study III)

The noise-induced changes on P1, N2, N4, and MMNs were first studied in 18 children at the age of 2 years (Study II). In addition, in order to investigate the developmental effects on the influence of noise on ERPs, a follow-up subgroup (N = 14) of the original children were studied again at the age of 4 years (Study III). Here the results from both groups are reported.

5.3.1 Obligatory responses

Obligatory responses (P1, N2, and N4) recorded during noise significantly differed from zero at both ages (Figure 14, Table 5, Study II, and Study III). There were no CON x Age interactions for the latency, amplitude, or amplitude distributions in the follow-up study group. Thus, noise influenced obligatory responses similarly at the ages of 2 and 4 years.

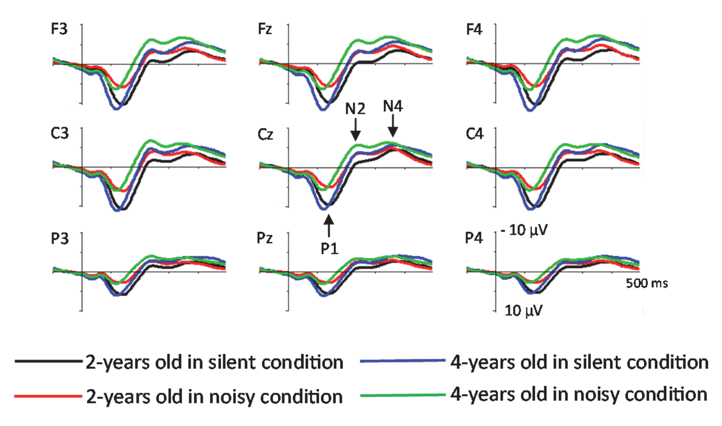

Fig. 14. The grand average waves for standard stimuli in the silent and noisy conditions at the ages of 2 and 4 years in typically developing children(N = 14, Study III). The negativity is plotted upwards.

Table 5. The characteristics of P1, N2, and N4 responses at the ages of 2 and 4 years in typically developing children in silent and noisy conditions (N = 14, Study III).

	At the age of 2 years		At the age of 4 years	
	Silent	Noisy	Silent	Noisy
P1 amplitude (μV)	10.6 (3.5)^1	5,9 (2.4)^1	11.2 (3.7)^1	6.5 (2.8)^1
N2 amplitude (μV)	-2,0 (2.2)^2	-4.1 (2.2)^1	-4.7 (3.1)^1	-6.6 (3.1)^1
N4 amplitude (μV)	-4.9 (2.5)^1	-4.9 (2.5)^1	-6.5 (2.7)^1	-7.2 (3.3)^1
P1 latency (ms)	139 (11)	141 (15)	117 (9)	116 (12)
N2 latency (ms)	249 (21)	249 (22)	243 (18)	236 (15)
N4 latency (ms)	375 (26)	365 (20)	393 (37)	365 (38)

$^1p < 0.001$, $^2p < 0.01$, standard deviation in the brackets

P1

The P1 was robustly elicited in both conditions and study groups. Noise had no significant effects on P1 latencies (Figure 14, Table 5, Study II and Study III). However, the amplitude of P1 was smaller in the noisy than the silent condition (the main effect for CON at the age of 2 years F(1,17) = 38, $p \leq 0.001$, $\eta_p^2 = 0.69$, post hoc $p \leq 0.001$; the main effect for CON at the ages of 2 and 4 years F(1,13) = 59, $p \leq 0.001$, $\eta_p^2 = 0.82$, post hoc $p \leq 0.001$).

Noise altered the anterior-posterior amplitude distribution of P1 (the main effect for AP at the ages of 2 and 4 years F(1,17) = 19, $p \leq 0.001$, $\eta_p^2 = 0.60$, Study III, the main effect for AP at the age of 2 years F(1,23) = 11, $p \leq 0.001$, $\eta_p^2 = 0.40$, post hoc $p \leq 0.001$). During noise the amplitude distribution was fronto-centrally maximal (post hoc $p \leq 0.001$) in Study II and Study III. In contrast, it the silent condition, P1 was fronto-centrally maximal at the age of 2 years (N = 18, post hoc $p \leq 0.001$, Study II) and frontally maximal in the follow-up group at the ages of 2 and 4 years (N = 14, post hoc $p \leq 0.03$, Figure 15, Study III). In both conditions and groups the amplitudes were the smallest at the parietal electrodes (post hoc $p \leq 0.001$).

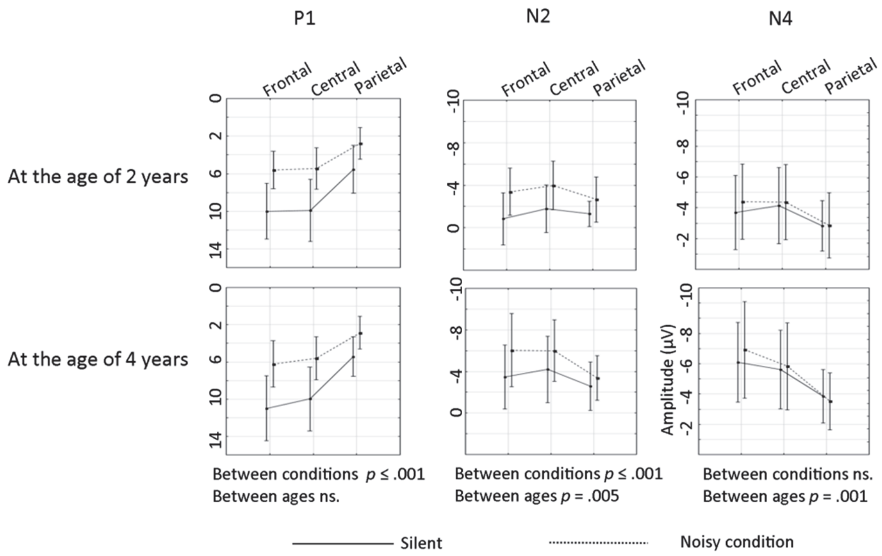

Fig. 15. The anterior-posterior amplitude distributions of P1, N2, and N4 responses in the silent and noisy conditions at the ages of 2 and 4 years in typically developing children (N = 14, Study III).

N2

N2 response was significant in both conditions and study groups with no noise-induced changes on its latency (Figure 14, Table 5, Study II, and Study III). The amplitude of N2 was larger during noise than the silent condition (the main effect for CON at the age of 2 years F(1,17) = 45, $p \leq 0.001$, $\eta_p^2 = 0.73$, post hoc $p \leq 0.001$, Study II; the main effect for CON at the ages of 2 and 4 years F(1,13) = 34, $p \leq 0.001$, $\eta_p^2 = 0.73$, post hoc $p \leq 0.001$, Study III).

The amplitude distribution of N2 showed no noise-induced changes at the age of 2 years. However, in the follow-up, the N2 amplitude distribution was centrally maximal in the silent condition (AP x CON interaction F(2,26) = 16, $p \leq 0.001$, $\eta_p^2 = 0.55$, post hoc $p \leq 0.001$, Figure 15) and fronto-centrally maximal during noise (post hoc $p \leq 0.001$).

N4

N4 response was studied only in Study III. It was significant in both conditions (Figure 14, Table 5, and Study III). Unlike the P1 and N2 latencies, the N4 latency diminished during noise (N = 14, F(1,13) = 25, $p \leq 0.001$, $\eta_p^2 = 0.66$, post hoc $p \leq 0.001$) but there were no noise-induced changes on the N4 amplitude.

The amplitude distribution of N4 changed during noise (the main effect for CON x AP F(2,26) = 7, 35, $p = 0.003$, $\eta_p^2 = 0.36$, Figure 15, Study III). The N4 voltage distribution was fronto-centrally maximal in the silent condition (post hoc $p \leq 0.001$) and frontally maximal in noise condition (post hoc $p \leq 0.002$).

5.3.2 Mismatch negativity

MMNs elicited by consonant, frequency, and vowel duration changes significantly differed from zero in the noisy condition at the age of 2 years (N = 18, Study II). In the follow-up subgroup (N = 14, Study III, Table 6, Figure 16), only the MMN elicited by the consonant change significantly differed from zero at both ages and the MMN elicited by the vowel duration change at the age of 4 years.

There were no noise-induced changes on the latencies of the significant MMNs in either of the groups (Study II and Study III, Table 7, Figure 16). Overall, MMNs were smaller in the noisy condition than silent condition (At the age of 2 years the main effect for CON F(1,17) = 9, $p = 0.009$, $\eta_p^2 = 0.34$, post hoc $p = 0.009$; at the ages of 2 and 4 years main effect for CON F(1,13) = 34, $p \leq 0.001$, $\eta_p^2 = 0.72$, post hoc $p \leq 0.001$).

Table 6. The characteristics of MMN amplitudes at the ages of 2 and 4 years in typically developing children in silent and noisy conditions (N = 14, Study III).

Response	Amplitude (µV)			
	At the age 2 years		At the age of 4 years	
	Silent	Noisy	Silent	Noisy
Consonant MMN	-2.2 (2.5)^{2}	-1.4 (1.4)^{2}	-1.9 (1.8)^{2}	-1.1 (1.9)^{3}
Frequency MMN	-1.7 (2.9)^{3}	-1.0 (2.9)^{ns}	-3.5 (3.2)^{2}	-1.3 (3.1)^{ns}
Intensity MMN	-1.7 (3.0)^{3}	-0.5 (3.0)^{ns}	-1.9 (2.5)^{3}	-1.3 (2.5)^{ns}
Vowel MMN	-1.5 (2.3)^{3}	-0.4 (2.9)^{ns}	-2.0 (1.8)^{1}	-0.7 (2.5)^{ns}
Vowel duration MMN	-4.2 (2.5)^{1}	-1.6 (3.0)^{ns}	-5.6 (3.0)^{1}	-2.1 (3.1)^{3}

$^{1}p < 0.001$, $^{2}p < 0.01$, $^{3}p \leq 0.05$, ^{ns} non-significant. Standard deviation in the brackets.

Table 7. The characteristics of MMN latencies at the ages of 2 and 4 years in typically developing children in silent and noisy conditions (N = 14, Study III). The latency of MMN to the vowel duration decrement is corrected regarding to the onset of deviance. Ns denotes non-significant MMN response.

Response	Latency (ms)			
	2-years-old		4-years-old	
	Silent	Noisy	Silent	Noisy
Consonant MMN	237 (32)	241 (33)	234 (31)	225 (32)
Frequency MMN	214 (26)	ns	224 (27)	ns
Intensity MMN	238 (26)	ns	233 (28)	ns
Vowel MMN	213 (22)	ns	201 (24)	ns
Vowel duration MMN	189 (21)	ns	177 (18)	178 (21)

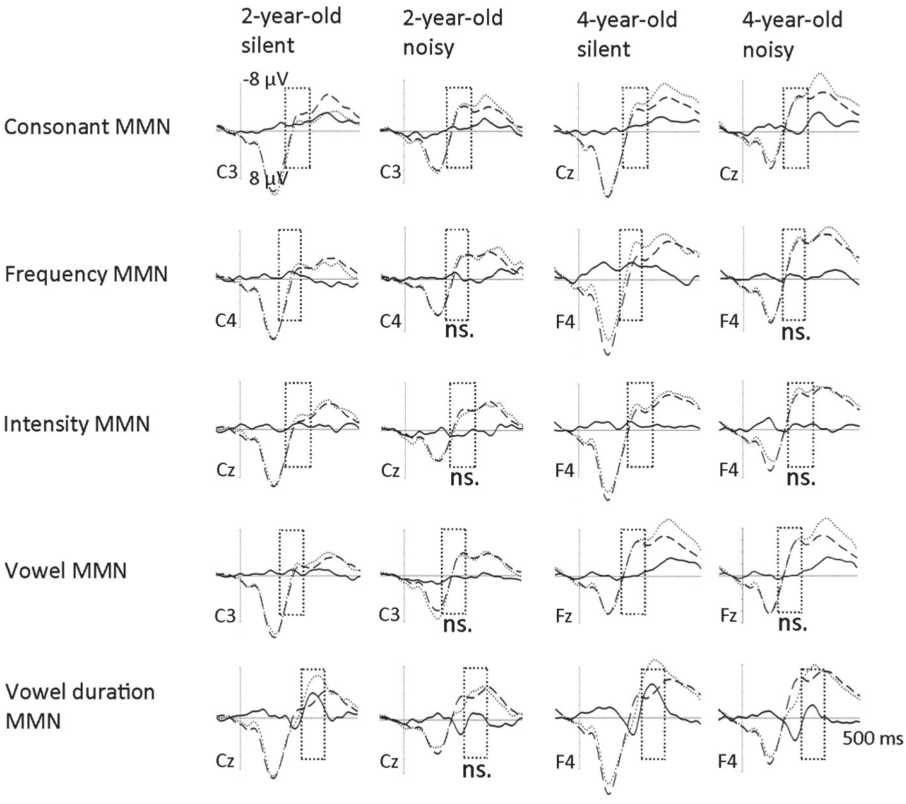

Fig. 16. The grand average waves for standard stimulus (dashed line), for five deviant types (dotted line), and the difference waves (solid line) at the ages of 2 and 4 years in

typically developing children (N = 14) in silent and noisy conditions. The time windows for the MMN peak detection are marked with squares, the negativity is plotted upwards, and Ns. denotes non-significant MMN response.

At the age of 2 (Study II), MMNs elicited by the vowel duration changes were the most robust in both conditions (the main effect F(2,34) = 6, $p = 0.008$, $\eta_p^2 = 0.25$, post hoc $p \leq 0.019$). The amplitude of MMNs to consonant, frequency, and vowel duration changes decreased during the noise (the main effect F(1,17) = 9, $p = 0.009$, post hoc $p = 0.009$, $\eta_p^2 = 0.34$). Noise changed the MMN amplitude distributions (CON x AP interaction F(2,34) = 6, $p = 0.006$, $\eta_p^2 = 0.26$). MMNs had a fronto-centrally maximal distribution in the silent condition (post hoc $p \leq 0.006$), while it was centro-parietally maximal and frontally minimal during noise (post hoc $p = 0.012$ between the frontal and central electrodes, post hoc $p = 0.07$ between the frontal and parietal electrodes).

In the follow-up subgroup (Study III), there were no effects of noise on the amplitude or amplitude distribution of MMN elicited by the consonant change at either age (Table 6). At the age of 4 years, in addition to MMN to consonant change, the vowel duration change-elicited a significant MMN response during noise. Its amplitude was smaller during noise than silence (F(1,13) = 41; $p \leq 0.001$, $\eta_p^2 = 0.76$, post hoc $p \leq 0.001$). Noise also affected the amplitude distribution of the MMN elicited by the vowel duration decrement (CON x AP x LR interaction F(2,32) = 3, $p = 0.044$, $\eta_p^2 = 0.20$). It was fronto-centrally maximal in silent condition (post hoc $p \leq 0.001$), but frontally maximal during noise (post hoc $p \leq 0.038$). Furthermore, it was stronger at Cz than C3 in the silent condition (post hoc $p = 0.038$), but smallest at Cz and strongest at C3 during noise (post hoc $p = 0.018$).

6 Discussion

The aims of this thesis were as follows. First, to determine the feasibility of the multi-feature paradigm with five types of deviant syllable stimuli and novel sounds for the toddler studies. The second aim was to investigate the developmental changes in CAP in typically developing children from 2 to 4 years. The third aim was to investigate noise-induced changes in CAP in typically developing children at the ages of 2 and 4 years.

The results of this thesis can be summarized to four major findings. First, the results indicate that the multi-feature paradigm provides feasible means to study CAP in toddlers. Second, the maturational changes in ERPs, decreased P1 and N2 latencies as well as increased N2, N4, and MMN amplitudes, which increased frontally the most, reflect maturational changes in CAP and neural system. Third, noise evidently changed CAP by decreasing P1 amplitude, increasing N2 and MMN amplitudes, and altering amplitude distributions of ERPs. Fourth, the effects of noise were largely similar at the ages of two and four years. Detailed discussion of the results is presented in chapters 6.1, 6.2, and 6.3.

6.1 Feasibility of the multi-feature paradigm for toddler studies

The feasibility of the multi-feature paradigm for assessing CAP was judged based on the presence and characteristics of significant ERP-responses. The standard and deviant syllable stimuli as well as novel sounds presented with the multi-feature paradigm elicited significant obligatory responses, MMNs and novelty P3. This indicates that the multi-feature paradigm with syllable stimuli and novel sounds provides feasible and time-efficient means to study CAP from different perspectives: speech sound encoding, pre-attentive speech sound discrimination of five different deviant types, and attentional mechanisms simultaneously in toddlers.

In this study, obligatory responses (P1, N2, and N4), suggested to reflect speech sound encoding and memory representation forming (Čeponienė *et al.* 2002, 2005), were robust and had similar timing in 2-year-old children as reported previously in studies using an oddball paradigm (Čeponienė *et al.* 2002, Choudhury & Benasich 2011). In addition, the amplitude distribution was fronto-centrally maximal, consistent with previous studies (Čeponienė *et al.* 2002; Choudhury & Benasich, 2011). So, among the varying deviants, the standard stimulus elicited significant and typical obligatory responses with similar characteristics as reported earlier with oddball, as expected.

The deviant syllables presented in the multi-feature paradigm elicited significant and stimulus-specific MMN responses in typically developing 2-year-old children. The characteristics of MMN were in line with the previous studies with similar stimuli as in this study embedded in the multi-feature paradigm in school-aged children (Kujala *et al.* 2010, Lovio *et al.* 2009) as well with tone stimuli in toddlers (Putkinen *et al.* 2012). In the current study, *MMN to the vowel duration change* was the largest MMN response, as also earlier reported in Finnish 6-year-old children (Lovio *et al.* 2009). This result might be explained by the linguistic relevance of vowel duration in Finnish (Jaramillo, Alku & Paavilainen 1999, Tervaniemi *et al.* 2006) tuning Finnish speaking children to vowel duration changes (Jaramillo *et al.* 1999) and/or by the large acoustic difference between the standard stimulus and the duration deviant (Kujala & Näätänen, 2010). Furthermore, the MMN elicited by the vowel duration change was characterized by a bilateral amplitude distribution. In contrast, *MMNs to frequency and intensity changes* were lateralized to the right side of the scalp similar to MMNs elicited by prosodic changes in adults (cf. Tervaniemi & Hughdahl, 2003). *MMN elicited by the consonant change* lateralized to the left hemisphere and *MMN elicited by the vowel change* had a similar tendency, but the result was not statistically significant. Taken together, significant and stimulus-specific MMN responses to each deviant suggest that toddlers are able to extract several speech sound features from a complex stimulus stream, which indicates the feasibility of the multi-feature paradigm. In addition, different MMNs for the different deviant types might reflect feature-specific neural processes of pre-attentive auditory discrimination.

Novelty P3 response, elicited by novel sounds embedded in the multi-feature paradigm, was a robust significantly elicited response in toddlers. Its magnitude, timing, and frontocentral amplitude distribution are in line with previous studies in 2-year-old children (Kushnerenko *et al.* 2002, Putkinen *et al.* 2012). Thus, it is possible to study the shifting of attention at the same time as sound encoding and pre-attentive auditory discrimination by using the multi-feature paradigm with novel sounds.

6.2 Developmental changes in event-related potentials

The developmental changes in ERPs were evident from 2 to 4 years of age thus reflecting the maturation of CAP and the central nervous system. The timing, magnitude, and amplitude distribution of ERPs changed as hypothesized.

6.2.1 Developmental changes in obligatory responses

The latencies of P1 and N2 responses altered developmentally, but the latency of N4 response showed no significant change from 2 to 4 years. The latency of P1, suggested to reflect basic sound encoding (Čeponienė *et al.* 2002, 2005), decreased as was assumed based on its role as a biomarker of auditory pathway maturation (Sharma *et al.* 1997, 2002) and earlier child studies (Jing & Benasich 2006, Paquette *et al.* 2015, Ponton *et al.* 2000). This might reflect maturational increment in neural processing capacity which enables faster processing. The N2 latency, proposed to index sound encoding (Čeponienė *et al.* 2005) together with memory representation forming for sounds (Anderson *et al.* 2010, Choudhury & Benasich 2011), also decreased as was assumed based on previous findings (Choudhury & Benasich 2011, Jing & Benasich 2006, Paquette *et al.* 2015, Sharma *et al.* 1997). Similar to P1 latency, this might reflect maturational changes in the neural processing yielding faster processing. The N4 latency also decreased, but the change was not statistically significant. Because of the lack of previous studies addressing developmental trajectories of N4 response elicited by syllables, further studies are needed to clarify the maturational changes of N4 timing. Overall, these results suggest that maturation alters the timing of sound encoding and memory representation forming as well as enables a faster CAP. This might be caused by increased myelination, synaptic efficiency, and number of neural connections between the ages of 2 and 4 years (Eggermont *et al.* 1988, Ponton *et al.* 2000). All of these changes might improve and speed up neural processing capacity thus yielding faster CAP.

Also the amplitudes of P1, N2, and N4 changed from 2 to 4 years. However, the developmental trajectories were different between the responses. The amplitude of P1 was developmentally stable, as reported previously in infants and children (from 3 to 36 months, Paquette *et al.* 2015; from 6 to 48 months, Choudhury & Benasich 2011; from 4 to 9 years, Čeponienė *et al.* 2002). Thus, the neural workload eliciting P1 might be similar between the ages of 2 and 4 years even though there are maturational changes in central nervous system at that time.

In the current study, the amplitude of N2 for syllable stimuli increased developmentally from 2 to 4 years. Previously the amplitude of N2 for vowel stimuli was shown to be stable from infancy to 7 years of age (Shafer *et al.* 2015). On the other hand, the amplitude of N2 for tone stimuli was suggested to diminish developmentally from 9 to 24 months (Jing & Benasich 2006) and from 4 years to adulthood (Čeponienė *et al.* 2002) by which it vanish. Based on current and previous studies, it might be suggested that developmental increment of N2 amplitude might reflect increased neural activity used for syllable processing (Choudhury & Benasich 2011). In addition, this variation in N2 amplitude changes between studies suggests that the developmental trajectories of N2 might differ between different stimulus types. Similarly to N2, the amplitude of N4 increased developmentally from 2 to 4 years of age. There is a lack of studies on this component, thus future studies are needed to form a more complete picture of its developmental trajectory. Overall, the amplitude changes in our study might be triggered by developmental changes in underlying synaptic density and function (Choudhury & Benasich 2011).

The amplitude distributions of P1, N2, and N4 also changed from 2 to 4 years. All of them increased frontally during development as previously reported by Ponton *et al.* (2000). This change might indicate maturational changes, altered synaptic or intra-cortical activity (Ponton *et al.* 2000) or possible orientation shift (Rosburg *et al.* 2004), in the neural activity of the frontal ERP generators.

6.2.2 Developmental changes in mismatch negativity

There were no developmental changes in the timing of MMN, but the magnitude and voltage distribution of MMN changed. From 2 to 4 years, the latencies of MMNs decreased, but the difference between ages was not statistically significant (see also Glass *et al.* 2008). Thus, it might be suggested that the developmental changes from 2 to 4 years of age in neural structures and function did not influence the timing of auditory discrimination in the current study, even though the timing of P1 and N2 altered developmentally.

The MMN amplitudes increased developmentally from 2 to 4 years. In accordance with this, Paquette *et al.* (2015) have reported similar developmental trajectories in MMNs for syllable stimuli from 12 to 36 months. These results differ from those found for MMNs elicited by tone stimuli, which were reported to decrease from 6 to 48 months (Choudhury & Benasich 2011) and from 12 to 36 months (Jing & Benasich 2006). The finding of developmentally enhancing

MMN amplitudes for speech sound changes might reflect improved discrimination accuracy of these sounds from 2 to 4 years of age since increased MMN amplitudes were suggested to reflect enhanced auditory discrimination (Kujala & Näätänen, 2010; Partanen *et al.* 2013c). In addition, this result might be based also on a strengthening of the memory traces for speech sounds from the age of 2 to 4 years.

Similarly to the obligatory responses, the MMN amplitude distributions changed developmentally. From 2 to 4 years, the MMN amplitude increased and the increment was largest at frontal regions. Previously, the developmental change of the frontal MMN component has not been reported at this age. However, this change might reflect the maturation of frontal components, caused by changes in synaptic or intra-cortical activity (Ponton *et al.* 2000) or possible orientation shift of temporal MMN components (Rosburg *et al.* 2004).

6.3 Noise-induced changes in event-related potentials

The noise-induced changes in ERPs were evident at the ages of 2 and 4 years. The latencies of the responses were to a large extent similar in noise and silence, but the amplitudes and amplitude distributions of both obligatory responses and MMNs were changed by noise. However, there were no major differences in the influence of noise on the responses between age groups.

6.3.1 Noise-induced changes in obligatory responses

Noise had no effects on the latency of P1 and N2 responses, suggesting no influence of noise on the processing speed of early phases of speech sound encoding and formation of memory representations. In contrast, the latency of N4 was diminished during noise. N4 is suggested to reflect higher-order processing (Čeponienė *et al.* 2005). However, due to the lack of knowledge on the functional role of N4, the whole functional meaning of this change is unclear. Altogether, the noise-induced changes on the timing of obligatory responses were similar at both ages.

All obligatory responses showed response-specific amplitude changes during noise. The P1 amplitude decreased during noise, as was previously reported by Anderson *et al.* (2010). This amplitude decrement might reflect degraded speech sound encoding during noise (Anderson *et al.* 2010). Acoustically, this might be caused by mixing of stimulus sounds and noise in the listening situation. Opposite to P1, the N2 amplitude increased during noise. Thus, more neural resources might be allocated for memory representation forming in noisy than in silent condition (Anderson *et al.* 2010). In addition, there were no noise-induced N4 amplitude changes, which might suggest that noise does not influence high-order processing. All the noise-induced amplitude changes were similar between the ages.

The amplitude distribution of obligatory responses showed also noise-induced changes. The P1 amplitude decreased (Study II and Study III) and the N2 amplitude increased the most frontally (Study III), but fronto-centrally in Study II. The N4 amplitude followed the same pattern with the frontal amplitude change during noise. Possibly, the frontal ERP generators, previously connected to attentional processes (Escera 2000, Rinne et al 2000), are more affected by noise than the generators in the sensory areas.

Opposite to the hypotheses, the noise-induced changes on obligatory responses were similar at the ages of 2 and 4 years. This might indicate that at the neural level 2- and 4-year-old children are equally vulnerable to the hampering effects of noise. Thus, it might be that maturation and developed language skills do not seem to compensate the detrimental effects of noise on sound encoding and memory representation forming.

6.3.2 Noise-induced changes in mismatch negativity

There were no noise-induced changes on latencies of MMNs in children, suggesting no noise influence on timing of auditory discrimination of speech sound features in children, as reported previously in adults (Kozou *et al.* 2005, see, however, contradictory results also reported by Kozou *et al.* 2005, Martin *et al.* 1999, Muller-Gass *et al.* 2001). MMNs were overall diminished during noise with no differences between the age groups, consistent with previously reported results on adults (Kozou *et al.* 2005, Martin *et al.* 1999, Muller-Gass *et al.* 2001). Thus, pre-attentive auditory discrimination becomes poorer during noise. This might have implications for language acquisition, as the auditory discrimination is an essential for it (Kuhl et al 2008, Saffran 2003) in typically developing children and especially in children with language problems (Vance & Martindale 2012, Ziegler *et al.* 2011).

When addressing amplitudes of each MMN response separately, the differences in the effects of noise between deviant types were clear. In 2-year-old children (Study II), only MNNs elicited by the consonant, frequency, and vowel duration deviants were significant during noise. However, noise decreased the amplitudes of these responses. In the follow-up (Study III), only the MMN elicited by the consonant change was significant in 2-year-old children. At the age of 4 years, in addition to MMN elicited by consonant change, also the MMN to vowel duration change showed significant response. All the other deviants did not elicited significant MMNs. Surprisingly, the amplitude of MMN for consonant change showed no noise-induced changes in the follow-up (Study III), unlike for the MMN to vowel change which diminished during noise. This finding was recently replicated in adults by Koerner *et al.* (2016), showing a more degraded MMN to vowel change than to consonant change in noisy conditions. The MMNs to intensity and vowel changes were not significant in noise in neither age group. Thus, the children's ability to discriminate speech sound features during noise alters and some speech sound changes are more vulnerable to noise than the others. This might have implications for learning of different aspects of language, from phonological to prosodic features, in noisy conditions in typically developing children and especially in children with language problems (Vance & Martindale 2012, Ziegler *et al.* 2011). However, these findings require further investigation in order to understand deeply the differences in the processing of vowels and consonant as well as the effect of noise on it.

While comparing the effects of noise at the ages of 2 and 4 years (Study III), the only difference found between the ages was significant MMN for vowel duration change at the age of 4 years compared to non-significant MMN response in 2-year-old children. All the other effects of noise were similar between the ages. Thus, opposite to our hypothesis, 4-year-old children were almost as vulnerable to the hampering effects of noise as they were at the age of 2 years. However, this result might also be due to the relatively small participant group in a follow-up, 14 children, which is further discussed later in chapter 6.4.

Also MMN amplitude distribution was changed by noise at the age of 2 years (Study II). Noise-induced MMN amplitude decrement was largest at frontal electrode locations. However, in the follow-up the MMN elicited by the vowel duration change showed an opposite tendency being frontally maximal during noise. Thus, the role of neural MMN generators might alter during noise, which is consistent with findings of Shtyrov *et al.* (1998) showing altered MMN in noisy conditions.

6.4 Methodological challenges and limitations

In order to evaluate methodological challenges and limitations of this study, the questions addressing participants and nature of research methods needs to be addressed. In the studies of this thesis, the number of participants was relatively small, especially in the follow-up (Study III). This might have hindered statistically significant findings concerning the possible influence of age on the effects of noise on CAP. However, the participants were their own references in the comparisons of the results between conditions and ages, which increased the statistical power of the results. In addition, the inter-subject variability was controlled by limiting the age range of the participants in order to avoid extensive developmental inter-subject variability and by selecting participants that have had a maximum of two episodes of acute otitis media, which was shown to alter CAP (Haapala *et al.* 2014). Another issue regarding participants is the participant recruitment, which was based on parents' voluntary participation. Thus, it is not guaranteed that the participant group evenly represents the entire diversity of the child population in Finland.

While the choice to use ERPs in the thesis studies has notable benefits, such as temporal accuracy, non-invasiveness, and suitability for child studies, ERPs have also limitations (Luck 2005). Well-known fact is that the spatial accuracy of ERPs is weak. Therefore, the result concerning spatial distribution of ERPs must be interpreted with caution. In addition, the stimuli were presented in a free field with loudspeakers. Thus, due to head movements, the stimuli might have variably entered to the child's ears during the EEG recordings, which could have influenced the lateralization of the responses. In addition, the ERP-analysis is based on averaging over several stimuli, trials and participants, which prevents the utilization of single participant data reliably.

In the statistical analysis, ANOVA includes repetitive t-tests, which might cause biased results. This issue was recognized and avoided by testing the sphericity of the data and by using Huynh-Felt or Greenhouse-Geisser correction, if necessary.

6.5 Clinical implications

The outcomes of this thesis have clear clinical implications. The feasibility of speech-resembling multi-feature paradigm promotes its utilization in studies addressing CAP in typically developing children and in clinical patient groups.

Also, the results from developmental trajectories of ERPs between ages of 2 and 4 years, which is an important period in language development, fills the gap in the understanding of typical development of CAP in children.

The results of this thesis together with previous studies confirm that noise in children's daily environments is not only uncomfortable , but has severe effects at the cognitive level, especially in speech processing. In young children, the plasticity of the brain is high and the auditory input has great impact on the CAP (Benasich *et al.* 2014). For that reason, the noise levels in children's environments should be decreased. This could be achieved by taking care of acoustical and pedagogical issues when planning or renovating buildings. The activity noise level can also be controlled by reducing the number of children in the groups (Shield & Dockrell 2004). For example, total number of the children could be limited or the teacher could divide the child group to smaller sub-groups. In addition, the children themselves can be informed about noise and its negative effects and guided to restrain their produced sound pressure level.

The results showed different effects of noise on different speech sound changes (Study II and Study III). Surprisingly, MMN to the consonant change was resistant tolerant to noise, while MMN to the vowel change was not present during noise. As Koernert *et al.* (2016), replicating findings of Study II and Study III, proposes, this issue should be taken into account by hearing aid manufacturers when fine tuning the speech-in-noise-settings of hearing aids.

The negative impact of noise on CAP, evident in typically developing children in the current thesis, might be even more pronounced in children with language and learning problems (Cunningham *et al.* 2011, Vance & Martindale 2012, Ziegler *et al.* 2011). Therefore, the results of this thesis promote the importance of the awareness of daily auditory environments of such children. In the speech and language therapy, evaluation of daily auditory environments should be an essential part of environmental assessment with all patients, not only with children with hearing problems. For logopedical intervention, the reduction of noise levels and time spent in noisy spaces should also be an essential part of intervention for all patients.

6.6 Future research

The data collected during studies I, II, and III also constitutes a source for future research in addition to utilization in this thesis. Also, the current findings bring up new study-questions. Because of the deleterious effects of noise to CAP, the most important question that has arisen is: What are the most effective and economical means to decrease the activity noise in the children's daily environment? Even though there are attempts to cut down noise levels in class rooms (Norlander *et al.* 2005), the strategies need to be re-evaluated to fit in the lives of toddlers and young children.

Novelty P3 was addressed only in Study I, because this thesis focuses on sound encoding and auditory discrimination. It was reported only in the silent condition in the 2-years-old children. In the future, the developmental trajectory and the influence of noise on novelty P3 are also worth of investigating in order to understand effects of noise and maturation on attention shifting in typically developing young children.

In addition, the current data offers possibilities to investigate responses other than those reported here. Among these are early differentiating negativity (EDN; Kuuluvainen *et al.* 2016), late discriminative negativity (LDN; Korpilahti *et al.* 1995), and re-orientation negativity (RON, Schröger & Wolf 1998). However, because this PhD thesis was focused to obligatory responses and MMN, those responses are not yet reported. In addition, EEG time/frequency analysis would provide more insight to the data of this thesis. In the future EDN, LDN, and RON should be studied and different analysis methods considered in order to facilitate our understanding of different stages of CAP.

The current data were collected in co-operation with a project investigating effects of ear infections on CAP (Haapala *et al.* 2014, 2016). In the future it would be interesting to study the effects of noise on CAP in children with a history of ear infections, which was shown to have long-term consequences on CAP. Are those children even more vulnerable to the negative effects of noise than children with no ear infection history in early childhood?

In addition, this follow-up study should be continued onward in order to provide wider developmental profiles of CAP in the same participants. Also the effects of noise on CAP could be addressed in developmental context from toddlers to school-aged children.

7 Conclusion

This thesis provides new information on the feasibility of the multi-feature paradigm, developmental changes on ERP morphology, and effects of noise on CAP in children. Based on the results of the study, it can be concluded that:

- The multi-feature paradigm with syllable stimuli and novel sounds is a feasible and time-efficient means to study sound encoding and workload needed for memory representation forming as well as pre-attentive auditory discrimination of several speech sound features and attention shifting processes reflected by ERPs in toddlers.
- The deviant-type specific MMN characteristics might reflect different underlying neural processes of pre-attentive auditory discrimination for different sound changes.
- The developmental changes in the timing, magnitude, and amplitude distribution of ERPs suggest maturational changes in the timing and neural mechanisms of CAP.
- Even mild background noise hinders sound encoding, increases the neural workload needed for memory representation forming, and degrades auditory discrimination, all essential for language development, at the ages of 2 and 4 years.
- The auditory discrimination of some speech sound changes is more vulnerable to noise than the others.

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Original publications

I Niemitalo-Haapola, E., Lapinlampi, S., Kujala, T., Alku, P., Kujala, T., Suominen, K., & Jansson-Verkasalo, E. (2013). Linguistic multi-feature paradigm as an eligible measure of central auditory processing and novelty detection in 2-year-old children. Cognitive Neuroscience, 4, 99–106.

II Niemitalo-Haapola, E., Haapala, S., Jansson-Verkasalo, E., & Kujala, T. (2015). Background noise degrades central auditory processing in toddlers. Ear & Hearing, 36, 342–351.

III Niemitalo-Haapola, E., Haapala, S., Kujala, T., Raappana, A., Kujala., T., & Jansson-Verkasalo, E. (2017). Noise equally degrades central auditory processing in 2- and 4-year-old children. Accepted for publication in Journal of Speech, Language, and Hearing Research. https://doi.org/10.1044/2017_JSLHR-H-16-0267

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