

# Early maturation of neural auditory novelty detection – Typical development with no major effects of dyslexia risk or music intervention



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## HIGHLIGHTS

- Novel sounds elicited novelty-P3 at ages of 0, 6, and 28 months, and late discriminative negativity (LDN) at 6 and 28 months.
- Novelty-P3 was largest at 6 months and its latency decreased by age, and LDN amplitude decreased and latency increased by age.
- Familial dyslexia risk or a passive music listening intervention in infancy had no major effects on the responses.

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## ABSTRACT

**Objective:** To determine the early development of novelty detection and the effect of familial dyslexia risk and infant music intervention on this development.

**Methods:** In the longitudinal DyslexiaBaby study, we investigated the maturation of novelty-P3 and late-discriminative negativity (LDN) event-related potentials to novel sounds at birth (N = 177) and at the ages of 6 (N = 83) and 28 months (N = 131).

**Results:** Novelty-P3 was elicited at all ages, whereas LDN was elicited at 6 and 28 months. Novelty-P3 amplitude was largest at 6 months, and its latency decreased with age. LDN amplitude decreased and latency increased between 6 to 28 months. Dyslexia risk or intervention had no effects, apart from a longer LDN latency in the high-risk than no-risk group.

**Conclusions:** Already neonates respond to novel environmental sounds, indicating prerequisites for detecting potentially relevant events at birth. Maturation influences neural novelty detection.

**Significance:** Novelty detection is crucial for perceiving important events, but its early development has been scarcely studied. We found, with a large sample, that neonates detect novel events, and showed the developmental pattern of its neural signature. The results serve as a reference for studies on typical and atypical novelty-detection development in infancy when behavioral testing is challenging.

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## 1. Introduction

The ability to detect novel events in the environment is crucial for survival and for adequately reacting to potentially important environmental occurrences. The orienting response (Sokolov et al., 2002) includes covert and overt responses related to searching for new information and preferentially processing it. Sounds that markedly differ from the preceding ones are likely to induce

the orienting response, since they often signal the appearance of a new object in the nearby environment or the occurrence of a significant event which could have relevance for survival. Orienting towards stimuli which are potentially biologically significant is the ontogenetically earliest expression of attention (Gomes et al., 2000; Kushnerenko et al., 2013). In early childhood, this ability also forms an important basis for learning, since it enables the detection and selection of relevant information from the environment. Despite its relevance, the early development of orienting or novelty detection has been scarcely studied.

Knowing how neural responses associated with novelty detection typically mature would promote their use as predictive markers of the development of attention shifting and its disorders.

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The neural basis of novelty detection can be studied with event-related potentials (ERP) since early infancy. In adults, novel sounds elicit an ERP complex including a negativity composed of N1 and mismatch negativity (MMN), followed by a positivity termed P3a or “novelty-P3”, and then, during certain experimental conditions, a reorienting negativity (RON; Escera & Corral, 2007; Barry et al., 2020). Whereas the MMN is associated with deviance detection and discrimination (Näätänen et al., 1987, 2019) and RON with re-orientation back to the primary task after the distraction (Escera et al., 2001), the novelty-P3 reflects the actual attention switch towards a potentially relevant event and its further evaluation (Friedman et al., 2001; Escera and Corral, 2007, for reviews). It is larger for widely-deviating distracting stimuli than for smaller deviances in both children and adults (Wetzel et al., 2006) and atypically strong in individuals with attention deficit and hyperactivity disorder (ADHD), reflecting an increased distractibility (e.g., Godefroid and Wiersema, 2017).

ERPs to auditory novelty have been scarcely studied in infancy and early childhood, and particularly longitudinal studies are rare (see, however, Katus et al. 2020, 2023). Both electroencephalography (EEG) and magnetoencephalography (MEG) recordings have shown that novel sounds occurring in sequences of repetitive sounds elicit a distinct response as early as at birth (Sambeth et al., 2006; Kushnerenko et al., 2002, 2007; Håden et al., 2013). These neonatal novelty-P3 responses have commenced in EEG recordings between 200–400 (Kushnerenko et al., 2007; Håden et al., 2013), and in the MEG recording as two peaks at 345 and 615 ms (Sambeth et al., 2006).

Cross-sectional studies on novelty-P3 in infancy suggest that it is still a broad and large response at the ages of 7 (Sandre et al. 2021) and 9 months (Marshall et al. 2009). Environmental novel-sound responses with a positive polarity were found to have a more frontal scalp distribution in 4- compared to 2-month-olds (van den Heuvel et al. 2015; see also Otte et al., 2013). Consistent with this, a neonatal positivity was found to have a centro-parietal scalp distribution (Håden et al., 2013), whereas older infants in other studies had a fronto-central novelty-P3 (Marshall et al. 2009; Sandre et al. 2021).

Some studies have reported also a negativity following the novelty-P3 already in newborns, here termed late discriminative negativity (LDN, also referred to as late negativity, LN, or negative component, Nc, see e.g., Kushnerenko et al., 2002, 2007). In line with the RON in adults, the LDN was suggested to reflect the infant’s ability to re-orient attention to the previous context after distraction/attention switching caused by a deviating stimulus (Kushnerenko et al., 2013). However, as most infant studies have not reported LDN-like responses to novel sounds, it is possible that this response is reliably elicited only later in development, e.g., at 2–3-years (Niemitalo-Haapola et al. 2013; Putkinen et al. 2012).

Recent studies from the BRIGHT project report, to the authors’ knowledge, the first longitudinal results on novelty-P3 maturation in infancy (Katus et al. 2020, 2023). The novelty-P3s and the following negativities (termed Nc) to novel sounds (termed “trial unique sounds”) grew in amplitude and decreased in latency between 1 and 5 months in infants in a developed country (United Kingdom; Katus et al. 2020), whereas no evidence of age-related changes was found in a developing country (Gambia), presumably due to environmental factors according to the authors (Katus et al. 2023).

The main aim of the current study was to longitudinally follow up responses elicited by novel sounds from birth to 6 and 28 months of age in a large group of children (data of 90–190 included depending on recording age) of the DyslexiaBaby research project (described in, e.g., Virtala et al. 2022). In this sample, 3/4 of the children have a familial risk for developmental dyslexia, which enabled us to additionally inspect the effect of dyslexia risk on the novelty responses and their maturation. Dyslexia is a heritable

reading-skill acquisition disorder, which is primarily thought to originate from a phonological deficit, including deficient phoneme representations and/or their poor access (Peterson & Pennington, 2015; Snowling and Melby-Lervåg, 2016; Ramus and Szenkowitz, 2008). Our previous studies on this sample investigating change-detection responses showed altered mismatch responses (MMR, small children’s counterpart of the MMN-P3-LDN response chain to changes in speech sounds) in the dyslexia risk group, suggesting phonological deficits (Virtala et al. 2022).

Besides phonological deficits and a range of other perceptual dysfunctions (Ramus, 2003), dyslexia is associated with attentional problems, and it is co-morbid with ADHD (Boada et al., 2012). For example, dyslexic individuals have a limited attentional capacity (e.g., visual attentional blink), they are slower than normal in shifting attention between sounds, and their attention disengages slowly (Hari and Renvall, 2001, for a review). A study including a dyslexic group without co-morbid ADHD found prolonged visual attentional blink time and deficits in processing dual targets and rapidly changing visual displays in this group (Laasonen et al., 2012). This suggests that attention deficits are associated with dyslexia even when the contribution of co-morbid ADHD is excluded.

Even though novelty-P3 can serve as a neural marker of impaired attention shifting or distractibility, very few studies have utilized this response for detecting possible attention deficits in dyslexia, and they have yielded contradicting results. One of them found an early component of the novelty-P3 and a negativity following it to be enhanced in dyslexic adults when stimuli were attended but not when they were ignored, interpreted as increased distractibility in dyslexia (Rüsseler et al., 2002). Another one, conducted in 8–12-year-old children, found diminished P3s to an occasional surprising (but not a novel, since the stimulus was repeated) sound in dyslexic participants (Holcomb et al., 1986).

The authors are aware of no previous studies of auditory novelty detection or distractibility in infants and small children at dyslexia risk. If attention switches towards environmental events too easily, it can distract the child from keeping focus on the primary task, impairing, for example, learning. If this type of a deficit is associated with dyslexia, it can be an additional challenge in learning besides reading difficulties. In the current study we investigated whether dyslexia risk is associated with novelty detection or distractibility in a sample in which we have minimized the comorbidity of ADHD by excluding children whose parents have ADHD in addition to dyslexia.

In addition, we could investigate the effect of a passive music listening intervention on attention shifting since in the DyslexiaBaby sample, 2/3 of the children at dyslexia risk participated in an intervention study determining whether language development can be supported with songs presented in infancy (Virtala et al. 2023). In these children, our results have so far shown that vocal music listening enhanced MMRs to phoneme changes (Virtala et al., 2023), consistent with previous studies showing beneficial effects of music on language development (Kraus & Chandrasekaran, 2010; Virtala & Partanen, 2018). In addition to language skills, previous studies have shown some beneficial effects of music on attention functions (Koshimori and Thaut, 2019, for a review). To our knowledge, ERP studies on these effects are largely lacking. However, in 2–3 year-old children, a higher amount of music activities at home was found to be associated with a smaller LDN to novel sounds, and a higher amount of parental singing to children was associated with a smaller novelty-P3 (Putkinen et al., 2013). These findings were interpreted as lower distractibility and more mature sound processing as a result of parental singing and music activities.

In the present study, we analyzed the emergence and maturation of the novelty-P3 and LDN responses elicited by rare novel sounds in a non-attended speech sound stream in the

DyslexiaBaby sample, and also compared the four subgroups (no dyslexia risk, dyslexia risk without intervention, dyslexia risk groups with a vocal/an instrumental music intervention from birth to 6 months). Based on the above-reviewed previous studies, we expected to find a novelty-P3 already in newborns, with possibly increasing amplitudes with age, while the emergence of the LDN was expected at least by 28 months. The scalp distributions of these responses were expected to shift towards frontal scalp areas with increasing age. Due to the scarce evidence of abnormalities in novelty-ERPs in dyslexia, we could not formulate a firm hypothesis on the group differences in novelty-P3s and LDNs. Music interventions and at-home musical activities including parental singing have shown some positive effects on attention as reviewed above. Possibly particularly the vocal intervention resembling parental singing might improve auditory attention as reflected in novelty-P3 and/or LDN amplitudes or latencies. However, since the intervention was passive, it is also possible that it has no influence on these attention-related responses.

**2. Methods**

*2.1. Participants*

Altogether 210 newborns were recruited to this longitudinal study during the mother’s pregnancy or approximately at the time of birth via social media advertisements and traditional media appearances, maternity wards and clinics, and via DyslexiaBaby study website (see Table 1 for sample sizes and background information). The recruitment was mainly targeted to dyslexic parents (target-N = 150), with non-dyslexic parents (target-N = 50) also being recruited. Only newborns at term were enrolled (gestational age at least 37 weeks and birth weight at least 2500 g), and they had to be healthy and have normal hearing. Evoked Oto-Acoustic

Emission (EOAE) test was routinely conducted at the hospital. EOAE was missing in two infants, but hearing was found to be normal when screened later in a maternity clinic. Finnish was required to be one of the native languages.

The parents in the control group with no dyslexia risk (one parent, if the other one was not available) had to report no suspected or diagnosed dyslexia and no other learning- or language-related disorders. Infants in the group at risk for dyslexia had to have one or two biological parents with dyslexia, which was confirmed by a health care professional’s diagnostic statement within five years. If it was missing, dyslexia was confirmed by a reading test in the current study, together with self-reported difficulties in reading and writing in childhood. A Finnish standardized reading test measuring the speed and accuracy of orally reading words, pseudo-words, and text, and writing speed, was used (Nevala et al., 2006). Criteria for dyslexia were performance of at minimum one standard deviation (SD) below-norm in reading or writing accuracy or speed in at least two out of four of the subtests. Some of the parents not entirely met the criteria but in case they reported evident childhood reading and writing difficulties and dyslexia in biological relatives, they were included as compensated dyslexics.

Infants with a parent with the following conditions were excluded: developmental language disorder but no dyslexia, diagnosed attention deficit disorder, an individualized curriculum in the elementary school, or indication of a non-heritable cause for the dyslexia (e.g., brain trauma; Fig. 1 “Parental diagnosis”). Infants with very severe illnesses affecting language development and the nervous system were excluded (e.g. severe dysmorphias, chromosomal abnormalities, Rolandic epilepsy, brain tumors; Fig. 1 “Child’s later diagnosis”). Additionally, problems related to measurement scheduling or data quality (Fig. 1) resulted in data exclusion of certain participants from that measurement point, and 5

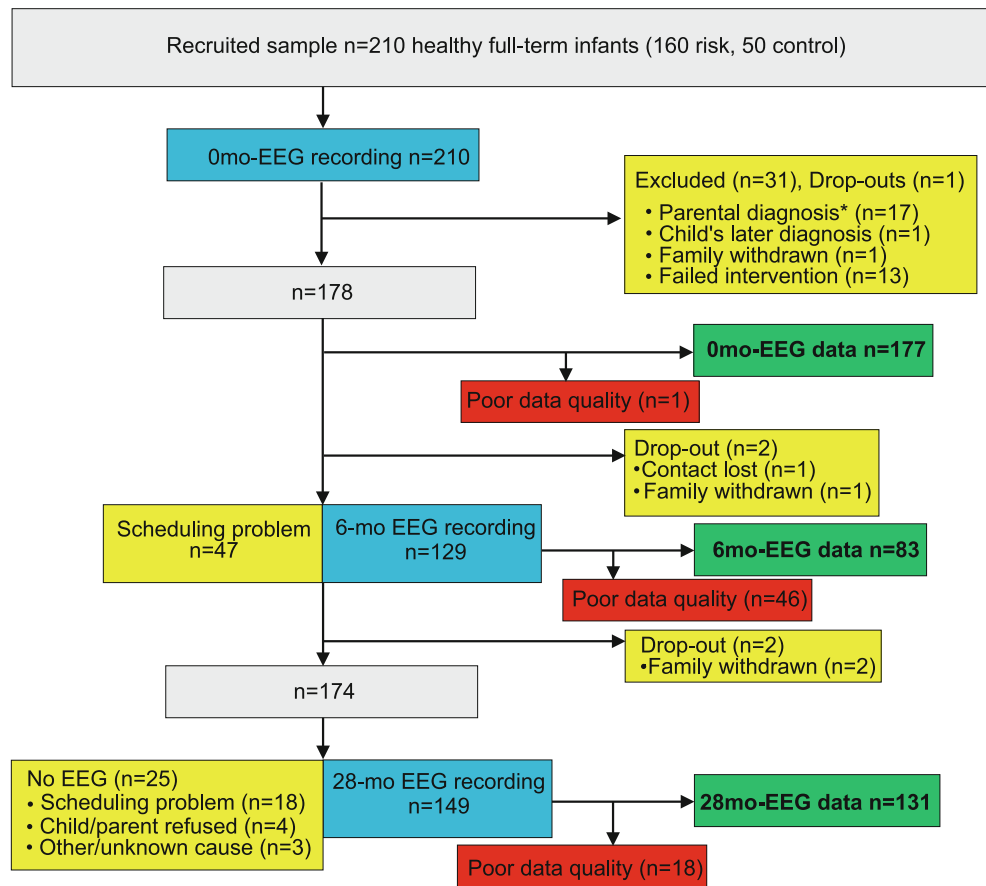
**Table 1**  
Sample sizes and background information in controls (con), risk group without intervention (no-int), and risk groups with the vocal (int1) or instrumental music listening intervention (int2) at birth, 6 months, and 28 months: sample sizes; gender distributions; parental education (edu); recording age; and birth-related information (unit specified). SD in parentheses refers to standard deviation. Parents in the high/low edu groups had/did not have higher education (tertiary education resulting in an academic degree).

	Birth			
	con	no-int	int1	int2
con/dyslexia risk	46/0	0/53	0/38	0/40
con/no-int/int1/int2	46/0/0/0	0/53/0/0	0/0/38/0	0/0/0/40
female/male	20/26	23/30	16/22	34/6
high/low edu	36/9	48/5	29/9	21/19
age, days (SD)	8.9 (5.2)	9.1 (3.9)	9.6 (3.8)	9.5 (3.5)
birth weight, g (SD)	3553.6 (533.0)	3581.3 (397.3)	3619.7 (418.3)	3587.2 (471.8)
birth height, cm (SD)	50.9 (2.2)	50.6 (1.7)	50.9 (1.8)	50.5 (2.3)
gestational age, w (SD)	40.1 (1.1)	40.1 (0.9)	40.2 (0.9)	40.0 (1.2)
last Apgar score (5/10 min)	9.5 (0.6)	9.5 (0.7)	9.5 (0.8)	9.4 (0.6)
6 months				
con/dyslexia risk	19/0	0/20	0/18	0/26
con/no-int/int1/int2	19/0/0/0	0/20/0/0	0/0/18/0	0/0/0/26
female/male	10/9	8/12	5/13	14/12
high/low edu	17/2	18/2	15/3	23/3
age, months (SD)	6.1 (0.3)	6.1 (0.3)	6.1 (0.3)	6.1 (0.4)
28 months				
con/dyslexia risk	32/0	0/39	0/27	0/33
con/no-int/int1/int2	32/0/0/0	0/39/0/0	0/0/27/0	0/0/0/33
female/male	14/18	19/20	10/17	18/15
high/low edu	29/3	36/3	24/3	27/6
age, months (SD)	28.3 (0.4)	28.1 (0.4)	28.1 (0.5)	28.1 (0.4)

Note 1. Two infants (from int1 and no-int groups), had an Apgar score of only 6, but they were in good health at the EEG recording at birth (age 13 d). The Apgar score was missing in two infants (from int2 and no-int groups), but there were no indications of health issues at the EEG recording at birth (7–8 d). Edu information was missing from one infant in the con group.

Note 2. Different data from partly these same infants have been published in Thiede et al. 2019; Kailaheimo-Lönnqvist et al. 2020; Virtala et al. 2022; Virtala et al. 2023; and Virtala, Kujala et al. 2023.

Note 3. Measurement age, gestational age, Apgar score, or birth weight and height did not statistically significantly differ between the four groups in One-way ANOVAs (in all  $p > 0.20$ , except for measurement age at 28 months,  $p = 0.07$ ). Gender distribution and the amount of high/low education among parents did not statistically significantly differ between the four groups in Pearson Chi-square tests (in all  $p > 0.20$ ).



**Fig. 1.** A flowchart describing the steps of participant selection including drop-outs and exclusions in the electroencephalogram (EEG) data at birth (0mo), six months (6mo), and 28 months (28mo). Blue boxes indicate the sample sizes participating in the EEG recordings at the three ages, and red and yellow boxes indicate the sample sizes for missing/excluded data due to poor data quality and other reasons (as specified in the figure), respectively. The final sample sizes used in the statistical analysis are presented in the green boxes and highlighted in bold. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.) Adapted from Virtala et al. (2022).

dropped out during this follow-up (Fig. 1 “Family withdrawn”, “Contact lost”). Thirteen additional children were excluded from the present study because they participated in a music intervention study at 0–6 months and failed to follow through with the intervention (for intervention details, see Virtala & Partanen, 2018; Virtala et al. 2023).

All children with an acceptable quality of EEG data recorded at least at one measurement point were included (Table 1). Of these 177 children of the final sample,  $N = 46$  were no-risk control children while  $N = 131$  were at familial dyslexia risk, of whom 78 participated in a vocal (int1) or an instrumental music listening intervention (int2) while 53 did not receive an intervention (no-int in Table 1).

This study, which belongs to the longitudinal DyslexiaBaby study, was approved by the Ethics Committee for Gynaecology and Obstetrics, Pediatrics and Psychiatry of the Hospital District of Helsinki and Uusimaa. The study was conducted according to the Declaration of Helsinki. A written informed consent was obtained from the infant’s parent or both parents in the first EEG recording session.

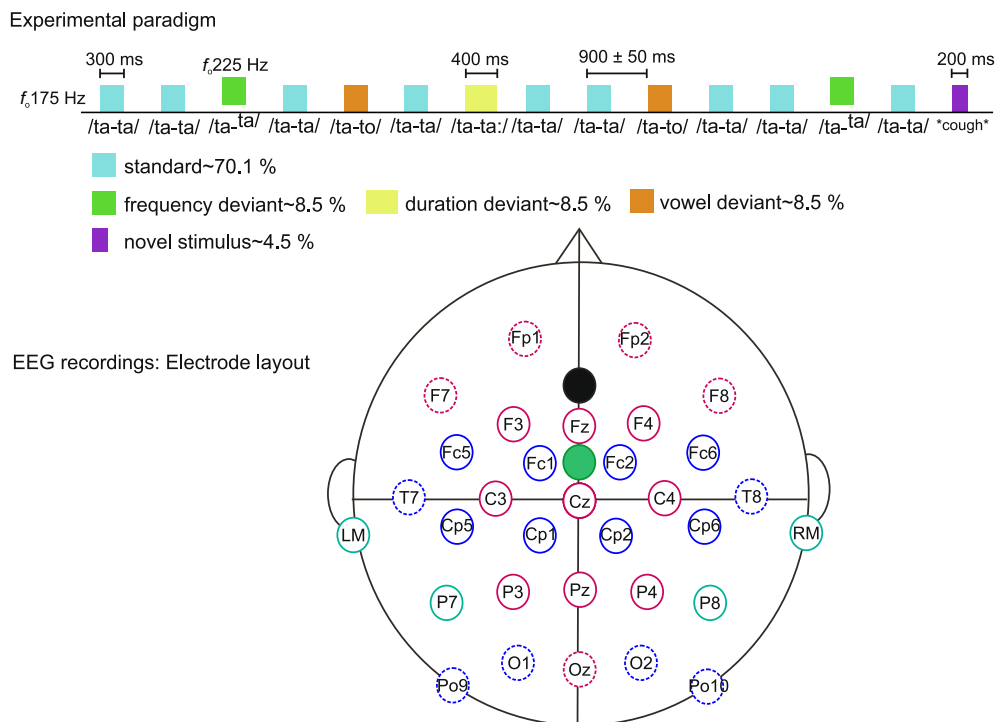
## 2.2. Experimental stimuli and paradigm

ERPs were recorded to occasionally presented novel sounds in a multi-feature oddball paradigm consisting of pseudo-words (for a more detailed description, see, e.g., Thiede et al., 2019). The novel sounds were of human and non-human origin (e.g., laugh, cry and

e.g., electric drill, telephone ring, respectively; 50 % each) and 200 ms long, including 10-ms rise- and fall-times. These 46 novel sounds were first used by Sorokin et al. (2010), where a detailed description of the novel stimulus selection and production can be found.

The /tata/ pseudo-word had a duration of 300 ms and was uttered by a native Finnish female speaker, with the stress on the first syllable conforming to Finnish, the native language of the participants (Pakarinen et al., 2014; Fig. 2). There were three auditory variants of the /tata/ pseudoword: 1) a vowel-duration deviant (second /a/ 158 ms instead of 71 ms), in which the total duration was 400 ms, 2) a frequency deviant, where the  $f_0$  of the second syllable was shifted 5 semitones from 175 to 225 Hz, and 3) a vowel deviant, where a naturally spoken /o/ was presented instead of /a/ in the second syllable. The average intensity level of the three variants were matched with that of the original /tata/ by root-mean-square normalization. Adobe Audition (CS6, 5.0, Build 708) and Praat (5.4.01) softwares were used in stimulus preparation.

In the stimulus sequences the /tata/ stimulus was the repeating standard (probability  $P \sim 0.71$ ), occasionally replaced by the three /tata/ variants as deviants ( $P \sim 0.085$  each) and the novel stimuli ( $P \sim 0.045$ ). The stimulus-onset asynchrony was 900 ms  $\pm$  50 ms, randomly alternating in 10-ms steps (Fig. 2). Four blocks of stimuli were presented, each including 472 stimuli (in total, 1340 standards, 160 of each deviant, and 85 novel sounds). Note that as there were a total of 46 different novel stimuli to be presented in the sequences, 39 of them were presented twice during



**Fig. 2.** Details of the paradigm and electroencephalogram (EEG) recordings. The experimental paradigm (adapted from Thiede et al. 2019) is presented on top and the electrode layout on bottom right corner. On top, the five stimulus types of the experimental paradigm are illustrated with different color squares as described, with time on the x-axis (in ms; 300 ms for all but the duration deviant and novel stimulus; with 900±/−50 ms stimulus-onset asynchrony) and fundamental frequency ( $f_0$ , in Hz; 175 Hz for all but the frequency deviant) on the y-axis. On the bottom right corner, pink circles depict the electrodes used in recordings at birth and six months and pink and blue circles at 28 months. The black and green circles illustrate the ground and active online reference electrodes; turquoise circles depict the electrodes used in re-referencing at all three ages. Dashed circles indicate peripheral electrodes not included in statistical analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the four sequences (3/39 during the same sequence and 36/39 in different sequences). The stimuli were presented otherwise randomly except that four standard stimuli started all blocks and each deviant and novel stimulus was followed by a standard stimulus. After this experiment, other EEG experiments were conducted if the child stayed calm (which will be reported elsewhere, e.g. Virtala et al. 2023).

### 2.3. EEG recordings

EEG (500 Hz sampling rate) was recorded with a BrainProducts QuickAmp amplifier (v. 10.08.14; software: BrainVision Recorder 1.20.0801, Brain Products GmbH, Gilching, Germany), sampled at 500 Hz, and low-pass filtered at 100 Hz. The average of all electrodes was used as the online reference. An electrode cap (ActiCap, Brain Products GmbH, Gilching, Germany) with 18 (at birth and 6 months) or 32 (at 28 months) electrodes placed according to the extended international 10/20 system (for details, see Fig. 2) was used. The stimuli were presented with Presentation 17.2 Software (Neurobehavioural Systems Ltd., Berkeley, CA, USA) via one (at birth and 6 months) or two (at 28 months) Genelec speakers at ~ 65 dB (sound pressure level, SPL) stimulus intensity at the participant's head. At all ages, identical protocol and equipment were used in EEG recordings, apart from age-specific procedures described below. The recordings including preparations took around 1–2 h at all ages.

*At birth.* EEG was recorded in a quiet room at Jorvi Hospital, Helsinki University Hospital, Espoo, Finland (N = 157/177 of the whole sample), or at the University of Jyväskylä, Finland, in a sound-proof laboratory (N = 20/177). Infants were lying on their back in a hospital crib, with the loudspeaker at ~ 40 cm from infant's head. The recording was conducted by a trained nurse or research assistant,

who monitored their state (using a response box, Cedrus RB844, Cedrus Corporation, California, USA, marking the state with button presses as 'active sleep', 'quiet sleep', 'awake', or 'intermediate sleep stage', based on Grigg-Damberger et al., 2007). The majority of the infants were asleep during the data collection. The ambient noise of the room at the infant's head was ~ 40 dB (SPL).

*At 6 months.* EEG was recorded at the same sites (Jorvi Hospital N = 70/83, University of Jyväskylä N = 13/83), with similar speaker placement, and intensity of ambient noise as at birth. The awake infants were sitting in the lap of the caretaker. The nurse or research assistant was entertaining the infant silently, showing mirrors, toys or making facial expressions, etc.

*At 28 months.* EEG recordings were conducted at the University of Helsinki in an electrically shielded, sound-proof laboratory (N = 128/142) and at University of Jyväskylä in the same laboratory as the recordings at birth and 6 months (N = 14/142). The awake children were sitting in a chair at 160 cm distance from the loudspeakers. The child was accompanied by a research assistant or a parent, watching a silent self-chosen cartoon during the recording. The child was requested not to move or talk and to try to ignore the stimuli presented. Time stamps related to moving or talking were registered in the continuous EEG data. They were taken into account during manual artefact rejection (see 2.4). The informed consent was obtained from the child. Prior to the laboratory visit, possible fears towards the EEG recording were minimized with an illustrated leaflet of the recording.

### 2.4. EEG data analysis

Those EEG data were excluded from the stimulus blocks which included loud voicing or crying of the child most of the time, as well as those during which the 6- or 28-month-old fell asleep. In

addition, due to technical problems, the data of one 28-month-old were excluded. These exclusions are included in Fig. 1 “poor data quality”.

Preprocessing was carried out with Matlab 2017a–2020a (The MathWorks, Inc., USA), with Toolboxes EEGLAB 14.0.0b and 2019\_0 (Delorme and Makeig, 2004) and ERPLAB 7.0.0 (Lopez-Calderon and Luck, 2014). First, EEG was filtered (0.025–40 Hz band pass) to exclude excessive artifacts and to visually identify “bad” electrodes including noisy (high-frequency, large-amplitude activity/massive drifting) signal. The maximum of five electrodes in the 0- and 6-month and six electrodes in the 28-month EEG were marked “bad”. Stimulus blocks including more noisy or flat electrodes were excluded. Bad electrodes at peripheral scalp locations (at birth and at 6 months: Fp1, Fp2, F7, F8, and Oz; at 28 months: additionally T7, T8, Po9, Po10, O1, O2, see Fig. 2) were discarded from the analysis, whereas the rest of the bad electrodes (at birth and at 6 months: F3, Fz, F4, C3, Cz, C4, P3, Pz, P4; 28 months: additionally FC5, FC1, FC2, FC6, CP5, CP2, CP3, CP6) were marked down to be later interpolated (maximum 2 per infant at birth and 6 months or 3 per child at 28 months). In the data of 28-month-olds, sections with strong muscle artifacts visually confirmed in the EEG and marked with time-stamps in the recording were manually omitted. Heart-beat and eye-movement artifacts observed in the 28-month data (at Fp1, Fp2, LM, or RM) were marked to be later removed.

Then, EEG was filtered with a 0.5–25 Hz band-pass, and re-referenced using an average reference including four electrodes at or near the mastoids (LM, RM, P7, and P8). Broken reference electrodes (a flat signal or a signal continuously  $> 250 \mu\text{V}$ ) and their contralateral pairs were eliminated, in which cases an average of the rest of the reference electrodes was used. If both left-/right-hemispheric reference electrodes were broken, the data of the corresponding stimulus block were rejected. Then, the non-peripheral electrodes that were marked down as bad were interpolated based on the signal in the remaining electrodes (spherical interpolation in ERPLAB). Heart-beat and eye-movement artifacts were corrected in the 28-month data using independent component analysis (ICA). The independent components detected with *fastica* (Hyvärinen, 1999) or, when not converging, *runica* algorithms in EEGLAB were compared with the raw-data artifact and its assumed scalp distribution to decide upon the component removal from the data. This was not done if the component removal from the data was not satisfactory based on visual inspection (e.g., the artifact was not reduced or the algorithm altered other elements of the data).

Epochs starting at 100 ms before and ending 840 ms after sound onset were extracted from the EEG, the 100-ms pre-stimulus interval being the baseline for amplitude quantifications. The following criteria were used to exclude artefact-contaminated epochs: amplitude exceeding  $\pm 120 \mu\text{V}$  at Fp1 and Fp2, epochs with a drift of  $> 100 \mu\text{V}$ , or epochs with data points  $\pm 3$  SD from the average amplitude of all epochs (EEGLAB, *jointprob* algorithm, for each electrode separately and averaged across electrodes). The remaining epochs were separately averaged for the standard and novel stimuli for each participant. Standard-stimulus epochs immediately following a novel or deviant stimulus were not included. Data of participants with less than 15 accepted epochs for novel sounds were excluded (at birth:  $N = 0$ , 6 months:  $N = 40$ , 28 months:  $N = 11$ ; included in Fig. 1 “poor data quality”).

The final total sample at the ages of 0, 6, and 28 months had on average 58 (range: 16–101), 26 (15–47), and 41 (17–67) accepted trials/infant for novel sounds. Difference curves were calculated by subtracting the response elicited by the standard stimulus from that elicited by the novel stimulus. The baseline correction was applied at  $-100$ – $0$  ms from the novel sound onset.

## 2.5. ERP quantification and statistical analysis

We employed cluster-based mass permutation tests, implemented in the Fieldtrip toolbox (Oostenveld et al., 2011; Maris & Oostenveld, 2007), to identify significant spatiotemporal windows of novel versus standard differences separately for each measurement time point. The analysis was conducted for data points between stimulus onset and the end of the epoch (840 ms). First, we identified time ranges with significant novel-standard differences ( $p < 0.05$ ) showing consistent polarity across adjacent time points and neighboring channels and then calculated the sum of  $t$ -values for each cluster. The test statistic was determined as the maximum sum of these  $t$ -values. To establish a null distribution, we randomly permuted the stimulus labels (novel vs. standard) 5000 times and computed the test statistic for each iteration. The cluster sum  $t$ -values obtained with the true labels were considered significant if they exceeded the top or bottom 2.5 percentile of the test statistics obtained with the permuted labels. All electrodes, except for the peripheral and reference ones, were included in the analyses (Fig. 2). Importantly, this approach effectively controls for the Type I error rate.

For the quantification of the novelty-P3 and LDN peak latencies and mean amplitudes, individual peak latencies were identified from wide time windows in a region-of-interest (ROI) including 6 electrodes which appeared to be the most appropriate according to the mass permutation tests (F3, Fz, F4, C3, Cz, and C4 for all responses except for LDN at 6 months, C3, Cz, C4, P3, Pz, P4) with an additional 10-Hz low-pass filter. From the large ROIs, mean amplitudes were calculated using original-filtered responses from time windows (width:  $\sim$ peak latency standard deviation) centered at the individual peak latencies. For improving signal-to-noise ratio in the 28-month-data, FC1, FC2, FC5, and FC6 were added to the mean amplitude calculation. These electrodes are located between the F- and C-rows of the large ROI (Fig. 2), therefore, their inclusion should not markedly influence the response latencies or amplitudes. This was separately done for data obtained at different ages and for those responses only that were, in the whole sample, statistically significant based on the mass permutation tests. The wide time windows used for peak latency search and (in brackets) widths of the time windows used for mean amplitude calculation were as follows: for the 0-month novelty-P3, 190–840 ms (100 ms), for the 6-month novelty-P3, 180–520 ms (60 ms), for the 6-month LDN, 500–840 ms (80 ms), for the 28-month novelty-P3, 120–520 ms (75 ms), and for the 28-month LDN, 610–840 ms (60 ms).

In case an individual peak latency was not found, peak latency was treated as a missing value, but for mean amplitude calculation, group average peak latency was used to center the time window. The amounts of missing peak values across groups were as follows: for novelty-P3's,  $N = 0$  at all ages; for LDN's,  $N = 3/90$  and  $N = 6/142$  for the 6-month and 28-month data, respectively. When the time window used for peak latency search ended at the end of epoch and the individual peak latency was close to the epoch end, the latest possible time window was used for mean amplitude calculation.

Linear mixed models (LMMs) implemented in R using the *lme4* package (Bates et al., 2007) were employed to investigate maturational changes in amplitudes and latencies in the large ROIs. Fixed factors included time and group, while participant was treated as a random factor. This analysis was restricted to responses which were statistically significant across the whole sample at least in two EEG recordings according to the mass permutation tests. Novelty-P3 and LDN were separately analyzed. Based on visual inspection of the average responses, the novelty-P3 appeared to have a non-linear development, with the largest response at the

age of 6 months. To test whether this non-linear trend was significant, we used the *glht* function from the *multcomp* package, applying a quadratic contrast to the age effect. The weights of 1, -2, and 1 were used corresponding to the three EEG-recording times. One Sample *t* tests (Bonferroni-corrections conducted for each age group for multiple comparisons) were used to determine whether the novelty-P3 and LDN were statistically significantly elicited within each group (no-risk, at-risk, vocal, instrumental).

### 3. Results

#### 3.1. Novelty-P3 and LDN in the whole sample

The responses of the whole sample are illustrated in Fig. 3 and the field trip analyses in Fig. 4. At birth, the novel sounds significantly elicited a broad novelty-P3 across all channels, and at 6 and 28 months, the novel sounds significantly elicited a fronto-central novelty-P3 followed by an LDN. At 6 months, the LDN was significant in the centro-parietal electrodes whereas at 28 months the LDN scalp distribution was fronto-central (Fig. 4).

#### 3.2. Novelty-P3 and LDN maturation and group comparisons

The responses in the four groups are illustrated in Fig. 5A, and mean amplitudes and peak latencies in Table 2. In all groups, the novelty-P3 was significant at ages 0, 6 and 28 months and the LDN at the ages of 6 and 28 months (all  $p < 0.001$ ). The results of the LMM analyses are reported in Table 3.

The LMM analysis on the maturation of novelty-P3 amplitude from birth to 28 months and LDN amplitude from 6 to 28 months yielded a significant main effect of time [novelty-P3:  $F(1, 383) = 6.125, p = 0.014$ ; LDN:  $F(1, 130) = 12.010, p < 0.001$ ; Table 3]. Whereas LDN amplitude decreased linearly with age, based on visual inspection of the waveforms, the change was not linear for the novelty-P3 amplitude that seemed to peak at 6 months (Fig. 3). This interpretation was supported by a significant quadratic contrast ( $p < .001$ ). The corresponding analyses for novelty-P3 and LDN latencies revealed a significant novelty-P3 latency decrease [main effect of Time:  $F(1, 383) = 126.044, p < 0.001$

and LDN latency increase [main effect of Time:  $F(1, 117) = 59.808, p < 0.001$ ]. The main effect of Group or the Group  $\times$  Time interaction did not reach significance for the amplitude or latency of either response (see Table 3).

In order to further investigate the possible effect of dyslexia risk on the novelty ERPs, we conducted four additional LMM analyses for novelty-P3 and LDN amplitude and latency and compared the control and high-risk groups, excluding those risk group children who took part in the music listening interventions or had parents with compensated dyslexia (the remaining at-risk children being a “high-risk group” in line with Virtala et al. 2022; sample details in Supplemental Table 1 and mean amplitudes and peak latencies in Supplemental Table 2; responses illustrated in Fig. 5B). We also conducted two additional Bonferroni-corrected One-sample *t*-tests to investigate the statistical significance of the novelty-P3 and LDN in the high-risk group. These analyses revealed that the novelty-P3 remained significant at the ages of 0, 6 and 28 months and the LDN at the ages of 6 and 28 months also in the high-risk group (all  $p < 0.001$ ). The LMMs revealed that only the LDN latency significantly differed between the groups  $F(1, 63) = 6.625, p = 0.012$ , with longer latencies in the high-risk than control group.

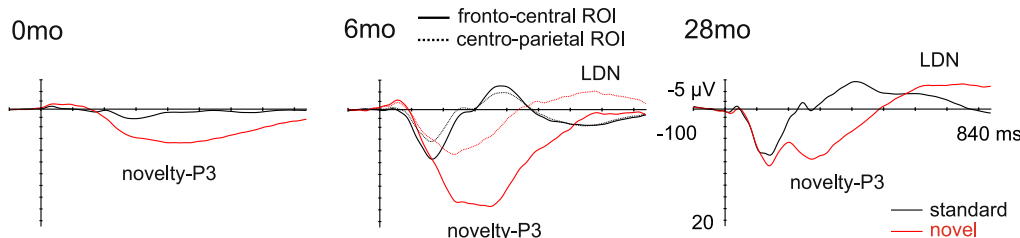
### 4. Discussion

The current study determined the maturation of auditory novelty detection as reflected by the novelty-P3 and LDN responses. Our sample included 83–177 children, who were longitudinally followed up by recording ERPs at birth and at 6 and 28 months. We investigated this development both in children with no inherited dyslexia risk and in children at this risk. Furthermore, the influence of a passive music listening intervention in infancy was taken into account in the analyses.

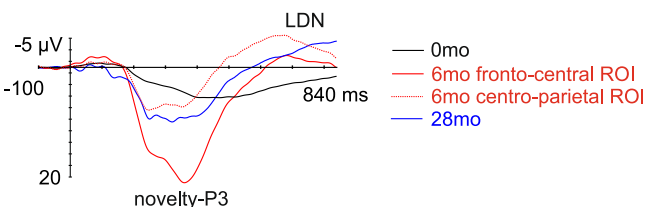
#### 4.1. The developmental pattern of novelty detection

We found that the novelty-P3 was significantly elicited in all groups and ages, whereas no LDN was found at birth but it was significantly elicited at the ages of 6 and 28 months in all groups. The novelty-P3 amplitude increased from birth to the age of 28 months,

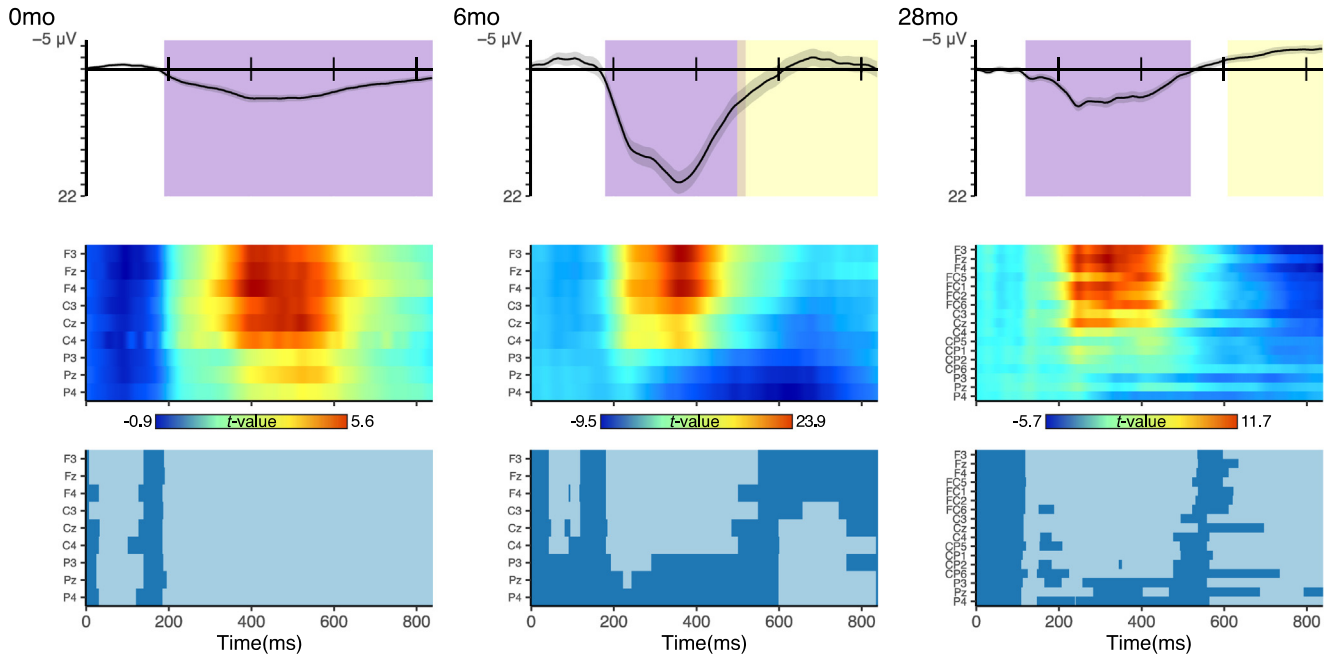
#### A. Standard and novel ERPs



#### B. Subtraction waveforms

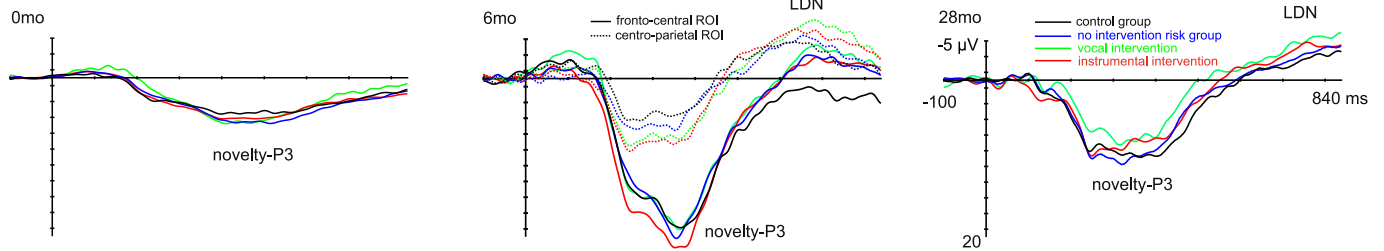


**Fig. 3.** Event-related potentials (ERPs) elicited by the standard and novel stimuli (A) and subtraction waveforms (B) (the response elicited by the standard stimulus subtracted from the response elicited by the novel stimulus) at each age in the whole sample. The solid lines represent ERPs and subtraction waveforms at a fronto-central region-of-interest (ROI): at birth (0mo) and six months (6mo), an average signal of electrodes F3, Fz, F4, C3, Cz, and C4, and at 28 months (28mo), an average signal of electrodes F3, Fz, F4, FC1, FC2, FC5, FC6, C3, Cz, and C4. At 6 months, the dashed lines additionally illustrate a centro-parietal ROI (average signal of electrodes C3, Cz, C4, P3, Pz, and P4), where the LDN was quantified.

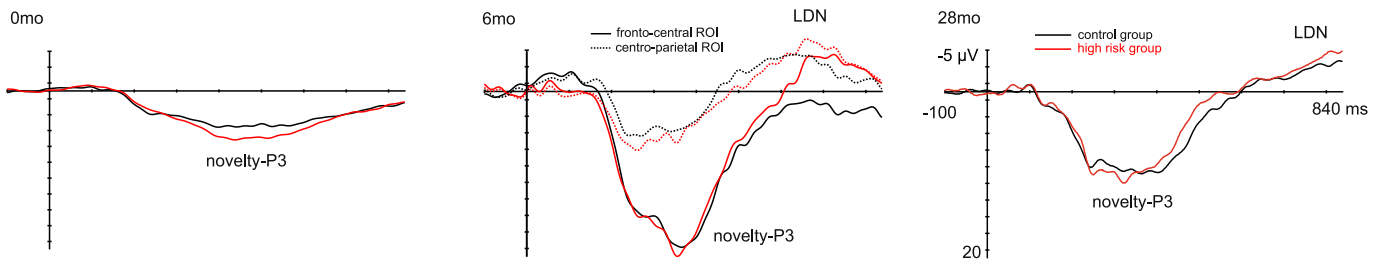


**Fig. 4.** Subtraction waveforms, heat maps, and results of cluster-based mass permutation test. Top row: Subtraction waveforms (the response elicited by the standard stimulus subtracted from the response elicited by the novel stimulus) at each age at a fronto-central region-of-interest (ROI): at birth (0mo) and six months (6mo), an average signal of electrodes F3, Fz, F4, C3, Cz, and C4, and at 28 months (28mo), an average signal of electrodes F3, Fz, F4, FC1, FC2, FC5, FC6, C3, Cz, and C4. Middle row: heatmaps illustrating the t-values for the novel minus standard event-related potential (ERP) responses (positive values illustrated with warm colors, negative values with cold colors) at all electrodes included in the analysis from the stimulus onset onwards. Bottom row: The panels show time ranges of statistically significant novel minus standard difference (in light blue) as determined by cluster-based mass permutation tests. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**A. Four-group comparison**



**B. Two-group comparison**



**Fig. 5.** Subtraction waveforms (the response elicited by the standard stimulus subtracted from the response elicited by the novel stimulus) from the risk children in different intervention groups and the control group are superimposed (A) and subtraction waveforms from the high-risk and control groups (B). The solid lines represent responses at a fronto-central region-of-interest (ROI): at birth (0mo) and six months (6mo), an average signal of electrodes F3, Fz, F4, C3, Cz, and C4, and at 28 months (28mo), an average signal of electrodes F3, Fz, F4, FC1, FC2, FC5, FC6, C3, Cz, and C4. At 6 months, the dashed lines additionally illustrate a centro-parietal ROI (average signal of electrodes C3, Cz, C4, P3, Pz, and P4), where the LDN was quantified.

the pattern of the change being non-linear with maximum amplitudes at 6 months. The LDN amplitude, analyzed from 6 to 28 months, in turn, decreased. The latency analysis yielded shortening of the novelty-P3 and prolongation of the LDN during the development. Also, the scalp distribution of these responses appeared to change during the development towards frontal scalp

areas, as suggested by the statistically significant clusters in the mass permutation test (Fig. 4). No Group or Group × Time interactions were found in the amplitude and latency analyses, suggesting no significant effect of dyslexia risk or music intervention on these responses. However, an additional analysis comparing children at high dyslexia risk who did not participate in the intervention and

**Table 2**

The mean amplitudes (in  $\mu\text{V}$ , with standard deviation, SD, in parentheses), peak latencies (in ms from deviance onset, SD in parentheses), and sample sizes (N) of each peak latency of statistically significant novelty-P3 and late discriminative negativity (LDN) responses in the whole sample and subgroups at birth (0mo), 6 months (6mo), and 28 months (28mo) at the quantified region-of-interest (ROI).

	mean amplitude, $\mu\text{V}$ (SD)	peak latency, ms (SD)	peak latency N
novelty-P3			
Birth			
control	6.11 (3.62)	484.43 (145.14)	46
no int	6.85 (3.86)	505.06 (141.45)	53
int1	6.60 (3.43)	469.32 (116.23)	38
int2	6.55 (4.02)	467.05 (136.13)	40
6mo			
control	20.37 (8.49)	356.63 (68.46)	19
no int	21.07 (9.10)	353.40 (59.97)	20
int1	19.68 (6.27)	328.67 (58.72)	18
int2	22.87 (9.41)	339.92 (50.08)	26
28mo			
control	12.02 (5.01)	326.13 (71.02)	32
no int	12.04 (5.35)	318.67 (60.94)	39
int1	9.55 (5.37)	309.33 (78.98)	27
int2	11.03 (4.97)	325.09 (83.47)	33
LDN			
6mo			
control	-6.43 (6.12)	634.00 (80.72)	18
no int	-6.86 (6.64)	680.74 (64.49)	19
int1	-7.98 (6.52)	669.89 (55.07)	18
int2	-8.20 (5.21)	638.04 (91.41)	25
28mo			
control	-4.20 (4.10)	729.31 (65.27)	32
no int	-4.69 (4.17)	744.72 (57.66)	39
int1	-6.21 (5.31)	734.54 (57.91)	26
int2	-5.13 (3.63)	741.10 (49.94)	29

*Note 1.* Peak latency was separately searched from each individual the data therefore containing missing values. Sample sizes available for each response in each age group are presented in the column “peak latency N”.

*Note 2.* At births and 6 months (6mo) the electrodes included in the ROIs are F3, Fz, F4, C3, Cz, and C4, except for the 6mo-LDNs, C3, Cz, C4, P3, Pz, and P4, and at 28 months (28mo), F3, Fz, F4, C3, Cz, C4, Fc1, Fc2, Fc5, and Fc6.

control children yielded a longer LDN latency in the high-risk than the control children.

These results show that the ability to detect novel auditory events is present since birth, as reflected by the significant elicitation of the novelty-P3 in all ages. This is an expected result, since the auditory system of newborn infants was shown to detect, besides novel sounds (Sambeth et al., 2006; Kushnerenko et al., 2002; 2007; Håden et al., 2013), even more subtle deviations in sound streams, such as phonetic changes (e.g., Partanen et al., 2013; Virtala et al., 2023) and violations of rules embedded in the sound stream (Carral et al., 2005; Virtala et al., 2023; Kujala et al., 2023). These results suggest that the neonatal brain has the readiness to react to potentially relevant novel events in the environment, which is a crucial first step in selecting relevant information and processing it then further. This serves as a basis for early learning and assimilation of new information in the memory representations.

The novelty-P3 observed in the current study was a slow late-peaking response at birth, increasing in amplitude and decreasing in latency by the age of 6 months, and then decreasing in both amplitude and latency by the age of 28 months. A pattern consistent with this was observed in a study following up the novelty-P3s and the following negativities (termed Nc) to novel sounds (termed “trial unique sounds”) in children from 1 to 5 months (Katus et al., 2020). However, in this and the current study, the children were mostly asleep during the first ERP recording, which can be expected to influence the amplitude and latency of this response (Friederici et al., 2002; Duclaux et al. 1991). The neurophysiological changes observed in the amplitudes and latencies

of novelty-P3 and LDN in the awake children from the age of 6 to 28 months are likely to reflect both the maturational changes of the neural network subserving attention shifting and the developing ability to control attention and resist attention switches caused by distracting events when focusing on a primary task (see Kushnerenko et al., 2013, for a review). Furthermore, it should be noted that during the early infancy there are major changes in the skull sutures, which can influence ERPs. It should also be taken into account that when being awake, there are more artefacts caused by muscle activity than during sleep and the rhythmic brain activity differs from that generated during sleep. However, since we recorded stimulus-locked responses using jittered stimulus presentation, these should not have a major effect on the results.

Our results on LDN suggest that it emerges by the age of 6 months, but the results are inconclusive, since the analysis period allowed by our stimulation rate might have been too short for detecting a potential later LDN in ERPs recorded at birth (see Figs. 3 and 5). From 6 to 28 months the LDN amplitude decreased and latency increased. This LDN, which is generated by neural mechanisms reacting to novel events, appears to have a different pattern of development than the LDN elicited by smaller changes with a lesser degree of novelty. Namely, an amplitude increase from 6 to 28 months was found in LDNs elicited by vowel duration and frequency changes in a repetitive pseudo word in largely the same sample as in the current study (Virtala et al., 2022). These results suggest that the LDNs elicited by these different types of deviations in different stimulus contexts may reflect distinct neural processes in the infant auditory system. The developmental changes in the novel-sound elicited LDN observed in the present study may result both from neurobiological maturational development and changes in attention-control abilities similarly as discussed above in relation to the novelty-P3 results.

Maturational changes were also observed in the scalp distributions of the responses. According to the heat maps illustrated in Fig. 4, the novelty-P3 was very broadly elicited at frontal, central, and parietal scalp areas at birth, whereas at later ages the positivity was more localized to frontal and central channels. Also, for the LDN, there was a shift from centro-parietal channels towards frontal scalp areas from 6 to 28 months, together with a notable latency shift. These results are consistent with previous studies reporting, for example, a more frontal scalp distribution of a positivity elicited by novel sounds in 4- than 2-year-old children (van den Heuvel et al., 2015). It could be speculated that these results reflect the maturation of attentional mechanisms which are largely regulated by the frontal brain areas.

#### 4.2. Novelty detection in dyslexia risk

Besides inspecting the typical developmental pattern of novelty detection, we utilized the possibility provided by the DyslexiaBaby project to determine the influence of dyslexia risk on novelty-P3 and LDN, which has scarcely been studied so far. The only significant effect of dyslexia-risk obtained in the current study was a longer LDN latency in high-risk than control children (Fig. 5), which might reflect sluggish re-orientation of attention from the distracting stimulus in the at-risk children (Fu et al., 2019; Hari and Renvall, 2001). It should be noted that we screened out families with parents who have ADHD. Therefore, our child participants represent only a subgroup of the population at risk for dyslexia, in which attention disorders are relatively prevalent (Boada et al., 2012).

Our current results on novel-sound elicited LDN, showing no amplitude differences between the dyslexia-risk and control groups, are distinct from the results obtained with the LDN recorded to speech sound changes in largely overlapping participant groups of the DyslexiaBaby project. Those results showed

**Table 3**

Results of the linear mixed models investigating changes in AMPplitudes and LATencies of the novelty-P3 and late discriminative negativities (LDNs) with time (for the novelty-P3, across 0, 6, and 28 months and for the LDN, across 6 and 28 months) in the whole sample. Reported are the effects of time, group, and their interactions (statistically significant  $p < 0.05$  effects are bolded). The first model included all the four subgroups (model “Four groups”: con, no-int, int1, and int2), while the second model only included the high-risk and control groups (model “Two groups”).

Model	AMP/LAT	Effect	df1, df2	F	p	
Four groups	Novelty-P3 AMP	Time	1, 383	6.125	<b>0.014</b>	
		Group	3, 383	1.021	0.383	
		Time × Group	3, 383	0.826	0.480	
	LAT	Time	1, 383	126.044	<b>&lt;0.001</b>	
		Group	3, 383	1.547	0.202	
		Time × Group	3, 383	0.728	0.536	
	LDN AMP	Time	Time	1, 129.830	12.010	<b>0.001</b>
			Group	3, 140.721	1.340	0.264
			Time × Group	3, 129.502	0.120	0.948
		LAT	Time	1, 116.533	59.808	<b>&lt;0.001</b>
			Group	3, 130.732	1.679	0.175
			Time × Group	3, 116.470	0.801	0.496
Model	Novelty-P3 AMP	Time	1, 173	8.385	<b>0.004</b>	
		Group	1, 173	0.050	0.824	
		Time × Group	1, 173	0.078	0.780	
	LAT	Time	1, 173	64.103	<b>&lt;0.001</b>	
		Group	1, 173	0.208	0.649	
		Time × Group	1, 173	0.218	0.642	
Two groups	LDN AMP	Time	1, 89	4.761	0.032	
		Group	1, 89	0.306	0.582	
		Time × Group	1, 89	0.000	0.997	
	LAT	Time	1, 56.153	27.830	<b>&lt;0.001</b>	
		Group	1, 62.957	6.625	<b>0.012</b>	
		Time × Group	1, 56.153	1.981	0.165	

group differences, the LDN being absent or diminished for some stimulus changes and enhanced for some other deviances in children at risk for dyslexia (Virtala et al., 2022). Together these previous and the current results suggest that whereas dyslexia risk is associated with poor stimulus discrimination, as reflected by MMRs and LDNs elicited by small changes (deviants) in stimulus sequences (Virtala et al., 2022), it is less connected with abnormal novelty detection, as shown by largely absent group effects on novelty-P3 and LDN.

#### 4.3. The influence of music intervention on novelty detection

This project also allowed us to determine the effects of a music intervention on the responses elicited by novel sounds. We found no significant effects of music intervention on these responses. There is some evidence on beneficial music intervention effects on attention, but the results are somewhat conflicting (Dumont et al., 2017). Training of pitch, rhythm, voice, melody, and basic musical concepts with perceptual, motor, and cognitive tasks was shown to improve executive functions in preschool children (Moreno et al., 2011). To our knowledge no studies have been reported on the effects of passive music listening on the early development of attention orienting and, therefore, we could not formulate firm hypotheses on these effects. Our finding of no effects of passive music intervention on novelty detection might be due to the low/no demands of passive music intervention on attentional mechanisms. However, beneficial effects of music on attention functions could be obtained with active forms of music intervention engaging attention efficiently.

#### 4.4. Limitations and summary

In the interpretation of the current results one should take into account a few limitations. The stimulation rate in the current study

was relatively short, the SOA being 900 ms +/-50 ms. This might result in an overlap of the ERP elicited by the previous stimulus and the presentation of a new stimulus. Due to this stimulation rate, also our analysis period was relatively short, which might have prohibited the detection of the LDN in the neonatal data. Since slower stimulation rates would lead to too long experiments for children or too small numbers of trials affecting the data quality, we had to make these compromises in choosing the stimulation rate. Additional limitations concern the data obtained at different ages. During the ERP recordings at birth, the infants were mostly sleeping, whereas they were awake in the rest of the recordings. While this limits the comparison of responses elicited at birth and later ages, recording newborns asleep is a standard protocol in the field in studies with passive stimulation protocols, since small infants sleep most of their time. Furthermore, skull sutures, changing during the early development, and differences in muscle activity and rhythmic brain activity during wakefulness and sleep might influence the responses. Future studies designed to estimate the effects of the stimulation rate, vigilance, and skull sutures would be welcome in order to refine the developmental pattern of auditory ERPs.

In summary, our longitudinal study determining the development of neural auditory novelty detection from birth to 28 months of age found that novel sounds elicit responses that likely reflect the precursors of attention shifting at birth. From 6 to 28 months of age, its amplitude and latency decrease and it becomes more localized to fronto-central scalp areas, possibly reflecting the first steps of the developing ability to control attention. The LDN, likely reflecting the precursors of attention re-orienting, emerges by six months to centro-parietal scalp areas. Its amplitude decreases and latency increases by 28 months, having largest amplitudes at fronto-central channels. No influence of familial dyslexia risk (apart from a longer LDN latency in these than control children) or passive music intervention was found.

## Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

## Disclosure statement

Financial Disclosure: none. Non-financial Disclosure: None.

## Authors' contribution

TK designed the study and provided resources. PV coordinated the participant recruitment and data collection. PV and VP analyzed the data and prepared the figures. TK, PV, and VP contributed to writing of the manuscript.

## Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

## Data sharing

The data can be made available by reasonable request from the principal investigator (TK).

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2024.09.005>.

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