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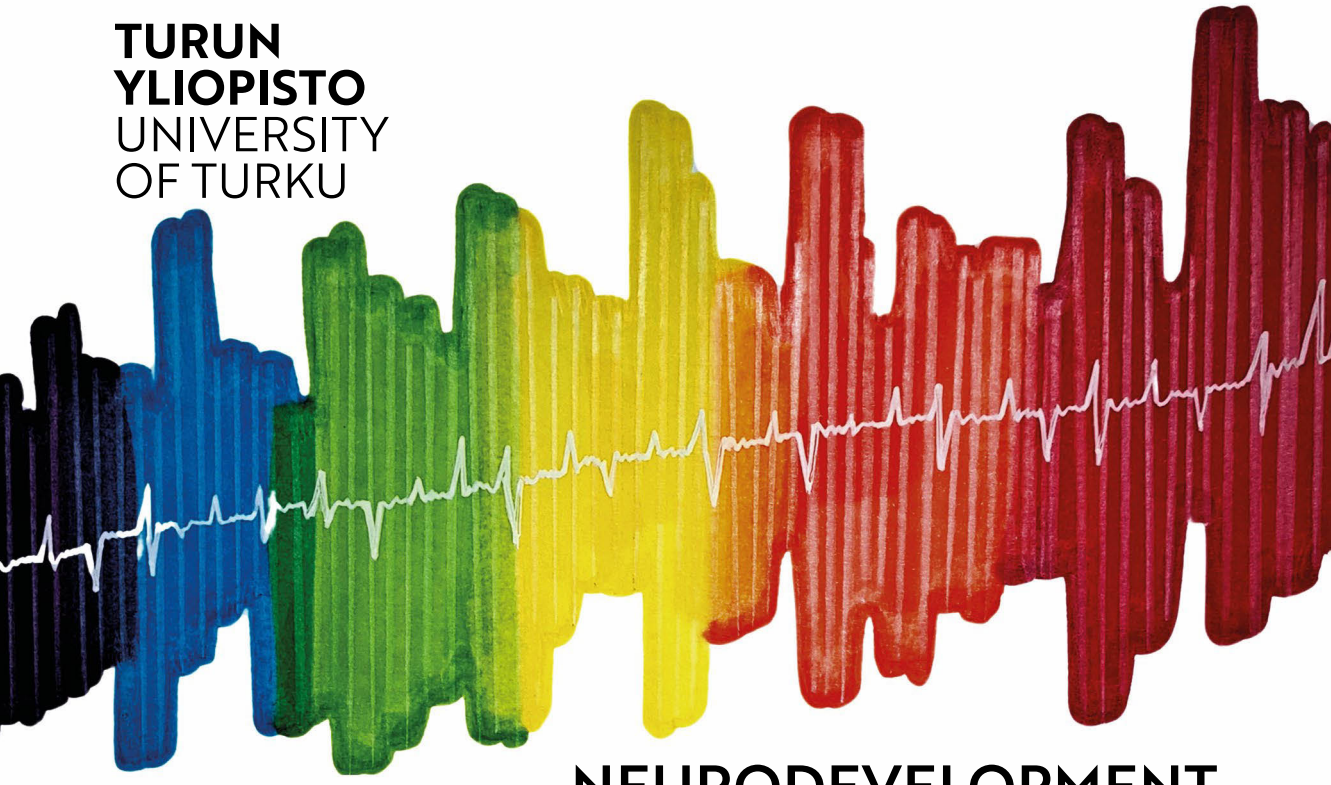

NEURODEVELOPMENT ACROSS EARLY LIFE: PRENATAL DISTRESS, PRETERM BIRTH, AND NEUROPHYSIOLOGICAL OUTCOMES

The FinnBrain Birth Cohort Study

Silja Luotonen

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SARJA – SER. D OSA – TOM. 1875 | MEDICA – ODONTOLOGICA | TURKU 2025

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University of Turku

Faculty of Medicine
Department of Clinical Medicine
Psychiatry
Doctoral Programme in Clinical Research

Supervised by

Associate professor Jetro Tuulari
Clinical Neurosciences
University of Turku, Finland

Assistant professor Henry Railo
Department of Psychology and Speech-Language Pathology
University of Turku, Finland

PhD Henriette Acosta
Department of Psychiatry and Psychotherapy
University of Marburg, Germany

Reviewed by

Professor Eero Kajantie
Clinical Medicine Research Unit
University of Oulu, Finland

Professor Deanne Thompson
Murdoch Children's Research Institute
Parkville, Victoria, Australia

Opponent

Professor Sampsa Vanhatalo
Helsinki University Central Hospital
and University of Helsinki, Finland

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For those who walk beside young minds,
guiding them toward their brightest futures.

UNIVERSITY OF TURKU
Faculty of Medicine
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Psychiatry
SILJA LUOTONEN: Neurodevelopment Across Early Life: Prenatal Distress, Preterm Birth, and Neurophysiological Outcomes. The FinnBrain Birth Cohort Study, 176 pp.
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ABSTRACT

During prenatal and early postnatal periods, the brain experiences rapid growth. Fetuses are vulnerable to prenatal distress and preterm birth, which can increase the risk of neurodevelopmental conditions. Identifying neural markers for early detection in at-risk individuals is crucial. Aperiodic neural activity could serve as a marker for neural maturation, yet knowledge is limited on how gestational duration shapes its trajectory over time. There is also a gap in research on prenatal stress effects in brain electrophysiology in toddlers.

We used functional neuroimaging to study age- and gestational duration-related neural activity changes in neonates and 3-year-olds, as well as the effects of maternal prenatal distress in 3-year-olds. In Study I, we used auditory event-related potentials (ERPs) of electroencephalogram (EEG) to explore links between maternal depressive symptoms and perception of emotionally charged auditory stimuli in toddlers. Study II investigated age- and prematurity-related changes in aperiodic activity in neonates, using functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) signal. Study III examined normal variation in gestational duration- and age-related effects on aperiodic and periodic activity of the EEG power spectra in neonates and toddlers.

Our results showed developmental changes in aperiodic activity, with steeper slopes of EEG power spectra related to longer gestational duration and higher BOLD baseline activity and steeper slopes related to greater postmenstrual age. Interestingly, these associations seemed to partially reverse after birth. Preterm neonates had flatter slopes and lower BOLD baseline activity compared to term-born neonates. Sex-specific differences were observed, with female neonates showing higher BOLD baseline activity but flatter slopes, and female toddlers exhibiting higher EEG beta center frequency values than males. Additionally, toddlers of mothers with higher prenatal depressive symptom scores showed weaker responses to happy sounds.

In conclusion, aperiodic activity reflects age-related changes in early life, likely indicating maturational changes in neurodevelopment, with sex-specific differences. This pattern may follow a reverse U-shaped curve from prenatal period through early life, with birth marking an apex point in the process. The results support previous findings that prenatal maternal depressive symptoms and gestational duration influence brain development, with effects observed up to 3 years of age.

KEYWORDS: neurodevelopment, EEG, fMRI, aperiodic activity, event-related potential, prenatal distress, preterm birth, neonate, preschool children

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Lääketieteellinen tiedekunta
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SILJA LUOTONEN: Aivojen kehitys ensimmäisten elinvuosien aikana: Raskaudenaikaisen stressialtistuksen ja ennenaikaisen syntymän yhteydet aivojen toimintaan. FinnBrain-syntymäkohorttitutkimus.
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TIIVISTELMÄ

Aivojen kasvu on nopeaa raskauden aikana, jolloin sikiö on altis ympäristötekijöille. Varhainen stressialtistus ja ennenaikainen syntymä voivat lisätä myöhempien kehityksellisten häiriöiden riskiä, joten riskilasten tunnistaminen on tärkeää. Aivojen aperiodinen aktiivisuus on lupaava aivojen kypsymisen kuvaaja, mutta sen raskauden kestoon liittyviä muutoksia ei juurikaan tunneta. Myöskään varhaisen stressialtistuksen yhteyttä taaperoikäisten aivojen toimintaan ei ole juuri tutkittu.

Väitöskirjan tavoitteena oli selvittää raskauden keston, raskaudenaikaisen stressialtistuksen ja iän yhteyksiä lapsen aivojen toimintaan aivosähkökäyrän (EEG) ja toiminnallisen magneettikuvantamisen (fMRI) avulla. Osatutkimuksissa tarkasteltiin: 1) Äidin raskaudenaikaisen masennusoireilun yhteyttä 3-vuotiaiden lasten tunnepitoisten ääniärsykkeiden havaitsemiseen herätevasteiden avulla; 2) ennenaikaisuuden ja hedelmöityshetkestä arvioidun iän yhteyksiä fMRI:n BOLD-signaalin aperiodiseen aktiivisuuteen vastasyntyneillä: ja 3) raskauden keston yhteyksiä EEG:n aperiodiseen ja periodiseen aktiivisuuteen vastasyntyneillä ja 3-vuotiailla.

Pidempi raskauden kesto oli yhteydessä jyrkempään EEG:n tehospektriin vastasyntyneillä ja 3-vuotiailla. Korkeampi hedelmöityshetkestä arvioitu ikä oli yhteydessä korkeampaan BOLD-signaalin tehospektrin tausta-aktiivisuuteen ja jyrkempään spektriin vastasyntyneillä. Lapsen syntymästä lasketun iän yhteydet näihin tekijöihin olivat osin päinvastaisia. Ennenaikaisesti syntyneillä lapsilla BOLD signaalin tehospektri oli loivempi ja tausta-aktiivisuus matalampaa, kuin täysiaikaisilla. Vastasyntyneillä tytöillä oli poikia loivemmat BOLD-signaalin tehospektrit ja korkeampi tausta-aktiivisuus, kun taas 3-vuotiailla tytöillä EEG:n beeta-aktiivisuuden keskitaajuudet olivat poikia korkeampia. Äidin voimakkaampi raskaudenaikainen masennusoireilu oli yhteydessä heikompaan reagointiin iloisiin ääniärsykkeisiin 3-vuotiailla lapsilla.

Tulokset viittaisivat siihen, että raskauden keston ja syntymän jälkeisen iän yhteydet aperiodiseen aktiivisuuteen olisivat osin päinvastaisia. Raskauden kestolla ja varhaisella stressialtistuksella saattaa olla pitkäkestoisia vaikutuksia lapsen aivojen toimintaan.

AVAINSANAT: aivojen kehitys, EEG, fMRI, aperiodinen aktiivisuus, herätevaste, ennenaikainen syntymä, raskaudenaikainen stressi, vastasyntynyt, lapsi

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Abbreviations

AAL	Automated Anatomical Labeling (brain parcellation scheme)
ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike information criterion (measure used to selection of statistical model)
ALFF	amplitude of low-frequency fluctuations (neuroimaging measure in BOLD signal)
ASR	Artifact Subspace Reconstruction (method for EEG preprocessing)
BMI	body mass index
BOLD	blood-oxygen-level-dependent (signal in fMRI)
dHCP	Developing Human Connectome Project
DoHaD	Developmental Origins of Health and Disease (hypothesis of fetal programming)
DTI	diffusion tensor imaging
DVARS	Temporal Derivative of Root Mean Square Variance over voxels (measure of the level of noise in fMRI)
EEG	electroencephalography
E-I	excitatory-inhibitory (signals that increase/suppress neuronal firing)
EPDS	The Edinburgh Postnatal Depression Scale
ERP	event-related potential (neuroimaging measure in EEG)
fMRI	functional magnetic resonance imaging
FOOOF	Fitting Oscillations and One Over F (tool for spectral parameterization)
FSL	FMRIB (fMRI of the brain) Software Library
GABA	gamma-aminobutyric acid (primary inhibitory transmitter in the brain)
gw	gestational week
HPA	hypothalamic-pituitary adrenal (neuroendocrine system involved in stress responses)
HSD2	11ß-hydroxysteroid dehydrogenase type 2 (enzyme regulating i.e., levels of active glucocorticoids in placenta)
ICA	Independent Component Analysis (method for signal processing)
LMP	last menstrual period

MAE	mean absolute error (measure used to evaluate the performance of predictive model)
MEG	magnetoencephalography
MMN	mismatch negativity (component of ERP)
NBIS	Neonatal Brain Imaging System
NIRS	near-infrared spectroscopy
PET	positron emission tomography
PREP	Early Stage Preprocessing (method for EEG preprocessing)
PSD	power spectra density (distribution of power as a function of frequency)
ROI	region-of-interest
SCL-90	Symptom Check-List
SSRI	selective serotonin reuptake inhibitor (class of medications primarily used to treat mental health conditions, such as depression)
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Luotonen, S., Railo, H., Acosta, H., Huotilainen, M., Lavonius, M., Karlsson, L., Karlsson, H., and Tuulari, J.J. Auditory Mismatch Responses to Emotional Stimuli in 3-Year-Olds in Relation to Prenatal Maternal Depression Symptoms. Frontiers in Neuroscience, 2022; 16.

II Suuronen, I.*, Luotonen, S.*, Railo, H., Airola, A., Bano, W., Merisaari, H., Pulli, E. P., Mariani Wigley, I. L. C., Vartiainen, E., Hashempour, N., Karlsson, H., Karlsson, L., Kringelbach, M. L., Batalle, D., & Tuulari, J. J. Aperiodic parameters of the fMRI power spectrum associate with preterm birth and neonatal age. *Manuscript.*

III Luotonen, S., Railo, H., Acosta, H., Huotilainen, M., Lavonius, M., Karlsson, L., Karlsson, H., and Tuulari, J.J. Gestational Duration and Postnatal Age - Related Changes in Aperiodic and Periodic Parameters in Neonatal and Toddler Electroencephalogram (EEG). *Human Brain Mapping*, 2025; 46(1).

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1 Introduction

Neurodevelopment refers to the process by which the nervous system develops and matures, encompassing the growth and organization of neurons, neural circuits, and brain structures from prenatal stages through adulthood. In mammals, the order and rate of neural maturation are variable, correlating closely with developmental duration, brain size, and longevity. From the evolutive perspective, humans exhibit an intermediate state of neural maturation at birth compared to other mammals, potentially crucial for communication development. Considering that human infants have relatively immature brains at birth, they transition from complete maternal dependence to a social environment at a relatively early stage compared to other mammals, which fosters slow, extended brain maturation and ultimately contributes to brain growth and the large brain characteristic of humans. (Hawkes & Finlay, 2018).

During brain development, various processes occur, such as the functional specialization of gray matter (like the cerebral cortex and subcortical nuclei) and the myelination of white matter, which links different areas of the brain (Dubois et al., 2014). Brain growth is most rapid during gestation and early postnatal life, with approximately 80% of adult size achieved by the age of two years (Knickmeyer et al., 2008). Despite the majority of network-architecture systems found in the adult brain being established before birth, the neonate brain continues to mature after birth (Silbereis et al., 2016). Both genetic programming and epigenetic and environmental factors, such as maternal and nutritional factors, influence development (Dubois et al., 2014).

This thesis contributes to current knowledge by addressing two key prenatal risk factors, maternal prenatal distress and preterm birth. Prenatal distress, marked by maternal psychological symptoms like depression, anxiety, and stress during pregnancy, affects up to 25% of pregnant women, making it a significant early-life stressor and heightening the risk of mental and behavioral disorders in offspring (Räikkönen et al., 2011; Tuovinen et al., 2021; Van den Bergh et al., 2020). Another prenatal risk factor, preterm birth, affects approximately 11% of births globally, leads to increased mortality and morbidity and poorer outcomes, with diverse etiologic pathways and two-thirds occurring without evident risk factors (Frey &

Klebanoff, 2016; Lawn et al., 2023; Vogel et al., 2018). Importantly, preterm birth increases the risk for various neurodevelopmental conditions (Allen, 2008; Taine et al., 2018). Understanding the factors that influence those neurodevelopmental outcomes is crucial for developing effective strategies for early detection and interventions.

Functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), offer a way to explore the changes in neural activity during development. In this thesis, we investigated gestational duration- and age-related alterations in neural activity during early development and also explored the influence of maternal prenatal distress and premature birth on neural activity. Our aim was to identify potential neural markers indicative of both typical and atypical brain maturation while also assessing the association between maternal prenatal distress and neural activity in offspring.

2 Review of the Literature

2.1 Neurodevelopment across early life

The human brain undergoes dramatic structural and functional changes during gestation and the first years of life. Understanding these structural and functional level processes gives a basis for understanding mechanisms of later neurodevelopmental disorders and, for example, possible mechanisms behind the effects of prenatal exposures or prematurity.

Age-related terminology used in this thesis is summarized in **Figure 1**.

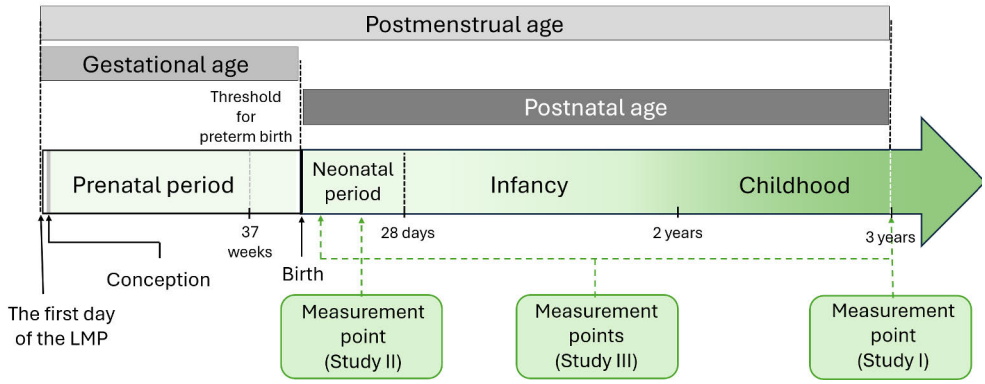

Figure 1. Key age-related terms in the context of early development of the child. LMP = last menstrual period. Author's own drawing.

2.1.1 Prenatal period

The prenatal period is characterized by rapid brain growth, involving the proliferation, migration, and differentiation of neural cells, laying the foundation for the majority of network-architecture systems found in the adult brain before birth (Silbereis et al., 2016). Genetic factors primarily drive the first and second trimesters, while environmental factors gain prominence in the third trimester (Pletikos et al., 2014).

At the structural level, the precursor of the central system, the neural tube, is formed in the process called neurulation around gestational week 3 (Stiles & Jernigan, 2010). Further, the precursor cells of neurons (neuroblasts) proliferate during gestational weeks 4–20 (Thomason, 2020) and begin to migrate. This is followed by synaptogenesis, wherein neurons establish connections with one another, leading to a genetically driven overproduction of dendrites and axons, later regressed by apoptotic cell death (Stiles & Jernigan, 2010). The brain undergoes rapid growth, with the emergence of first sulci and gyri visible already by mid-gestation (Silbereis et al., 2016). Indicating maturation of the white matter of the nervous system, myelination of axons begins in late gestation, continuing into early adulthood (Thomason, 2020).

Alongside structural development, the functional organization of the brain also changes. The brain activity transfers from endogenous and spontaneous neural activity to adult-like, sensory-driven activity. (Vasung et al., 2019). Early brain activity shows incoherent and unorganized patterns (Thomason, 2020). Neurons achieve the capability to fire repetitive action potentials through synaptogenesis, resulting in spontaneous neural activity around gestational week 18 (Cadwell et al., 2019; Thomason, 2020). By gestational week 26, structural thalamocortical connections are established, enabling the fetus to form behavioral responses to external stimuli – a crucial step towards adult-like sensory-driven neural activity (Silbereis et al., 2016; Vasung et al., 2019).

2.1.2 Neonatal period

After birth, the rapid growth of the brain, especially of gray matter, occurs (Bethlehem et al., 2022), with the neonate brain achieving approximately 36% the size of an adult brain at the postnatal age of 2–4 weeks (Knickmeyer et al., 2008). While primary cortical areas (e.g., motor, somatosensory, visual, and auditory cortices) can be already identified at this age, association cortices remain less clearly detected (Tau and Peterson, 2010).

Progressive and regressive developmental processes (e.g., myelination, synaptogenesis, and apoptosis) continue in early postnatal life (Tau and Peterson, 2010). Though neuroblast proliferation and migration is largely a prenatal event, nonneuronal (glial) precursor cells continue proliferating and migrating after birth, having simultaneous timing with rapid myelination onset and continuing throughout childhood (Stiles & Jernigan, 2010; Tau & Peterson, 2010; Thomason, 2020).

2.1.3 Infancy and early childhood

Brain volume undergoes dramatic change in the first years of life (Bethlehem et al., 2022), achieving about 70% of its adult size by 1 year of age and about 80% of adult size by age 2 years (Knickmeyer et al., 2008). Also, rapid synaptogenesis persists during the first two years of life, peaking depending on the cortical region between 3 months and 2 years of postnatal age, before gradually decreasing throughout childhood and adolescence (Huttenlocher, 1979; Stiles & Jernigan, 2010).

Subsequently, refinement of synaptic connections occurs, where unnecessary or unused synapses are eliminated (synaptic pruning) and existing synapses remodeled by their activity, resulting in a more organized and efficient neural network (Tau and Peterson, 2010), which seems to be a major task of the early postnatal brain (Silbereis et al., 2016). The time course of synaptic pruning after birth shows regional variation, with sensory and motor cortices undergoing remarkable synaptic fine-tuning already during the first years of life, while higher cognitive function-associated regions show synaptic pruning occurring throughout adolescence (Tau and Peterson, 2010). Additionally, during early development, the timing of sensory input appears to be crucial in shaping neural circuits, as the loss of certain experiential input can permanently restrict the development of those functional capacities (Silbereis et al., 2016). Myelination of white matter axons shows rapid progress during the first year of life, then continuing slower (Gao et al., 2009). Also, myelination shows regional differences in its pace, showing posterior-anterior as well as subcortical-cortical directions, where sensory pathways seem to myelinate first, followed by motor pathways and, finally, association areas (Tau and Peterson, 2010). Main neurodevelopmental phases at the cellular level across early life have been presented in **Figure 2**.

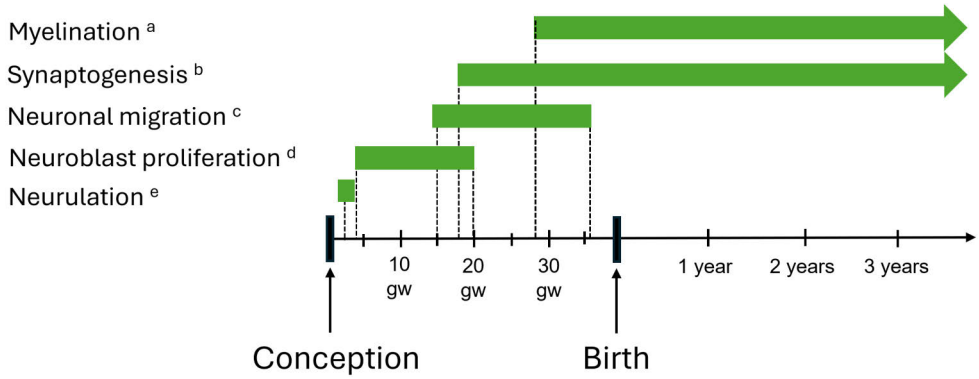

Figure 2. Time schedule of neurodevelopmental phases at the cellular level during early life. [a] (Dubois et al., 2014). [b] (Kwan et al., 2012). [c] (Vasung et al., 2019). [d] (Thomason, 2020). [e] (Stiles & Jernigan, 2010). gw = gestational week. Author's own drawing.

2.1.4 Perspective of excitatory-inhibitory (E-I) balance

For optimal brain functioning, the balance between excitatory (neuron-firing-rate-promoting) and inhibitory (neuron-firing-rate-suppressing) activity is crucial. Imbalances in this excitatory-inhibitory (E-I) balance are associated with various neurological and psychiatric conditions, such as autism spectrum disorders, schizophrenia, anxiety, cerebral ischemia, traumatic brain injuries, epilepsy, and substance abuse. (Sears and Hewett, 2021).

Gamma-aminobutyric acid (GABA) signaling regulates excitatory neural activity through inhibitory interneurons in the fully matured adult brain (Gascoigne et al., 2021). GABAergic signaling also plays a role in cerebral blood flow regulation via neurovascular coupling (Nippert et al., 2018). GABA-driven force development and activation of GABAergic synapses likely occur in early childhood, while the spontaneous frequency of mature interneurons occurs later in childhood to adolescence (Gascoigne et al., 2021).

Comparing research on rodents and humans leads to the assumption that the change from an excitatory to an inhibitory GABA-driven force occurs in early childhood (Gascoigne et al., 2021). Around 3 years of age, humans show signs of early GABA development (Xu et al., 2011). The rapid maturation of GABAergic systems occurs during late gestation and early postnatal life (Basu et al., 2021). However, the notion that this maturation would extend into late adolescence lacks existing evidence (Kilb, 2012).

In summary, E-I balance is crucial for normal brain function, impacting overall neural circuit activity. Recognizing the developmental timeline of E-I balance provides insights into interpreting brain electrical activity measurements in early life.

2.2 Functional neuroimaging methods for studying neural activity

Functional neuroimaging includes various sets of techniques to capture and observe the activity of the brain, such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and near-infrared spectroscopy (NIRS). In this thesis, we focus on two mainstream functional neuroimaging techniques: fMRI and EEG.

2.2.1 Electroencephalography (EEG)

Electroencephalography (EEG) is one of the oldest and most powerful noninvasive brain imaging tools to study electrophysiological dynamics (i.e., electrical activation) of the brain. It reflects the simultaneous activation (i.e., excitatory/inhibitory post-synaptic potentials) of a large population of neurons,

measuring electrical fields via electrodes placed on the scalp (Cohen, 2017). Perhaps the greatest advantage of EEG is its high temporal accuracy, while its spatial accuracy remains limited, due to, for example, spatial summation and scalp-level blurring effect (Burle et al., 2015; Cohen, 2017). Also, it must be noted that while EEG is limited to large, synchronous neuron populations, small-scale and asynchronous activity remain much more difficult to study (Cohen, 2017).

In this thesis (Studies I and III), we were especially interested in following EEG metrics: mismatch responses as well as periodic and aperiodic activity (Chapter 2.4). First, we used these metrics to study auditory stimulus perception in toddlers of prenatally distressed mothers. Second, we used them to examine age- and gestational duration-related effects on electrical activity in the neonatal and child brain.

2.2.2 Functional resonance imaging (fMRI)

In contrast to EEG, fMRI has high spatial resolution, making it a crucial tool to study localized brain activity in humans (Logothetis, 2008). Magnetic resonance imaging is based on measuring the activity of hydrogen nuclei in water in a magnetic field. Functional MRI (fMRI) can be used as a tool to study neural activity indirectly, based on the hemodynamic response (change in blood flow) (Sharma, 2012).

More precisely, the blood oxygen-level-dependent (BOLD) signal of fMRI derives from the local concentration of deoxygenated hemoglobin in the brain (Sharma, 2012). While the changes in the BOLD signal are often interpreted in terms of neural activity (increased blood flow as a response to neurons' increased energy needs), it is likely that both vascular and neuronal factors contribute through neurovascular coupling, resulting in a feed-forward relationship where neuronal signaling influences blood flow reciprocally. When interpreting BOLD signal measurements in developmental neuroscience, it is important to consider age-related differences in vascular and neuronal factors, as baseline blood flow decreases with age, without necessarily corresponding to changes in underlying neuronal activity (Murta et al., 2015; Tsvetanov et al., 2021). Finally, the interpretation of BOLD signal is an ongoing challenge (Chen et al., 2020), but fMRI scans are common, and the search for novel neuroimaging biomarkers is an enticing possibility that was included in this thesis.

In Study II of this thesis, we were especially interested in how the postmenstrual age of the neonate associates with BOLD signal changes in fMRI. In structural MRI studies (for example, Taoudi-Benchekroun et al., 2022; Wilson et al., 2021), this relationship has been unraveled with quite strong associations, while fMRI studies (for example, Eyre et al., 2021) have shown much weaker associations, leading to a need for more accurate brain metrics for maturational processes in the neonatal brain.

In this thesis, we bridged this gap by introducing modelling of aperiodic activity in neonatal fMRI (Chapter 2.4.2).

2.3 Brain metrics for studying neural activity

2.3.1 Mismatch responses of event-related potentials

Event-related potentials (ERPs) represent stimulus-locked and swift neural responses, derived from EEG recordings. They serve as windows into the reception and processing of sensory information and cognitive activity. (Duncan et al., 2009). Among the various components of ERPs, one extensively studied is the mismatch negativity (MMN), a reflection of the cortical discrimination of changes within a sequence of stimuli, i.e., deviants vs. standard stimuli (Näätänen et al., 2004). The mismatch response can be extracted by subtracting the deviant stimulus ERP from the standard stimulus ERP (Näätänen et al., 2004). Importantly, MMNs can be recorded regardless of the subject's attention focus, making them particularly valuable for investigating neural responses, especially in young children (Putkinen et al., 2012).

For auditory stimuli, the primary neural generators of MMN are located in the auditory cortices of the temporal lobes of the brain (Pakarinen et al., 2014). While the typical MMN peak activation occurs with a latency of 100-250 ms, ERPs can additionally reveal later MMN-like amplitude differences (Putkinen et al., 2012) and we are referring to them as “mismatch responses” later in this thesis and Study I.

In this thesis (Study I) we employed mismatch responses (**Figure 3**) to study the impact of prenatal maternal distress on emotional auditory stimuli perception in toddlers. While prior MMN studies predominantly focus on prenatal distress effects in infants, our research covered the age gap by focusing on toddlers, one of the crucial developmental stages.

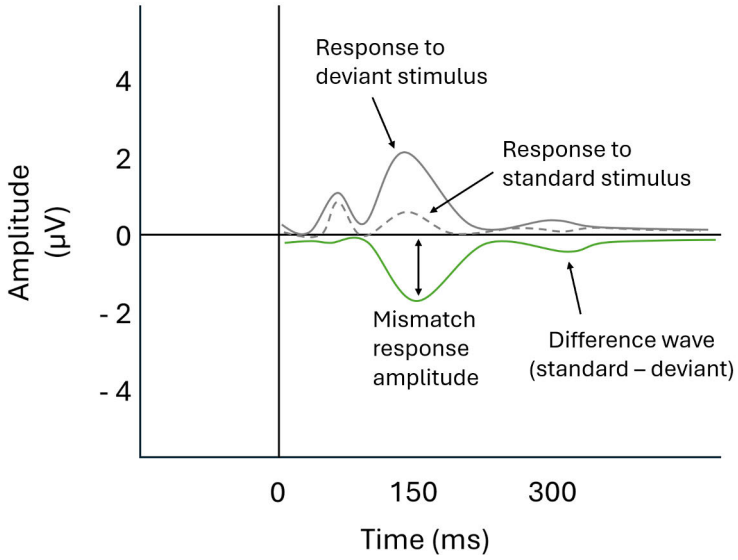

Figure 3. Summary of the mismatch response extraction. Author's own drawing.

2.3.2 Aperiodic and periodic components of power spectrum

Brain signals consist of mixed periodic (oscillatory) and aperiodic (1/f-like) properties. Periodic activity is characterized by distinct peaks in the power spectrum observed at regular intervals, while aperiodic activity exhibits a 1/f distribution of signal power across frequencies (Donoghue et al., 2020). The term "1/f-like" refers to the shape of the background pattern in the spectral density, where power tends to decrease at higher frequencies, resulting in a 1/f shape (Miller et al., 2009). Periodic activity can be detected as peaks of power above the aperiodic component (Donoghue et al., 2020). Understanding these components enhances our comprehension of brain function and its connection to neurodevelopmental processes.

Aperiodic activity is defined with two parameters: offset and exponent. The exponent describes the slope of the power spectrum, representing the distribution of aperiodic power across the frequencies, while the offset describes the uniform shift in power across the frequencies (**Figure 4**). Contrary to its earlier designation as "1/f noise" (Voytek and Knight, 2015), recent studies support the idea that the aperiodic activity is a signal itself, as its slope has been labeled as the "brain fingerprint," due to its reliability as a biomarker to exhibit subject-specific properties (Demuru and Fraschini, 2020; Pathania et al., 2021; Sorrentino et al., 2023).

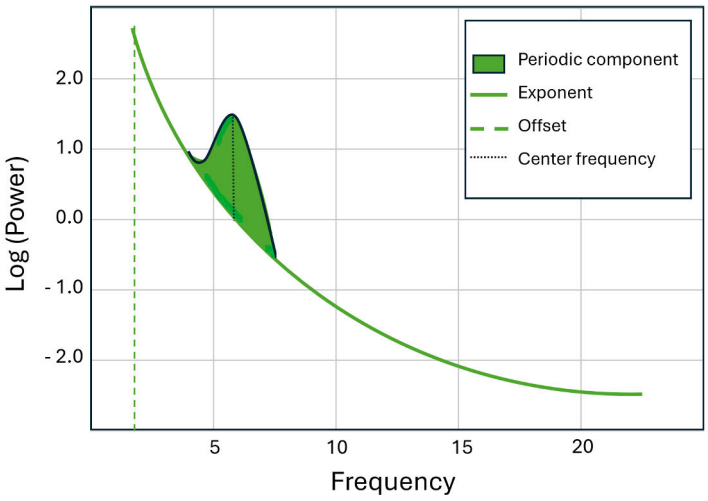

Figure 4. Power spectra with its periodic and aperiodic components. Exponent means the slope of the aperiodic component of the power spectrum. Author's own drawing.

Aperiodic activity offers insights into brain maturational processes, as extensive prior research suggests that aperiodic activity tends to decrease from infancy to adulthood (Cellier et al., 2021; Clark et al., 2024; Hill et al., 2022; McSweeney et al., 2023; Rico-Picó et al., 2023; Schaworonkow and Voytek, 2021; Tröndle et al., 2022). The offset correlates with neuronal populational spiking (Manning et al., 2009), being a robust marker for cortical network interactions (Ibarra Chaoul and Siegel, 2021), while the exponent appears to reflect underlying cortical synaptic currents, etc., excitatory/inhibitory (E-I) balance (Gao et al., 2017).
In this thesis (Study II and III), our focus centered on exploring age-related effects in periodic and aperiodic activity of the brain, with a particular interest in those related to gestational duration. Demonstrating novelty and encompassing various age points, we investigated these effects in both EEG and fMRI measures in both neonates and toddlers.

2.4 Early life stressors and neurodevelopment

Early life stress encompasses stress experienced from the prenatal period through the first years of life. Its definition varies across studies, often including prenatal distress such as maternal depressive or anxiety symptoms (Lautarescu et al., 2020). Additionally, prior research has identified various early life stressors, including but not limited to alcohol, tobacco, drugs, SSRI (selective serotonin reuptake inhibitor) medication, maternal obesity, malnutrition, proinflammatory states, and parental socioeconomic status (for a review, see: Miguel et al., 2019; Pulli et al., 2019;

Rakesh et al., 2023). In this thesis, we will focus on two early life stressors: prematurity and prenatal maternal distress and their associations with offspring brain activity.

2.4.1 Fetal programming hypothesis

The Developmental Origins of Health and Disease (DOHaD) hypothesis is a broad framework, suggesting that exposure to adverse environmental experiences during critical periods of early development may permanently modulate the structure and function of cells, organs, and physiological systems in a time-, tissue-, and challenge-specific manner (Barker, 1998). One component of the DoHaD framework, the fetal programming hypothesis, suggests that perinatal influences can "program" certain traits or vulnerabilities of the fetus, increasing the risk of cardiovascular, metabolic, neuroendocrine, and psychiatric disorders in adulthood (Räikkönen et al., 2011).

Although the biological purpose of fetal programming is not entirely clear, it has been proposed to prepare the fetus to adapt to the later environment, providing an adaptive Darwinian advantage. However, resulting changes can be disadvantageous if the intended developmental plasticity and the adult environment do not align. For instance, if the fetal phenotype adapts to survive undernutrition, but the environment provides an abundance of food, this conflict could potentially increase the risk of developing metabolic diseases. (Harris and Seckl, 2011).

In mechanisms of fetal programming, two major pathways have been proposed: fetal malnutrition and overexposure to glucocorticoids, whose effects likely at least partially overlap and interact with each other (Harris and Seckl, 2011; Räikkönen et al., 2011; Seckl and Holmes, 2007). Also, the role of epigenetic mechanisms, i.e., molecular mechanisms altering gene expression, in mediating the relationship between fetal development and adult health is demonstrated (Doi et al., 2022). The fetal programming hypothesis serves as a frame of reference for examining early life stressors, such as prematurity and prenatal stress, and understanding their effects on later life development.

2.4.2 Prematurity

Preterm birth is defined, according to the World Health Organization (WHO), as birth before 37 weeks of gestation are completed (WHO, 1977). Globally, preterm birth affects approximately 11% of births, with mortality and morbidity outcomes poorer in infants born preterm, especially in the shortest gestations (Lawn et al. 2023; Vogel et al., 2018). Etiologic pathways that result in preterm birth are diverse, and although risk factors of preterm birth, including socio-demographic, nutritional, inflammatory, medical, obstetric, and environmental ones, are recognized,

approximately two-thirds of preterm births occur without an evident risk factor (Frey and Klebanoff, 2016; Hunter et al., 2023; Vogel et al., 2018). Preterm births have wide implications for offspring later health, and increased risk for various neurodevelopmental conditions such as cognitive, sensory, language, visual-perceptual, attention, and learning deficits, as well as cerebral palsy, have been documented (Allen, 2008; Taine et al., 2018). Understanding the factors that influence those neurodevelopmental outcomes is crucial for developing improved treatment and rehabilitation strategies.

Preterm birth related changes in total brain volume and grey matter volume

Preterm birth is associated with altered brain development, with the maturational stage of the brain at the time of birth playing a major role (Ortinau and Neil, 2015). Preterm birth is associated with smaller brain volumes (Alexander et al., 2019; Inder et al., 2005; Parikh et al., 2013; Thompson et al., 2007; Vasu et al., 2014), even in those infants born preterm with low risk for neurodevelopmental deficits (born between 30 and 34 weeks of gestational age without major neonatal morbidity or cerebral pathology) (Soria-Pastor et al., 2009). The reduction in grey matter volume in preterm-born children compared to their term-born peers has been observed not only in school-age children (Kelly et al., 2024) but also in adults (systematic review & meta-analysis: Kelly et al., 2023). This might be a result of short gestational duration, as during the postmenstrual weeks 29–41, grey matter volume of the newborns increases about threefold in MRI measures (Hüppi et al., 1998). Also, regional differences exist with term-born infants having more grey matter in sensorimotor and visual cortices, as well as in parieto-occipital regions, compared with preterm infants near the term age. Changes in brain regional volumes have shown utility to predict long-term cognitive outcomes of neonates. (Peterson et al., 2003).

Preterm birth related changes in white matter myelination

Exposure of the developing brain to effects of preterm birth has been thought to disrupt myelination, likely at least partially mediating its effects on later poorer cognitive, neurodevelopmental, and neuropsychiatric outcomes (Tau and Peterson, 2010). The underlying causes of disturbed myelination are probably multifactorial. First, the most rapid myelination during gestation seems to take place in the very late phase of the gestation: while at postmenstrual week 29, the majority of white matter appears unmyelinated, between postmenstrual weeks 36–40, the proportion of total brain volume containing myelinated white matter increases from 1 to 5% (Hüppi et al, 1998). Second, preterm infants are at high risk for developing white matter injury

when exposed to hypoxic insults and/or perinatal infections, further negatively impacting the development, maturation, and cell death of oligodendrocytes, finally resulting in myelination deficits (van Tilborg et al., 2016, 2018). The effect of prematurity on brain white matter volume in children has been primarily studied in neonates, but it has also been associated with a global reduction in cerebral volume as late as at 12 months of age (Benavides et al., 2019). This reduction in global brain volume has been observed even in adults, when comparing preterm individuals to their full-term same-sex siblings (Kuula et al., 2022). Notably, the reduction in brain volume reported by Kuula et al. (2022) appeared to be specific to grey matter, as white matter volumes did not differ between preterm and full-term siblings. Additionally, Benavides et al. (2019) identified sex-specific differences, with gestational age being associated with lower cortical grey matter volume in males and reduced cerebral white matter volume in females. However, the sample size in this study was relatively small (16 preterm and 17 full-term infants). In summary, there are clear structural changes in the cortical grey matter and the white matter that follow preterm birth.

Preterm birth related changes in neural networks

Prior functional neuroimaging studies support more unorganized microstructure of brain networks in preterm compared to term-born infants. Examining very preterm infants (gestational age at birth < 32 weeks) at term-equivalent age with diffusion tensor imaging (DTI), Bouyssi-Kobar et al. (2018) found higher diffusivity in the prefrontal, parietal, motor, somatosensory, and visual cortices in preterm compared to term-born infants, suggesting delayed maturation of these cortical areas. Premature birth seems to have significant alterations on the local topology of the structural network, especially in subcortical systems and limbic/paralimbic areas (Zheng et al., 2023), as well as widespread impairments on the functional connectivity of resting state networks and abnormally increased lateral motor network connectivity (Eyre et al., 2021). The findings from neural network alterations may explain the specific difficulties, such as impaired cognition, in preterm infants.

Preterm birth related changes in neural activity

In a recent fMRI study employing spontaneous BOLD signal for studying amplitudes of low-frequency fluctuations (ALFFs), moderate/late preterm newborns (born after 32 but before 37 weeks of gestation) showed altered ALFF values compared to term-born newborns, mostly in the primary sensory and motor cortices (Wu et al., 2016). In addition to that, frequency band-dependent changes occurred as greater ALFF

values in lower frequency bands were observed in the primary somatosensory cortex in preterm newborns. Findings support that primary somatosensory and motor regions, major cortical hubs during the neonatal period, show preterm-related alterations in their development.

Prior EEG studies of preterm-born neonates reveal a developmental progression from desynchronized neural activity patterns towards more synchronized activity, mainly through spatiotemporal differentiation, when transferring from early preterm neonates (24–27 gestational weeks) to later preterm ones (more than 29 gestational weeks) (Kostović & Judaš, 2002). Notably, as thalamocortical connections, enabling the ability to respond to environmental stimuli, form around gestational week 26, very preterm-born neonates show immaturity of cortical electrical responses. Cortical evoked potentials continue to develop across the first years of life, paralleling the growth of corticocortical connections. (Kostović and Judaš, 2002).

Prematurity & Developmental outcomes

As discussed above, the etiological pathways leading to preterm birth and its long-term implications for offspring health are diverse (Hunter et al., 2023; Allen, 2008; Taine et al., 2018). Preterm birth remains a leading cause of neonatal mortality worldwide (Ashorn et al., 2023). While lower gestational age and birth weight are strongly associated with severe cognitive impairment during the first years of life, this association tends to weaken over time, becoming less pronounced in later childhood and adolescence (Brydges et al., 2018). The long-term effects of moderate and late preterm birth on cognitive and mental health outcomes are generally mild, and findings regarding their impact in adulthood remain inconsistent (Fernández de Gamarra-Oca et al., 2021).

A long-standing question in neonatal and developmental research is the extent to which later developmental outcomes following preterm birth are driven by prematurity itself versus the underlying causes of preterm birth. In a recent review, Ashorn et al. (2023) propose a conceptual framework for the causes and consequences of being a small vulnerable newborn, encompassing preterm birth, small for gestational age, and low birth weight (<2500 g). They suggest that many long-term consequences are shared by both preterm birth and fetal growth restriction and that contextual factors (e.g., community and societal influences) play a crucial role in predisposing mothers and fetuses to exposures that lead to preterm birth (Ashorn et al., 2023). However, further research is needed to identify the mediating factors linking prematurity to later neurodevelopmental outcomes.

Summary

Taken together, preterm birth is associated with several aspects of brain development, and the results show also sexual dimorphism. However, it is worth noting that some preterm children might reach developmental milestones in time or even early, thanks to early extrauterine stimulation, supporting the idea that development is not purely dependent on cerebral maturation but also affected by environmental stimuli. (Den Ouden et al., 1991). Prior studies highlight the importance of revealing underlying factors mediating the effects of prematurity on later neurodevelopmental outcomes. However, the need for more accurate fMRI-based brain metrics to study maturational processes in the neonatal brain exists.

2.4.3 Prenatal distress

Prenatal distress encompasses maternal psychological symptoms of depression or anxiety and perceived stress linked to daily hassles or major life events (Karlsson et al., 2018). During the pregnancy, up to 25% of women experience stress, anxiety, and/or depression on a pathological level, making prenatal distress a considerable early-life stressor (Adamson et al., 2018). Exposure to maternal distress during pregnancy heightens the risk of various mental and behavioral disorders by influencing child brain development, leading to a need to investigate further the links between the prenatal stress and the neural processing in offspring (Räikkönen et al., 2011; Tuovinen et al., 2021; Van den Bergh et al., 2020).

Role of fetal glucocorticoid exposure

Aligning with the hypothesis of fetal programming, the proposed mediator of prenatal distress effects on offspring neurodevelopment is prenatal glucocorticoid exposure, which can be either endogenous or excess (Harris and Seckl, 2011). Glucocorticoids play a crucial role in fetal development during gestation, contributing to the maturation of the lungs and proper brain development. This involves initiating terminal maturation, remodeling axons and dendrites, and affecting cell survival. (Harris and Seckl, 2011).

However, the balance of glucocorticoid levels can be disrupted by factors such as maternal distress or maternal glucocorticoid therapy, the latter of which is commonly used when at risk of preterm delivery to e.g., accelerate fetal lung maturation (McGoldrick et al., 2020; Räikkönen et al., 2011; Räikkönen et al., 2020). Mechanisms exist to shield a developing fetus from high maternal glucocorticoid levels, primarily through the expression of 11ß hydroxysteroid dehydrogenase type 2 (HSD2) in the placenta, which inactivates maternal endogenous glucocorticoids. Nevertheless, excess corticosteroids can efficiently pass through the placenta, as they

are poor substrates for HSD2, and subsequently convert to physiological cortisol within fetal tissues. (Räikkönen et al., 2011). Furthermore, approximately 10–20 % of maternal endogenous glucocorticoids can pass the placental barrier, exposing the developing fetus to the effects of maternal distress (Murphy et al., 2006).

In the offspring exposed to prenatal distress, impaired negative feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis has been proposed to be an underlying pathophysiological mechanism (Huizink et al., 2004). A number of prospective longitudinal studies have indicated changes in HPA-axis activity in offspring with prenatal distress exposure. However, the nature of the associations varied in terms of stress measures used, offspring age, and HPA axis function measure type. (Van den Bergh et al., 2020). HPA axis activity is influenced by genetic factors as well, and the role of these is not yet fully understood (Van den Bergh et al., 2020). Thus, studies examining potential influences of genetic variations and epigenetic control on neurodevelopment are required.

Noteworthy is that, while prenatal stress exposure might set certain developmental risks (as we will discuss in the next chapter), the early postnatal environment factors such as the quality of caregiving, socioeconomic status, social support, and cognitive/linguistic stimulation can moderate the associations between the prenatal stress and offspring's brain structure and function (Nolvi et al., 2023).

Effects on offspring neurodevelopment

Prenatal distress has been linked to direct effects on various aspects of neurodevelopment during the prenatal period, including neurogenesis, neuronal migration, cellular differentiation, and synaptic refinement (Fatima et al., 2017). Animal studies have shown developmental differences in amygdala nuclei and decreased hippocampal volume in response to prenatal stress in rats and rhesus monkeys, both of the brain areas playing a central role in emotional processing (Coe et al., 2003; Kraszpulski et al., 2006). Parallel findings have been obtained in humans, as MRI measures have demonstrated impaired fetal biochemistry, hippocampal growth, and accelerated cortical folding in fetuses exposed to prenatal distress (Wu et al., 2020). Further, smaller amygdala volumes have been associated with prenatal distress exposure in newborn boys, but not girls, as well as with lower stability of the frontoparietal network in neonates exposed to prenatal distress (Lehtola et al., 2020; Tuulari et al., 2024). Stress-related changes may show long-lasting nature, as prenatal maternal depressive symptoms have been associated with smaller amygdala volumes on MRI, even at the age of 4 years (Acosta et al., 2020), as well as higher fractional anisotropy in 5-year-old boys, in a sex-specific manner (Kumpulainen et al., 2023).

At the level of developmental outcomes, maternal prenatal distress has been associated with altered neurodevelopment in offspring, ranging from birth to early adulthood (review: Räikkönen et al., 2011). Long-term outcomes associated with exposure to prenatal stress include, for example, attention deficits and hyperactivity, as well as behavioral and emotional problems during (pre-)school age (Niederhofer & Reiter, 2004). In adolescence, cognitive control problems as well as higher levels of depressive symptoms have been reported in offspring exposed to prenatal stress (Räikkönen et al., 2011; Van den Bergh et al., 2008).

Finally, it is worth noting that the developmental changes induced by prenatal distress may not be entirely clear in terms of their impact on future outcomes. However, there is some evidence suggesting that low to moderate levels of prenatal stress may play an adaptive role, whereas higher levels could result in negative neurodevelopmental outcomes (Fatima et al., 2017). Additionally, the effects of prenatal stress may be moderated by later postnatal environments, such as parental caregiving quality, social support, or socioeconomic status (Nolvi et al., 2023).

Findings from EEG studies

Prior EEG research is predominantly centred on maternal prenatal anxiety as the primary indicator of prenatal distress (Otte et al., 2015; van den Heuvel et al., 2018), though some studies focused on maternal depressive symptoms also exist (Goodman et al., 2021; Gustafsson et al., 2018). Methodologically, these studies have primarily focused on ERPs (Otte et al., 2015; van den Heuvel et al., 2018) and frontal asymmetry in electrophysiological activity (Goodman et al., 2021; Gustafsson et al., 2018). Most prior research has concentrated on infants (Goodman et al., 2021; Gustafsson et al., 2018; Otte et al., 2015) or older children, such as 4-year-olds (van den Heuvel et al., 2018). However, little is known about ages in between. Therefore, there is a clear need for EEG studies targeting the toddler age group.

Prenatal anxiety symptom-related studies show variation in their type of stimuli and age groups used. Also, associations between prenatal stress and neural responses seem to vary, as Otte et al. (2015) suggest stronger reactions, evidenced by larger P350 amplitudes, to fearful auditory stimuli in infants exposed to prenatal maternal anxiety, while van den Heuvel et al. (2018) showed that children of prenatally anxious mothers exhibited stronger attention, indicated by larger late positive potential amplitudes, to neutral but not to unpleasant pictures. Aligned with this, maternal mindfulness during pregnancy has also been associated with fewer attentional resources to frequent irrelevant sounds, measured with ERPs (van den Heuvel et al., 2015). Results might reflect that exposure to prenatal distress, in that case to prenatal anxiety symptoms, could be seen as impaired adaptation to neutral stimuli, indicated as higher attention towards harmless environmental stimuli, and

that pregnancy-related interventions can moderate this effect. However, the number of studies is still low, and further studies are needed in various age groups.

Prenatal depressive symptom-related studies have primarily focused on functional measures such as EEG frontal asymmetry, while gaps in studies examining offspring emotion perception or emotional processing exist. Prior studies suggest that even the subclinical levels of prenatal maternal depressive symptoms may have potential effects on infant electrophysiological activity, and one potential trait marker of a child's vulnerability to maternal depression could be relative frontal EEG asymmetry. It is also proposed that prenatal depression may better predict offspring's EEG activity compared to postnatal or concurrent depression (Goodman et al., 2021; Gustafsson et al., 2018).

Summary

Prenatal distress is common and can have various long-term impacts on offspring neurodevelopment, although the mediating mechanisms as well as impact on future outcomes are not yet completely understood. Especially epigenetic mechanisms and moderate effects of offspring sex and resilience-promoting factors need further investigation.

Despite the existing body of literature, mainly focusing on infants, the association between maternal prenatal stress and a toddler's neural perception and processing of emotional information remains largely unexplored. This thesis aims to bridge this gap by investigating the impact of prenatal maternal depressive symptoms on the subsequent differences in emotion sound perception in offspring at the age of 3 years.

3 Aims

The aim of this thesis was to utilize functional neuroimaging techniques to examine changes in neural activity related to age, gestational duration, and prenatal distress in neonates and toddlers. Our research investigates how neural activity develops during early stages of life, particularly focusing on the impact of maternal prenatal distress and premature birth. Our objective was to identify potential neural indicators of both normal and delayed brain maturation, as well as to demonstrate the relationship between maternal distress and neural activity in offspring.

Aims of the studies were:

- Study I: To examine the effects of prenatal distress (prenatal maternal depression symptoms) on 3-year-olds neural responses to emotionally uttered auditory stimuli, using auditory ERPs in EEG.
- Study II: To utilize spectral parameterization, a method previously primarily used in electrophysiological studies, to investigate age- and prematurity-related changes in aperiodic parameters from the fMRI BOLD signal power spectrum in neonates.
- Study III: To investigate age- and gestational duration-related effects using both periodic and aperiodic parameters of the EEG power spectrum in neonates and 3-year-olds.

4 Materials and Methods

4.1 Ethics

The FinnBrain Birth Cohort Study has been approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK: 57/180/2011, 15.3.2016§109), and the studies were conducted according to the Declaration of Helsinki. The Developing Human Connectome Project (dHCP) is approved by the UK National Research Ethics Authority (14/LO/1169). A written informed consent was collected from parents for their children to participate in studies.

4.2 Participants

4.2.1 FinnBrain Birth Cohort Study (Study I and III)

Studies I and III of this thesis were part of the FinnBrain Birth Cohort Study (Karlsson et al., 2018), a prospective population-based pregnancy cohort with 3803 recruited families during the years 2011-2015 at the first trimester ultrasound. FinnBrain is focused on investigating the effects of early-life stress on the development of the child using multidisciplinary methods.

Participants of both studies were born during the years 2013–2015. Neonates (Study III) were recruited for an EEG recording at the maternity wards of Turku University Hospital on average 1–2 days after birth. 3-year-olds (Study I and III) were recruited during the years 2016–2018 from Southwest Finland. Demographics of the participants and their mothers are presented in **Table 1** and **Table 3** (neonates) as well as **Table 2** and **Table 4** (toddlers).

Table 1. Demographics of neonates and their mothers (continuous variables) of FinnBrain Birth Cohort Study from Study III (N = 73).

	N	MEAN	SD	RANGE
NEONATES				
Gestational weeks at birth	73	40.0	1.3	36.1–42.3
Apgar (5min)	73	9.1	0.5	8–10
Birth weight (g)	73	3549.9	476.3	2740–5470
Birth length (cm)	73	50.4	2.2	46.0–57.0
Postmenstrual age at EEG recording (weeks)	73	40.2	1.3	36.4–42.4
Postnatal age at EEG recording (days)	73	1.5	1.1	0–5
MOTHERS OF NEONATES				
Age at delivery (years)	73	30.6	4.3	22–42
Pre-pregnancy BMI (kg/m^2)	73	23.5	3.3	17.1–36.4

Table 1 footnote | Abbreviations: N = number of participants; SD = standard deviation; g = gram; BMI = body mass index; cm = centimeter; Apgar (5min) = newborn health assessment scale 1-10 assessed 5min postnatally (Appearance, Pulse, Grimace, Activity, Respiration). Some data is missing due to missing questionnaire and register data acquisition.

Table 2. Demographics of toddlers and their mothers (continuous variables) of FinnBrain Birth Cohort Study from Study I (N = 58) and Study III (N = 56).

	N		MEAN		SD		RANGE	
TODDLERS	**Study I**	**Study III**	**Study I**	**Study III**	**Study I**	**Study III**	**Study I**	**Study III**
Gestational weeks at birth	58	56	39.8	39.9	1.4	1.3	36.3–42.3	36.9–42.3
Apgar (5min)	58	56	9.1	9.0	0.5	0.6	8–10	7–10
Birth weight (g)	58	56	3598	3627	544	529	2580–5470	2600–5470
Postnatal age at EEG recording (months)	58	56	37.2	36.7	1.0	1.0	35.2–38.7	34.75–38.17
MOTHERS OF TODDLERS	**Study I**	**Study III**	**Study I**	**Study III**	**Study I**	**Study III**	**Study I**	**Study III**
Age at delivery (years)	58	56	30.6	30.8	4.3	4.3	19–39	19–39

	N		MEAN		SD		RANGE	
Pre-pregnancy BMI (kg/m^2)	58	56	24.5	24.7	4.3	4.9	19.0–37.0	19.2–37.0
Maternal depressive symptoms (EPDS) at gw 24	58	-	4.93	-	4.63	-	0.0–17.0	-
total score of 11-12	2	-		-		-		-
total score of 13-14	3	-		-		-		-
total score of > 14	3	-		-		-		-
Maternal depressive symptoms (EPDS), 3 months postpartum	53	-	4.34	-	4.07	-	0.0–16.0	-
Maternal depressive symptoms (EPDS), 6 months postpartum	46	-	4.63	-	5.12	-	0.0–23.0	-
Maternal depressive symptoms (EPDS), 12 months postpartum	41	-	4.46	-	4.57	-	0.0–19.0	-
Maternal depressive symptoms (EPDS), 24 months postpartum	33	-	4.40	-	4.07	-	0.0–14.0	-
Maternal anxiety (SCL-90) at gw 24	58	-	3.82	-	4.34	-	0.0–16.7	-
Maternal anxiety (SCL-90), 3 months postpartum	53	-	2.66	-	3.35	-	0.0–15.0	-
Maternal anxiety (SCL-90), 6 months postpartum	46	-	2.76	-	4.91	-	0.0–28.0	-
Maternal anxiety (SCL-90), 24 months postpartum	33	-	2.88	-	3.90	-	0.0–16.0	-

Table 2 footnote | Abbreviations: N = number of participants; SD = standard deviation; g = gram; BMI = body mass index; gw = gestational week; cm = centimeter; Apgar (5min) = newborn health assessment scale 1-10 assessed 5min postnatally (Appearance, Pulse, Grimace, Activity, Respiration); EPDS = The Edinburgh Postnatal Depression Scale; SCL-90 = Symptom Check List. Some data is missing due to attrition in questionnaire and register data acquisition.

Table 3. Demographics of neonates and their mothers (categorical variables) of FinnBrain Birth Cohort Study from Study III (N = 73).

	N	MISSING	%
NEONATES			
Sex	73	0	
female	40		54.8
male	33		45.2
MOTHERS OF NEONATES			
Native language	67	6	
finnish	64		95.5
swedish	3		4.5
Educational level (gw 12)	67	6	
Matriculation examination or lower	28		41.8
Higher vocational training	18		26.9
University degree or higher	21		31.3
Monthly income (gw 12)	67	6	
< 500 €	5		7.5
501–1000 €	9		13.4
1001–1500 €	14		20.9
1501–2000 €	27		40.3
2001–2500 €	7		10.5
2501–3000 €	1		1.5
3001–3500 €	3		4.5
3501–4000 €	1		1.5
Alcohol use during pregnancy (gw 12)	67	6	
no	50		74.6
once in a week	5		7.5
1–2 times per month	4		6.0
more rarely than once in a month	7		10.4
Drug use during pregnancy (gw 12)	67	6	
yes	1		1.5
no	66		98.5

	N	MISSING	%
Tobacco smoking during pregnancy (gw 12)	66	7	
yes	11		16.7
no	55		83.3
Marital status	73	0	
Married	36		49.3
Unmarried	35		48.0
Divorced	1		1.4
Registered partnership	1		1.4

Table 3 footnote | Abbreviations: N = number of participants; y = years; gw = gestational week; Some data is missing due to attrition in questionnaire and register data acquisition.

Table 4. Demographics of toddlers and their mothers (categorical variables) of FinnBrain Birth Cohort Study from Study I (N = 58) and Study III (N = 56).

	N		MISSING		%	
TODDLERS	**Study I**	**Study III**	**Study I**	**Study III**	**Study I**	**Study III**
Sex	58	56	0	0		
female	31	28			53.4	50.0
male	27	28			46.6	50.0
Day care status (at age of 2y)	34	35	24	21		
At home	14	11			41.2	31.4
Nursery school	13	9			38.2	25.7
Family day care	6	13			17.6	37.1
Shift nursery school	1	1			2.9	2.9
Number of siblings (at the age of 4y) [a]	31	33	27	23		
0 siblings	10	12			32.3	36.4
1 sibling	19	20			61.3	60.6
2 siblings	2	1			6.5	3.0
MOTHERS OF TODDLERS	**Study I**	**Study III**	**Study I**	**Study III**	**Study I**	**Study III**
Native language	58	55	0	1		
Finnish	56	54			96.6	98.2

	N		MISSING		%	
Swedish	1	1			1.7	1.8
Other	1	0			1.7	0.0
Smoking during pregnancy at gw 12	58	51	0	5		
no	55	47			94.8	92.2
yes	3	4			5.2	7.8
Drinking during pregnancy at gw 12	54	51	4	5		
no	47	42			87.0	82.4
once in a week	2	2			3.7	3.9
1–2 times per month	2	3			3.7	3.9
more rarely than once in a month	3	4			5.6	7.8
Drinking during pregnancy at gw 36	54	-	4			
no	50	-		-	92.6	-
more rarely than once in a month	4	-		-	7.4	-
Use of drugs during pregnancy	54	51	4	5		
no	54	51			100.0	100.0
Educational level	58	55	0	1		
Matriculation examination or lower	14	11			24.1	20.0
Higher vocational training	24	21			41.4	38.2
University degree or higher	20	23			34.5	41.8
Monthly income (gw 12)	58		0			
< 500 €	6				10.3	
501–1000 €	7				12.1	
1001–1500 €	8				13.8	
1501–2000 €	24				41.4	
2001–2500 €	10				17.2	
2501–3000 €	3				5.2	

Table 4 footnote | Abbreviations: N = number of participants; y = years; gw = gestational week; Some data is missing due to attrition in questionnaire and register data acquisition. [a] Half-siblings and different parent siblings are also included.

Technical issues with the EEG amplifier led to the exclusion of data from 53 participants in the 3-year-old dataset due to poor-quality data. The exclusion criteria

of studies, number of excluded participants, and final sample sizes are presented in **Table 5**.

Table 5. Sample sizes, excluded participants, and exclusion criteria for Studies I and III.

	3-YEAR-OLDS (STUDY I)	**3-YEAR-OLDS (STUDY III)**	**NEONATES (STUDY III)**
Original sample size	123		158
Excluded (no sleep data)	NA		39
Omitted due to technical problems	53		NA
Excluded by visual quality check	NA	11	39
Gestational age < 36 gw	1	1	1
SSRI using during pregnancy	5 [a]	1 [b]	4 [b]
5min Apgar < 7	1	1	-
Birth weight < 1800 g	-	-	-
Missing information of postnatal age	-	-	1
Poor data quality in data processing	5 [c]	-	1 [d]
Final sample size	**58**	**56**	**73**

Table 5 footnote | Abbreviations: gw = gestational week; SSRI = selective serotonin reuptake inhibitor. NA = Not applicable. Apgar = newborn health assessment scale 1-10 assessed 5min postnatally (Appearance, Pulse, Grimace, Activity, Respiration). [a] SSRI use at first trimester of gestation, also missing values included. [b] SSRI use at first or third trimester of gestation, no missing values included. [c] Poor data quality in EEG preprocessing. [d] Poor fit in spectral parameterization. Exclusion criteria of studies are marked inside the grey box.

4.2.2 Developing Human Connectome Project (Study II)

Study II used preprocessed data released as part of the Developing Human Connectome Project (dHCP) data release 3.0, consisting of 887 rs-fMRI scans from 783 neonatal research subjects between 27-45 weeks of age (359 females, 424 males), 205 of whom were born preterm. The Developing Human Connectome Project is an observational, cross-sectional open science program dedicated to mapping the connectivity of the human brain during early development, with its main goal to create a dynamic map of the human brain across early development (Edwards et al., 2022). Demographics of the participants are presented in **Table 6** and **Table 7**.

Table 6. Demographics of neonates (continuous variables) from Developing Human Connectome Project from Study II (N = 599). No missing values from any of participants.

	N	MEAN	SD	RANGE
Gestational age at birth (weeks)	599	38.4	3.9	23.0–42.7
Postmenstrual age at scan (weeks)	599	40.8	2.4	27.4–44.7
Postnatal age at scan (weeks)	599	2.5	3.5	0.0–19.6
Birth weight (kg)	599	3.1	0.9	0.5–4.8
Head circumference at scan (cm)	599	33.6	6.8	0.0–39.5

Table 6 footnote | Abbreviations: N = number of participants; SD = standard deviation; kg = kilogram; cm = centimeter.

Table 7. Demographics of neonates (categorical variables) from Developing Human Connectome Project from Study II (N = 599).

	N	%
Prematurity	599	-
term	483	80.6
preterm	116	19.4
Sex	599	-
male	323	53.9
female	276	46.1

Table 7 footnote | Abbreviations: N = number of participants.

Term-born infants were selected from postnatal wards based on clinical well-being, while preterm-born infants were recruited from both the neonatal unit and postnatal wards. Infants were excluded if they had a history of severe compromise at birth necessitating prolonged resuscitation, a diagnosed chromosomal abnormality, or any contraindication to MRI scanning. The final study group comprised infants who did not require treatment for clinically significant brain injury. The number of excluded participants and final sample sizes are presented in **Table 8**.

Table 8. Sample sizes and excluded participants for Study II.

	NEONATES (STUDY II)
Original number of scans/participants	887/783
Excluded scans based on quality control	105
Scans from non-singleton participants	129
Number of good-quality scans for singleton participants	605
Poor fit in spectral parameterization	6
Final sample size	**599**

4.3 Questionnaire data (Study I)

4.3.1 Maternal self-reported pre- and postnatal distress

Self-reported data of maternal depressive and anxiety symptoms during pregnancy were gathered at gestational weeks 14, 24, and 34, as well as 3, 6, and 24 months postpartum. Additionally, depressive symptoms were assessed at 12 months postpartum. The Edinburgh Postnatal Depression Scale (EPDS), a validated instrument comprising 10 items rated on a four-point Likert scale, was employed for evaluation (Cox et al., 1987). Higher total scores, ranging from 0 to 30, indicate a greater likelihood of clinical depression. EPDS has demonstrated validity in screening depressive symptoms during both antenatal and postnatal periods (Kozinszky and Dudas, 2015). Furthermore, the anxiety subscale from the Symptom Checklist (SCL-90) was utilized, consisting of 10 items rated on a five-point Likert scale. This subscale evaluates symptoms associated with high manifest anxiety, including restlessness, nervousness, cognitive signs of anxiety, and panic attacks (Derogatis et al., 1976).

Sum scores for both the EPDS and SCL-90 at gestational week 24 were computed, with missing values replaced by the mean of available data (up to three missing values per participant). These scores were utilized as predictors in the analyses, while sum scores at subsequent postpartum time points were reported as demographics in **Table 2**.

4.4 Data acquisition and preprocessing

4.4.1 EEG recording (Study I and III)

Recording setup:

Both neonatal and 3-year-old EEG measurements were recorded using an actiCAP electrode cap (EASYCAP, Germany) and a BrainVision Quickamp amplifier (Brain Products, Germany). In neonates, EEG was recorded with 16 channels, while in 3-year-olds, 32 electrodes were utilized. Electrode placement followed the international 10–20 system (**Figure 5**). The original sampling frequency was 500 Hz for neonates and 250 Hz for 3-year-olds. To ensure consistency for subsequent analyses, neonatal EEG data were down sampled to 250 Hz. Reference and ground electrodes were positioned on the forehead.

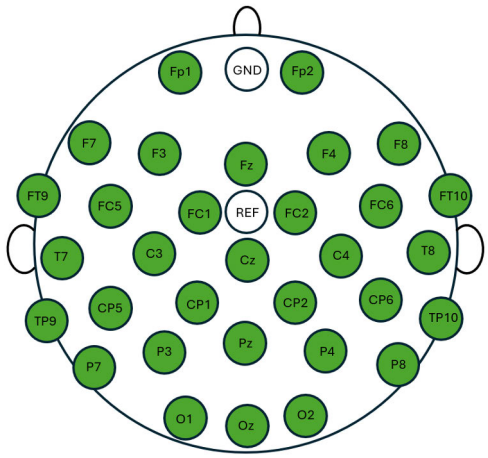

Figure 5. Example of 10-20 electrode setup used in EEG recordings (toddlers, 32 electrodes). Author's own drawing.

Neonate measurement (Study III):

EEG measurements were performed within two hours after feeding the neonates to ensure they were in a calm sleep phase and minimize potential restlessness. Following electrode preparation, if necessary, attempts were made to induce the neonates into sleep using a pacifier or mild glucose solution. The researcher visually assessed the neonate's alertness, and the recording session was terminated immediately if prolonged crying occurred.

During the recording, three types of data were collected sequentially: 1) auditory paradigm + sleep data, consisting of three types of emotionally valenced pseudo-words (duration approximately 12 minutes; for a detailed presentation of the multi-feature paradigm, refer to Kostilainen et al., 2018)), 2) pseudo-word paradigm data (duration approximately 14 minutes), and 3) sleep data (duration approximately 0-20 minutes). Sleep data was recorded only if the neonate was still sleeping after blocks 1) and 2). Neonates were positioned on their left side, with the right ear facing upwards. Emotionally valenced auditory stimuli were presented twice from a loudspeaker approximately 1 meter from the neonate, at a standard volume of 60 dB. The total duration of the measurement session was approximately 45 minutes.

Toddler measurement (Study I and III):

Before EEG recordings, each family received an email containing a brief introduction to the visit's agenda, accompanied by a few pictures for the child to view. This aimed to familiarize the family, particularly the child, with the upcoming visit. Measurement visits were scheduled to accommodate family routines, including both weekdays and weekends, as well as morning and afternoon slots to choose. To establish a comfortable atmosphere at the start of each visit, a teddy bear wearing the electrode cap was presented, guiding the child through the preparation steps. Meanwhile, during the approximately 15-minute electrode setup, the child had the opportunity to watch a self-selected animated series.

During the recording, unlike in neonates, only auditory paradigm data was recorded. The child was seated either alone on a chair or on their mother's lap, with stimuli presented from a loudspeaker positioned 1.25 meters away at a volume of 60 dB. A room divider between the child and the investigator helped to minimize potential distractions. The auditory paradigm (duration of one session approximately 5 minutes) was presented twice for each child, with the option for a short break (approximately 5 minutes) between recording sessions if required. To enhance compliance and minimize motion artifacts during EEG recording, children were engaged with a silent video featuring abstract shapes, originally designed for functional MRI (Inscapes movie, Vanderwal et al., 2015). Additional comfort items such as toys and drawing tools were provided only if necessary. The total duration of the measurement session was approximately 45 minutes.

Auditory paradigm:

In 3-year-olds and neonate EEG recording, the multifeature MMN paradigm by Näätänen et al. (2004), subsequently expanded to include emotional stimuli variants

by Pakarinen et al. (2014), was used (for a comprehensive description of the experiment, see: Kostilainen et al., 2018 and Lavonius et al., 2020).

The paradigm comprises a standard stimulus, consisting of a bisyllabic pseudo-word (/ta-ta/), and four distinct types of linguistically relevant deviant stimuli. Standard stimuli have a duration of 336 ms and a probability of occurrence of 46% (200 trials in one recording). The deviants vary from the standard stimulus in terms of slight changes in vowel duration, vowel alteration, intensity, or frequency. Additionally, the paradigm includes three emotionally loaded uttered stimuli, featuring angry, sad, and happy variants of the /ta-ta/ pseudo-word, resented infrequently in the stimulus stream, with durations of 388 ms, 337 ms, and 436 ms, respectively, each with a probability of occurrence of 3% (12 trials in one recording for each emotion). Stimuli were presented with a stimulus onset asynchrony of 650 ms.

In Study I, the paradigm was administered twice for each participant, resulting in a total of 400 trials for the standard stimulus and 24 trials for each emotion variant per child.

4.4.2 Resting state fMRI scanning (Study II)

We used a subset of the openly available dHCP data set, third release, consisting of 887 resting state fMRI scans from 783 neonates.

Neonatal Brain Imaging System (NBIS) was utilized for data collection, comprising a specialized 32-channel array coil and a positioning device. The use of NBIS alongside advanced techniques designed to minimize disturbance to the sleeping infant and the need for scan repeats has been shown to yield significant improvements. Specifically, studies have demonstrated a 2.4-fold increase in signal-to-noise ratio compared to using an adult coil, along with a remarkable 90% completion rate of the scan protocol (Hughes et al., 2017).

4.5 Preprocessing

4.5.1 EEG (Study I and III)

The EEG data were preprocessed using MATLAB (Study I: r2017b; Study III: r2018b; The MathWorks, Inc.) with the EEGLAB toolbox (v13.5.4b; Delorme and Makeig, 2004)).

In Study I, we employed the PREP (Early Stage Preprocessing, Bigdely-Shamlo et al., 2020) pipeline for data preprocessing. This standardized pipeline is designed to eliminate unwanted artifacts and contaminants from noisy data channels. As part of the preprocessing steps, we removed the line frequency (in Finland, 50 Hz) and

its harmonics. Additionally, the data were referenced using the robust average reference algorithm.

In Study III, EEG data from both neonates and 3-year-olds underwent visual assessment, and datasets displaying consistently poor data quality were excluded (in neonates, N = 39; in 3-year-olds, N = 11). To preprocess the data, the Artifact Subspace Reconstruction (ASR; Kothe & Jung, 2014) method was applied using the *clean_artifacts* function with default settings. ASR is a validated method for automatic artifact removal that utilizes statistical and machine learning techniques to identify, model, and eliminate artifacts, specifically designed for selective artifact removal while aiming to preserve the underlying neural signals (Chang et al., 2020). Following artifact removal, any removed channels were interpolated, and the data were re-referenced to a common average reference.

4.5.2 fMRI (Study II)

Initial preprocessing of the fMRI data was conducted by dHCP, following the steps outlined below. We used this preprocessed data for further analyses.

The data was preprocessed using a dedicated pipeline optimized for neonatal imaging, as described in Fitzgibbon et al. (2020). This pipeline addressed susceptibility dynamic distortion as well as intra- and intervolume motion effects, corrected with a bespoke pipeline (J. L. Andersson et al., 2001; J. L. R. Andersson et al., 2003, 2017, 2018). To remove signal artifacts related to head motion, cardiorespiratory fluctuations, and multiband acquisition, 24 extended rigid-body motion parameters and single-subject ICA noise components identified with the FSL FIX tool (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's Software Library, version 5.0) were regressed out. Denoised data were then registered into T2-weighted native space using boundary-based registration (Greve and Fischl, 2009) and further aligned to a standard space based on a age-specific template from the dHCP volumetric atlas (Schuh et al., 2018) with diffeomorphic multimodal registration (Avants et al., 2008).

For each participant, fMRI timeseries were defined using the same data as in a prior study (França et al., 2024). The T2-weighted volume was parcellated into 90 cortical and subcortical parcels using the AAL (Automated Anatomical Labeling) atlas (Tzourio-Mazoyer et al., 2002), mapped to the neonatal brain, and manually corrected into the dHCP high-resolution template (Schuh et al., 2018). Non-linear registration based on diffeomorphic symmetric image normalization (SyN; Avants et al. (2011)) was employed to align the AAL atlas with each subject's native space using T2-weighted contrast and previously obtained segmentation. Grey matter segmentation and parcels were then propagated into each subject's fMRI space using transformations obtained from boundary-based linear registration from the

functional dHCP preprocessing pipeline (Fitzgibbon et al., 2020). Average BOLD timeseries were calculated for each AAL atlas parcel within their intersection with grey matter, deep grey matter, and basal ganglia segmentation masks.

Volumes with DVARS (the root mean square intensity difference between successive volumes) > 1.5 interquartile range above the 75th centile after motion and distortion correction were identified using *fsl_motion_outliers* in FSL and considered as motion outliers (Eyre et al., 2021). The number of motion-outlier volumes for each subject was recorded and included as a random effect in multilevel regression analyses. This was justified since we wanted to keep the entire timeseries data for later modeling and ICA-based was deemed effective in noise removal.

4.6 Event-related potentials (Study I)

Preprocessed EEG data were epoched to −100 to 550 ms epochs with baseline correction from −100 ms to 0. A high-pass filter of 1 Hz was applied. Artifactual trials were eliminated using the pop_jointprob function with local and global thresholds set to 4, along with rejection of trials with transients exceeding ± 150 μV at any recording electrodes. Participants with less than 10 out of 24 (41.6%) trials remaining after rejection were excluded from further analyses. On average, each participant retained 19.2 valid trials for the angry stimulus (SD 5.72), 18.5 trials for the sad stimulus (SD 7.01), and 18.2 trials for the happy stimulus (SD 5.86) remained.

Epochs for each stimulus type were averaged separately, and the difference wave (standard – deviant; mismatch response) was computed for each participant and emotional stimulus. Difference waves with amplitudes exceeding ± 50 μV were eliminated. Three electrodes (F3, Fz, and F4) were chosen by visual inspection for further analyses based on their most negative difference between standard and emotional sounds throughout the recording. This was consistent with previous findings showing MMNs can frequently be seen as negative displacement at the frontocentral and central electrodes (Näätänen et al., 2007).

Finally, the mean mismatch response amplitude values of the three frontal electrodes were averaged together ("F-electrodes") and separately calculated for three different time windows, chosen by visual inspection: early (80–120 ms), intermediate (240–280 ms), and late (350–450 ms). ERP waveforms are presented in **Figure 6**.

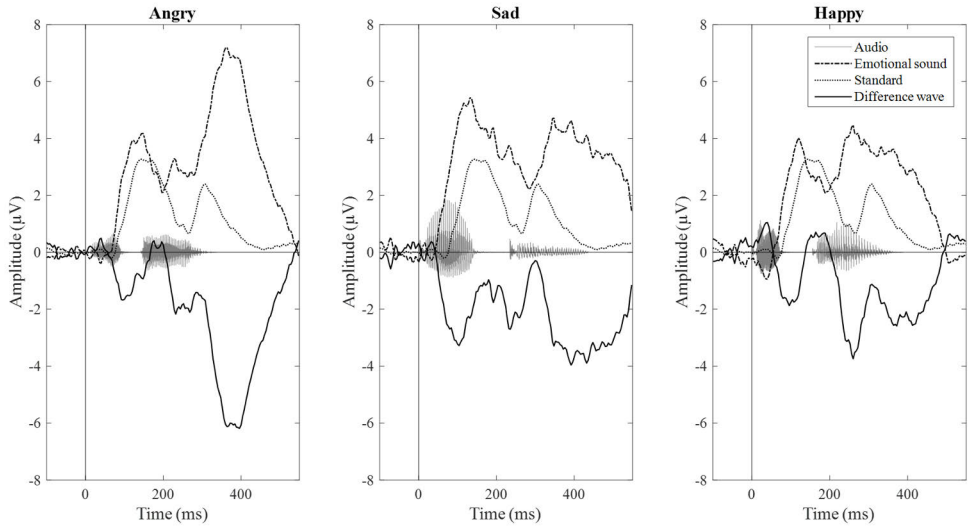

Figure 6. ERP waveforms for emotional auditory stimuli (angry, sad, and happy). Reprinted from Study 1 which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

4.7 Spectral parameterization (Study II and III)

4.7.1 fMRI BOLD-signal (Study II)

It has been proposed that low-frequency fluctuations of the BOLD signal, typically ranging from 0.01 to 0.1 Hz, encompass both periodic and aperiodic components (Murphy et al., 2013). The Spectral Parameterization (SpecParam, formerly FOOOF) method allows for the differentiation of these components (Donoghue et al., 2020). Furthermore, the high temporal resolution of the dHCP data (0.392 seconds) offers new insights into the power spectrum of the data.

In Study II, the power spectrum estimation and spectral parameterization were conducted on neonatal fMRI BOLD signal data for each of the 90 regions of interest (ROIs) separately.

Power spectra estimation

We estimated and parameterized the power spectrum between 0.01 and 0.15 Hz using multitaper spectral analysis (Thomson, 1982) for each fMRI time series representing a region-of-interest-specific BOLD signal.

Spectral parameterization

Python-based SpecParam/FOOOF toolbox (version 1.1.0) was used to parameterize the spectral data by separating the aperiodic and periodic components of the signal. For a summary on frequency range selection in earlier studies on BOLD signal, see e.g., Glerean et al. (2012). As the frequency range of interest was so narrow, we set the minimum width of oscillation peaks to 0.001 Hz while specifying no maximum width. Based on earlier work by Li et al. (2021), we set the threshold value for oscillatory peaks to 1.5 SD over the mean, as well as the maximum number of peaks to find to 2. The aperiodic fit was generally acceptable across the ROIs, but it was highest for somatosensory areas.

Aperiodic and periodic parameters

Spectral parameterization resulted in aperiodic parameters (exponent and offset) of the fMRI BOLD signal for 90 regions of interest for the AAL atlas spanning cortical and subcortical grey matter, from which values from precentral (motor) gyri and postcentral (somatosensory) gyri were used in further statistical analyses. These areas were chosen as they show early maturation, and the aperiodic fit reliability was among the highest for these areas (mean R^2 0.94 for precentral and 0.93 for postcentral gyri).

4.7.2 EEG (Study III)

The power spectrum estimation and spectral parameterization were conducted separately for three data sets: neonate sleep data, neonate auditory paradigm data, and toddler auditory paradigm data.

Power spectra estimation

First, we followed Schaworonkow & Voytek (2021) by segmenting the continuous EEG data of each participant and electrode channel into 30-second segments to enhance the reliability of our parameter values. After that, Welch's method was employed to calculate the power spectral density (PSD) for each segment, with a window length of 500 samples and 50% overlap.

Spectral parameterization

The Python-based SpecParam toolbox was used to parameterize the spectral data by separating the aperiodic and periodic components of the signal. We parameterized the spectra in the 1–45 Hz frequency range, to cover the canonical (M)EEG

frequency bands from theta to beta (Pernet et al., 2020) and to avoid the electrical line frequency peak at 50 Hz. The settings of SpecParam closely followed the prior infant study of Schaworonkow & Voytek (2021), with the following settings: peak width limits = [1.5, 12.0], maximum number of peaks = 5, peak threshold = 2.0, minimum peak height = 0.0, and aperiodic mode: 'fixed'.

Aperiodic and periodic parameters

From the SpecParam outputs, the parameters (offset, exponent, and center frequencies from fitted oscillations) from model fits with R^2 values > 0.95 were retained for further analyses (1 neonate excluded). Absolute error of the SpecParam fit was inspected, following Ostlund et al. (2022), and based on that, aperiodic offset was decided to be calculated as a power of aperiodic curvet at 2.5 Hz, prior recommended by Wilkinson et al. (2024). Parameter values were averaged over the segments, resulting in one parameter value (offset, exponent, or center frequency) per electrode for each participant.

For aperiodic parameters (exponent and offset), we visually inspected the correlation between the gestational duration (weeks) and aperiodic parameters in both neonate and 3-year-old data. These revealed a global positive correlation between gestational duration and exponent across the scalp in the toddler dataset. Following Hill et al. (2022) and Stanyard et al. (2024), we averaged the data across the electrodes to obtain a "global" exponent and offset value reflecting the mean signal across the scalp, aiming also to avoid the problem of multiple comparisons.

For periodic parameters (center frequency), the peak parameters were extracted from the periodic signal for selected frequency bins (theta: 4–8 Hz, alpha: 8–12.5 Hz, beta: 12.5–30 Hz). These frequency bins were selected based on recommendations by Pernet et al. (2020) as well as visual inspection of the center frequencies of fitted oscillations. Center frequency values from fitted oscillations partly overlapped in these frequency bins, leading us to average the fitted center frequency values within selected frequency bins. Correspondingly to aperiodic parameters, visual inspection of gestational age and center frequency correlations revealed broad negative correlation between gestational age and theta center frequency in neonates, prompting us to average center frequency values across electrodes to obtain "global" aperiodic-adjusted center frequency values reflecting the mean signal across the scalp.

4.8 Statistical analysis

4.8.1 Study I

Statistical analyses were performed using MATLAB (r2017b, The MathWorks, Inc.) and IBM SPSS Statistics 25.

Two-tailed one-sample t-test

First, a two-tailed one-sample t-test was used to evaluate the mismatch response amplitudes to determine if they significantly differed from 0 μV in each of the three time windows.

Linear mixed-effects regression model

Second, linear mixed effects regression models, using the *fitlme* function, were employed to examine if maternal prenatal depressive symptoms could predict mismatch response amplitudes to emotional auditory stimuli in children. Models were run separately for each of the three time windows. Fixed effects were maternal depressive symptoms (EPDS sum score at gestational week 24), postnatal age of the child at EEG measurement (months, z-scored), sex of the child (0 = male, 1 = female), and the emotional category of the stimulus (happy as a baseline category, 0 = sad, 1 = angry) and their interaction terms with maternal depressive symptoms. Random effect was the intercept for the subject. The inclusion of inter-participant variation in all emotion categories in random-effect structures did not enhance model fit according to the Akaike information criterion (AIC); thus, the results are reported based on the random-intercept model.

Model selection and diagnostics

Model selection was done by trying different combinations of either only the main effect of sex/age or also their interaction terms with depressive symptoms in the model and then selecting the model with the lowest AIC value. The visual inspection of residual plots did not reveal any significant deviations from normality. The outliers were detected by visual inspection of residual plots separately in each time window and were excluded from the regression model (n = 3 in early, n = 2 in intermediate, and n = 3 in late time window).

Sensitivity analyses

To control the possible effect of maternal anxiety (SCL-90 sum score at gestational week 24), it was initially considered as a fixed effect but was ultimately excluded due to nonsignificant main effects or interactions. Similarly, to control possible three-way interactions, terms involving sex/age, depressive symptoms, and emotion category did not yield significant results and were omitted from the final model.

Finally, additional analyses using the sum score of distress (SCL-90 score + EPDS score) instead of depressive symptoms did not show statistically significant effects on child mismatch response amplitudes.

4.8.2 Study II

Statistical analyses were performed using RStudio (2022.07.1+554) and JASP (2022, version 0.16.3).

Linear mixed-effect regression models

Linear mixed effects regression models, using the *lmer* function of the *afex* package of RStudio, were used to estimate the associations between the aperiodic parameters (exponent or offset) of fMRI BOLD signal and preterm birth, sex, postmenstrual age at scan, and postnatal age. Analyses were performed using maximum likelihood estimation, and models were run separately for each of the aperiodic parameters (exponent/offset). Fixed effects were postmenstrual age of neonate at scan (weeks, z-scored), postnatal age of neonate at scan (weeks, z-scored), sex of the neonate (0 = male, 1 = female), and premature birth (0 = term, 1 = preterm), as well as hemisphere (0 = left, 1 = right). Interaction terms with ROI (0 = postcentral gyri, 1 = precentral gyri) were included. Additionally, in the offset model, exponent (z-scored) was included as a fixed effect to control the possible effects of exponent changes on offset values. The intercepts for the subject were modeled as random effects, including the random slopes for motion outliers (number of outliers based on DVARS; z-transformed).

Model selection and diagnostics

The models initially included only main effects of independent variables, but with the addition of interaction terms with ROI, model fit improved based on a lower Akaike information criterion (AIC) and statistically significant results from likelihood ratio tests. Although the prematurity variable showed moderate to high correlation with other age variables, its inclusion improved model fit as evidenced by lower AIC values and nearly statistically significant likelihood ratio tests (for the

exponent model p = 0.09 and for the offset model p = 0.06). The singularity of the models was checked and not detected.

Visual assessments of model assumptions revealed slight deviations in the Q-Q plot of the exponent model, which improved after residual outlier detection and exclusion (± 3SD, N = 26), while the offset model showed no need for outlier exclusion and supported normal distribution of residuals.

For the correlation matrix of model variables, see **Table 9**.

Table 9. Correlation matrix (Spearman correlations) for the main variables of interest, conditioned on outliers based on DVARS (measure of the level of noise in fMRI) from Study II.

	1.	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**
1. Exponent	1							
2. Offset	-0.792	1						
3. PMA at scan	-0.185	0.27	1					
4. Age	-0.551	0.367	0.363	1				
5. Sex	-0.089	0.133	0.05	0.017	1			
6. Prematurity	-0.326	0.14	-0.361	0.489	0	1		
7. Hemisphere	0.012	0.002	0	0	0	0	1	
8. ROI	0.036	0.128	0	0	0	0	0	1

Table 9 footnote | Abbreviations: PMA at scan = postmenstrual age (PMA) of the neonate at scan (weeks); Age = postnatal age (age from birth; weeks); Sex = biological sex of the child (male = 0, female = 1); Prematurity = term versus preterm birth (term-born = 0, preterm = 1; postmenstrual age at birth < 37 weeks); Hemisphere = left (= 0) or right (= 1) side of the brain; ROI = region of interest (postcentral = 0 or precentral = 1 gyri.

Machine learning analyses

In our machine learning-based analyses, we employed l1- and l2-regularized regression models (ElasticNet; Zou and Hastie, 2005a) to predict neonate postmenstrual age and postnatal age separately, utilizing four machine learning models with exponent or offset parameters from all ROIs as predictors. To address the impact of preterm birth, models were trained and tested on both the full sample and term-born participants separately, resulting in eight analysis settings.

Feature ranking was conducted using the model's beta coefficients, and the regularization strength and l1/l2-norm ratio were tuned via nested cross-validation with 10 outer and 5 inner folds and 10 repeats. Prior to model fitting, data

standardization was performed at runtime for each cross-validation fold to prevent data leakage. Python 3.9.12 with external libraries Numpy 1.21.6, Pandas 1.4.4, and Scikit-learn 1.2.1 were utilized for the analysis, and model performance was evaluated in terms of coefficient of determination (R^2) and mean absolute error (MAE) in weeks of age. Results were analyzed separately for offset and exponent-based features, as well as for both postnatal and postmenstrual age.

4.8.3 Study III

Statistical analyses were performed using RStudio (2022.07.1+554) and JASP (2022, version 0.16.3).

Neonates: Multilevel models

Multilevel models from the nlme package in RStudio (Pinheiro et al., 2007) were employed to study the relationship between aperiodic and periodic parameters and gestational duration. Analyses were performed using maximum likelihood estimation, and models were run separately for each of the parameters (exponent/offset/center frequencies (theta/alpha/beta)). Fixed effects were gestational duration (weeks, z-scored), postnatal age of the neonate at EEG measurement (days, z-scored), condition (0 = sleep, 1 = auditory paradigm + sleep), sex of the child (0 = male, 1 = female; categorical variable), and birth weight of the neonate (kilograms, z-scored). Random effect was the intercept for the subject.

Unlike in Study II, we used gestational duration as a covariate instead of postmenstrual age in Study III. The main reason for this choice was the postnatal age (0–5 days) of the neonates, which would lead to a stronger correlation between postmenstrual age and postnatal age compared to Study II, where the postnatal age of the neonates was notably higher (mean 2.5 weeks). To avoid multicollinearity, we selected gestational duration as the covariate of interest in Study III.

Neonates: Model selection and diagnostics

The selection of fixed effects for the models was based on their theoretical relevance and previous studies (McSweeney et al., 2023). The independent variables were chosen by adding them into the model one by one. Although the addition of sex slightly increased AIC in all models, it was included to maintain congruence between neonate and 3-year-old models. Participant identifier was treated as a random effect. To control the possible effect of exponent on offset values, aperiodic exponent (z-transformed) was added as an independent variable in the offset model. Attempts to

include interaction terms of Condition with gestational duration, age, sex, and birth weight individually yielded statistically significant effects only in *Condition x Gestational duration* in the beta center frequency model. Otherwise, no statistically significant interactions were observed, and adding them to models resulted in increased AIC values, so the interaction terms were included only in the beta center frequency model as described above.

Residual outliers (± 3SD) were excluded as needed, with no outliers in the theta/beta center frequency models, but three outliers in the exponent model, two outliers in the offset model, and one outlier in the alpha center frequency model. Model assumptions were visually assessed with residual vs. fitted plots, Q-Q plots, and histograms of residual terms estimated to be acceptable.

Consequently, following McSweeney et al. (2023) we also formed quadratic models that included the square of gestational duration as a predictor. The quadratic model fitted the data significantly better only in the beta center frequency model (L. ratio = 4.62, p = 0.03). In other models, linear models seemed to fit the data significantly better (exponent: L.ratio = 0.65, p = 0.42; offset: L.ratio = 1.81, p = 0.18; center frequency (theta): L.ratio = 0.41, p = 0.52; center frequency (alpha): L.ratio = 0.53, p = 0.47). In beta center frequency model, the interaction term of *Condition* with *Gestational duration* ^{2} was not statistically significant and therefore excluded from the final model. We report results from the quadratic model in beta center frequency, while otherwise results of the linear models are reported in the Results section.

Neonates: Sensitivity analyses

As sensitivity analyses, maternal pre-pregnancy BMI (kg/m2), maternal tobacco smoking (during the first trimester of pregnancy), and PMA (gestational duration + postnatal age) were individually added as fixed effects to the model. Model diagnostics continued to meet acceptable standards, and no statistically significant effects of BMI, tobacco smoking, or postmenstrual age were observed. Also, stepwise regression models supported that gestational duration was a better predictor for aperiodic exponent than postmenstrual age, as R^2s of the models were higher in models using gestational duration as the independent variable when compared to those models where gestational duration was replaced with PMA.

Toddlers: Linear regression models

The linear regression models, using the *lm* function, were used to study the associations between the aperiodic (exponent or offset) or periodic parameters (center frequency) and gestational duration. Independent variables were gestational

duration (weeks, z-scored), postnatal age at EEG measurement (months, z-scored), sex of the child (0 = male; 1 = female; categorical variable), and birth weight of the child (kilograms, z-scored). The dependent variable in linear regression models was either offset, exponent, or center frequencies (theta/alpha/beta).

Toddlers: Model selection and diagnostics

The independent variables were selected for the models by individually adding them and assessing their impact on the AIC. Birth weight reduced AIC values of the exponent and offset models, supporting its inclusion.

Model assumptions were evaluated, with low variation inflation factors across all models (< 1.61). Residuals were found to be normally distributed based on Shapiro-Wilk tests (p = 0.71/0.20/0.04/0.61/0.84). While the p-value of the Shapiro Wilk test was < 0.05 in the theta center frequency model, the visual inspection of model diagnostics indicated acceptable results. Correlations of the residuals were high (> 0.98), and no residual outliers (defined as values greater than +3 SD or less than -3 SD from the mean) were present in any of these models.

Toddlers: Sensitivity analyses

As sensitivity analyses, maternal pre-pregnancy BMI (kg/m2), maternal tobacco smoking (during the first trimester of pregnancy), and PMA of the child were individually added as independent variables to the model. Model diagnostics remained within acceptable ranges, and no statistically significant effects of BMI, tobacco smoking, or postmenstrual age were detected. Also, stepwise regression models supported that gestational duration was a better predictor for aperiodic exponent than PMA, as R^2s of the models were higher in models using gestational duration as the independent variable when compared to those models where gestational duration was replaced with PMA.

5 Results

In the results section, we first report our age-related findings from Studies I–III in chronological order, beginning with gestational duration-, postmenstrual age-, and postnatal age-related results from Studies I–III and concluding with the effects of early life stressors (prematurity and prenatal maternal depressive symptoms) from Studies II and I.

5.2 Gestational duration (Study III)

Positive association with exponent (in EEG) in neonates and toddlers:

In both neonates as well as in 3-year-olds, a positive association between the exponent of EEG spectral power and gestational duration was found. In toddlers, this association was stronger, while in neonates, the association was nearly statistically significant. This implies that longer duration of gestation is associated with a steeper distribution of power across the frequencies (**Table 10** and **Figure 7B**).

Quadratic effect on beta center frequency (in EEG) in neonates:

In addition, we found a quadratic effect of gestational duration on beta center frequencies in neonates, as well as a borderline statistically significant interaction effect between gestational duration and condition (auditory paradigm + sleep/sleep alone). An association between gestational duration and beta center frequency seems to be positive until around gestational week 40-41, after which it turns negative. Also, neonates born after gestational week 38 show higher beta frequencies during the auditory paradigm + sleep when compared to sleep state (**Table 10A** and **Figure 7A**).

Table 10. Effects of gestational duration on aperiodic / periodic parameters. A) Neonates (Study III). B) Toddlers (Study III).

A) NEONATES (STUDY III)

Outcome variable	Predictor	Estimate	SE	t value	p value
Exponent (EEG)	Gestational duration [a]	0.06	0.03	1.91	0.061
Center frequency of the beta (12.5–30 Hz) frequency band (EEG)	Gestational duration [a]	-0.13	0.14	-0.92	0.361
	Gestational duration [2, a]	-0.14	0.06	-2.12	0.037
	Gestational duration [a] x Condition	0.23	0.12	2.00	0.050

B) TODDLERS (STUDY III)

Outcome variable	Predictor	Estimate	SE	β	t value	p value
Exponent (EEG)	Gestational duration [a]	0.07	0.02	0.45	3.00	0.004

Table 10 footnote | Abbreviations: EEG = electroencephalography; SE = standard error; β = standardized beta coefficient. [a] Notably is, that gestational duration is z-transformed before including linear/mixed-effects model. When interpreting results, Estimate describes a change of outcome variable, when predictor increases by one standard deviation. Condition: 0 = sleep, 1 = auditory paradigm + sleep.

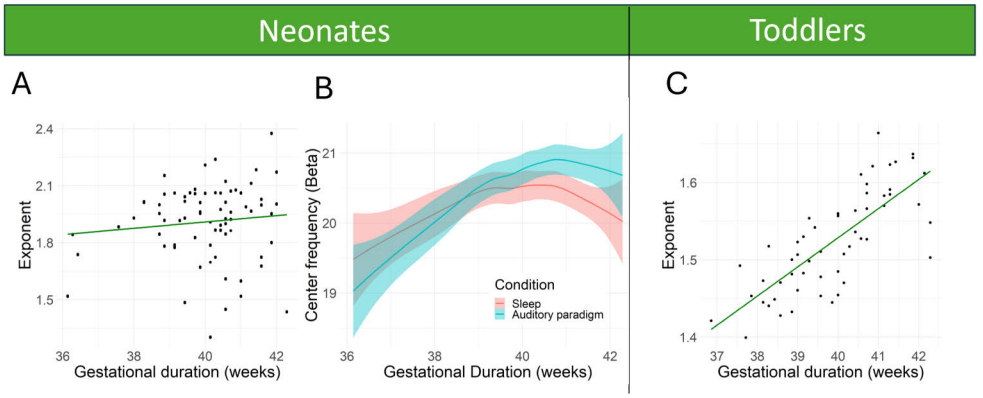

Figure 7. A) Scatterplot of predicted values of the exponent across gestational duration (weeks) from the linear models in neonates from Study III. B) Nonlinear effect of gestational duration on predicted beta center frequency values by condition (auditory paradigm + sleep / sleep) in neonates from Study III. The plot accounts for both the linear and quadratic components of the gestational duration. Shaded ribbons indicate 95% confidence intervals. **B) Scatterplot of predicted values of the exponent across gestational duration (weeks) from the linear models in toddlers from Study III.** Modified from Study III, which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Summary

Longer gestational duration seems to predict higher exponent values of offspring, reflecting a steeper slope in the power spectrum and more prominent low-frequency fluctuations of the signal. The effects of gestational duration on beta center frequencies demonstrate a quadratic nature. Changes in aperiodic exponent may reflect gestation-related changes in synaptic currents, suggesting a shift of the global E-I balance toward inhibition. The effect can be observed even in 3-year-olds.

5.3 Postmenstrual age (Study II)

Region-dependent effects on exponent (in fMRI BOLD signal) in neonates:

Postmenstrual age of the neonate was not directly associated with the exponent of fMRI BOLD signal power spectrum, but the interaction effect of postmenstrual age and brain region of interest was revealed, indicating that the association between postmenstrual and exponent was different in precentral and postcentral regions. In precentral gyri, there was negligible decrease in exponent observed as a function of postmenstrual age, while in postcentral gyri, exponent increased as postmenstrual age increased (**Table 11** and **Figure 8A**).

Positive association with offset (in fMRI BOLD signal) in neonates:

The statistical analysis revealed a positive association between neonate postmenstrual age and offset of fMRI BOLD signal spectral power, which was dependent on the brain region of interest (ROI). Practically, offset increased as the postmenstrual age increased, and this increase was greater in the precentral vs. postcentral region (**Table 11** and **Figure 8B**).

Table 11. Effects of postmenstrual age and its interaction terms on aperiodic parameters from Study II.

NEONATES (STUDY II)

Outcome variable	Predictor	Estimate	SE	t value	p value
Offset (BOLD signal)	Postmenstrual age [a]	0.06	0.01	4.07	< 0.001
	Postmenstrual age [a] x ROI	0.04	0.01	4.88	< 0.001
Exponent (BOLD signal)	Postmenstrual age [a]	0.02	0.02	0.87	0.385
	Postmenstrual age [a] x ROI	-0.03	0.01	-3.12	0.002

Table 11 footnote | Abbreviations: BOLD = blood oxygen-level-dependent; SE = standard error; ROI = region of interest. [a] Notably is, that postmenstrual age is z-transformed before including linear/mixed-effects model. When interpreting results, Estimate describes a change of outcome variable, when postmenstrual age increases by one standard deviation.

Postmenstrual age can be predicted using offset and exponent (in fMRI BOLD signal) in neonates:

Results showed moderate to relatively high accuracy (mean test R^2 0.20–0.41), supporting that postmenstrual age of the neonate can be predicted using offset and exponent for supervised machine learning regression (**Table 12**).

Table 12. Cross-validated performance estimates for analyses predicting postmenstrual age at scan using offset and exponent features. Sample sizes: full sample = 599; term-born = 483.

NEONATES (STUDY II)

Feature	Sample	Train R^2	Test R^2	Train MAE	Test MAE
Offset (BOLD signal)	full	0.50	0.35	1.29	1.42
	term-born	0.48	0.32	0.96	1.08
Exponent (BOLD signal)	full	0.39	0.20	1.37	1.51
	term-born	0.44	0.31	0.98	1.08
Both offset and exponent (BOLD signal)	full	0.67	0.41	1.04	1.32
	term-born	0.57	0.35	0.86	1.04

Table 12 footnote | Abbreviations: BOLD = blood oxygen-level-dependent; MAE = mean absolute error (weeks).

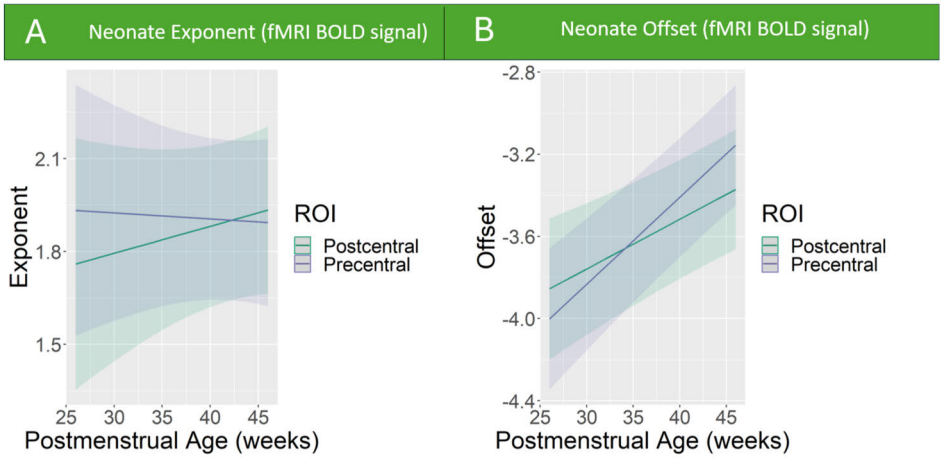

Figure 8. Postmenstrual age (weeks) and predicted A) aperiodic exponents and B) aperiodic offsets (conditioned on random effects) from the pre- and postcentral gyri from Study II. Shaded ribbons indicate 95% confidence intervals. ROI = region of interest. Modified from Study II, which is licensed under a Creative Commons Attribution-NoDerivatives International License (https://creativecommons.org/licenses/by-nd/4.0/).

Summary

Higher neonate postmenstrual age seems to associate with higher offsets and, depending on brain region, also higher exponents. Higher offsets indicate increased power of BOLD signal, while higher exponents suggest steeper power distribution across frequencies. Observed changes may reflect maturational changes, such as increasing neuronal firing rates and synaptic changes in the fetal brain during gestation. Finally, the offset and exponent of the fMRI BOLD signal show potential utility to capture key features of postmenstrual brain development.

5.4 Postnatal Age (Study II and III)

Negative association with exponent (in fMRI BOLD signal) in neonates:

Postnatal age of the neonate showed a negative association with the exponent of the fMRI BOLD signal power spectrum, parallel in both brain regions (pre- and postcentral gyri). This indicates that exponents decreased as a function of postnatal age (**Table 13A** and **Figure 9A**).

Decreasing regional differences in offset (in fMRI BOLD signal) in neonates:

The interaction effect of postnatal age and brain region of interest was statistically significant, indicating that the difference in offset values between pre- and postcentral gyri (see: 5.6 Asymmetry and differences between motor and somatosensory areas) narrows as postnatal age increases, resulting in this regional difference disappearing at approximately 20 weeks of postnatal age (**Table 13A** and **Figure 9A**).

Negative associations with offset and theta center frequency (in EEG) in neonates:

Postnatal age showed statistically significant associations with offset and theta center frequency in neonates but not in toddlers. Findings suggest a decrease in the baseline power across frequencies as well as age-related progression of theta oscillations toward lower frequencies during the first days after birth (**Table 13B** and **Figure 9B**).

Table 13. Effects of postnatal age on aperiodic parameters from Studies II and III.

A) NEONATES (STUDY II)

Outcome variable	Predictor	Estimate	SE	t value	p value
Exponent (BOLD signal)	Postnatal age [a]	-0.17	0.03	-6.04	< 0.001
Offset (BOLD signal)	Postnatal age [a]	-0.02	0.02	-1.42	0.156
	Postnatal age [a] x ROI	-0.02	0.01	-1.98	0.048

B) NEONATES (STUDY III)

Outcome variable	Predictor	Estimate	SE	t value	p value
Offset (EEG)	Postnatal age [a]	-0.07	0.03	-2.35	0.022
Center frequency of the theta (4–8 Hz) frequency band (EEG)	Postnatal age [a]	-0.14	0.06	-2.30	0.024

Table 13 footnote | Abbreviations: BOLD = blood oxygen-level-dependent; SE = standard error; β = standardized beta coefficient; ROI = region of interest. [a] Notably is, that postnatal age is z-transformed before including linear/mixed-effects model. When interpreting results, Estimate describes a change of outcome variable, when postnatal age increases by one standard deviation.

Postnatal age can be predicted using offset and exponent (in fMRI BOLD signal) in neonates:

Results showed moderate to relatively high accuracy (mean test R^2 0.22–0.40), supporting that postnatal age of the neonate can be predicted using offset and exponent for supervised machine learning regression (**Table 14**).

Table 14. Cross-validated performance estimates for analyses predicting postnatal age at scan using offset and exponent features. Sample sizes: full sample = 599; term-born = 483.

NEONATES (STUDY II)

Feature	Sample	Train R^2	Test R^2	Train MAE	Test MAE
Offset (BOLD signal)	full	0.31	0.24	1.83	1.88
	term-born	0.50	0.36	0.74	0.83
Exponent (BOLD signal)	full	0.30	0.22	1.82	1.89
	term-born	0.48	0.36	0.75	0.82
Both offset and exponent (BOLD signal)	full	0.32	0.24	1.81	1.87
	term-born	0.58	0.40	0.67	0.79

Table 14 footnote | Abbreviations: BOLD = blood oxygen-level-dependent; MAE = mean absolute error (weeks).

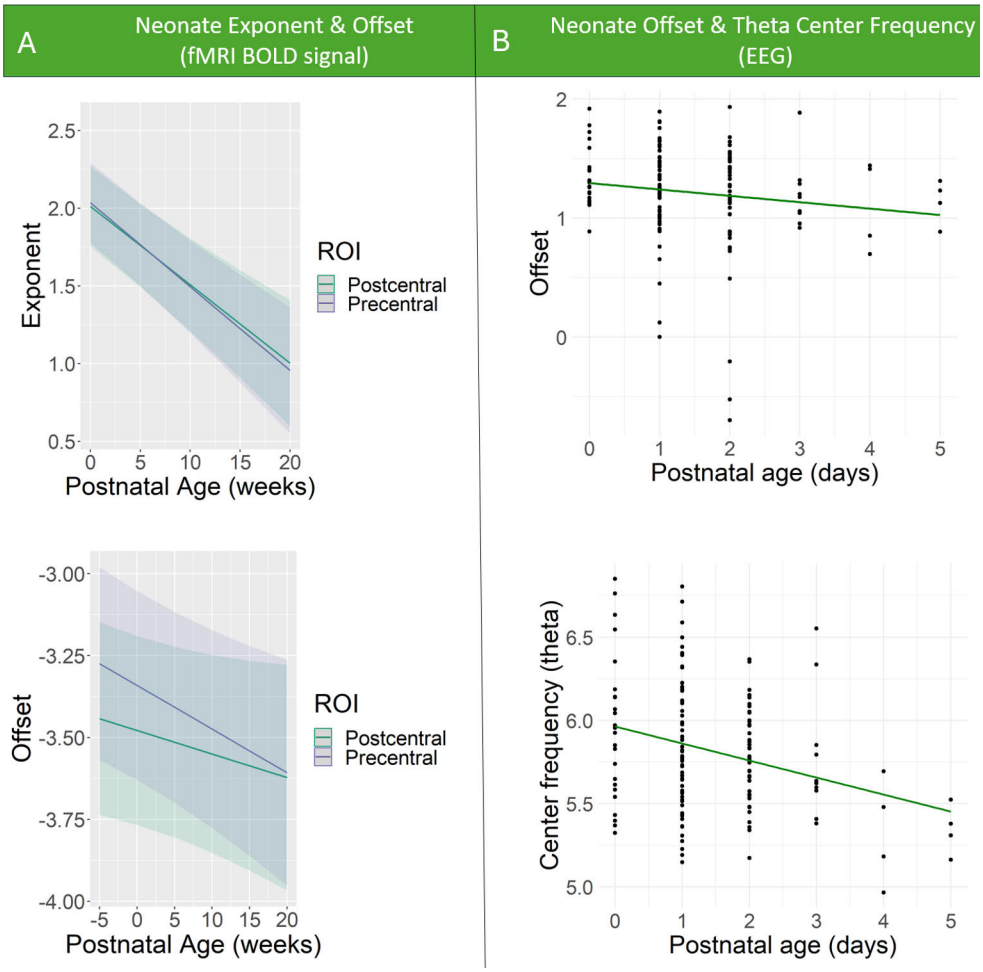

Figure 9. **A) Postnatal age (weeks) and predicted aperiodic exponents and offsets (conditioned on random effects) from the pre- and postcentral gyri from Study II**. ROI = region of interest**. B) Fitted lines to the predicted data points of the offset and theta center frequency values from linear mixed-effects models in neonates from Study III.** Modified from Study II and Study III. Study II is licensed under a Creative Commons Attribution-NoDerivatives International License (https://creativecommons.org/licenses/by-nd/4.0/), and Study III is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Summary

Postnatal age is negatively associated with the exponent in neonate fMRI BOLD signal, as well as offset and theta center frequency in neonate EEG. These changes may reflect age-related changes in synaptic electric currents as well as functional adaptations to the extrauterine environment and/or maturation-related changes in sleep architecture. The overall baseline power of the BOLD signal shows regional

heterogeneity, which seems to disappear during the first postnatal weeks. Finally, the offset and exponent of the fMRI BOLD signal show potential utility to capture key features of postnatal brain development.

5.5 Sex-related differences (Study II and III)

Differences in exponent and offset (in fMRI BOLD signal) in neonates:

The neonate sex was negatively associated with the exponent as well as positively associated with the offset of the fMRI BOLD signal power spectrum, indicating overall smaller exponents and higher offsets in females compared to males (**Table 15A** and **Figure 10A**).

Differences in beta center frequency (in EEG) in toddlers:

The sex of the child was positively associated with the beta center frequency, suggesting higher beta center frequency values in females compared to males (**Table 15B** and **Figure 10B**).

Table 15. Effects of sex on aperiodic and periodic parameters from Study II and Study III.

A) NEONATES (STUDY II)

Outcome variable	Predictor	Estimate	SE	t value	p value
Exponent (BOLD)	Sex	-0.09	0.03	-2.76	0.006
Offset (BOLD)	Sex	0.04	0.02	-2.08	0.038

B) TODDLERS (STUDY III)

Outcome variable	Predictor	Estimate	β	SE	t value	p value
Center frequency of the beta (12.5–30 Hz) frequency band (EEG)	Sex	0.47	0.35	0.18	2.61	0.012

Table 15 footnote | Abbreviations: BOLD = blood-oxygen-dependent; EEG = electroencephalography; SE = standard error; β = standardized beta coefficient.

Figure 10. A) Sex-related differences in neonate exponent and offset in fMRI BOLD signal from Study II. Vertical lines present 95% confidence intervals around the average predicted value for each group. **B) Sex-related differences in toddler beta center frequency in EEG from Study III.** Individual predicted values are displayed as points, while the boxplots summarize the distribution within each group. The boxes represent the interquartile range (the middle 50% of the data), with the line inside each box indicating the median predicted value. Whiskers extend to the smallest and largest values within 1.5 times the interquartile range, with outliers shown as individual points outside this range. Modified from Study II and Study III. Study II is licensed under a Creative Commons Attribution-NoDerivatives International License (https://creativecommons.org/licenses/by-nd/4.0/). Study III is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Summary

In general, female neonates seem to have higher offsets but smaller exponents in fMRI BOLD signal, indicating a flatter slope of the power spectrum but higher baseline power of the signal across the frequencies in females compared to males. Furthermore, aperiodic-adjusted beta center frequency is higher in female toddlers compared to males. While results may reflect maturational differences between females and males, the topic needs further study.

5.6 Asymmetry and differences between motor and somatosensory areas (Study II)

Asymmetry of offset (in fMRI BOLD signal) in neonates:

The side of the hemisphere (right/left) was positively associated with the offset, although the effect size was relatively small. Results suggest slightly higher offset values in the right hemisphere, compared to the left hemisphere (**Table 16**)

Differences in offset (in fMRI BOLD signal) between motor and somatosensory areas in neonates:

The region of interest was positively associated with offset in fMRI BOLD signal in neonates, indicating higher offsets in precentral gyri (motor area) compared to postcentral gyri (somatosensory area) (**Table 16**).

Table 16. Effects of region of interest and hemisphere on offset values from Study II.

		NEONATES (STUDY II)			
Outcome variable	**Predictor**	**Estimate**	**SE**	**t value**	**p value**
Offset (BOLD)	ROI	0.12	0.01	12.16	< 0.001
	Hemisphere	0.01	0.01	1.98	0.048

Table 16 footnote | Abbreviations: BOLD = blood-oxygen-dependent; EEG = electroencephalography; SE = standard error; ROI = region of interest.

Summary

Results revealed higher overall aperiodic activity of fMRI BOLD signal in right versus left hemisphere and motor versus somatosensory areas, likely reflecting asymmetry- and region-dependent differences in neural activity.

5.7 Condition-related differences (Study III)

The positive associations between condition (sleep vs. auditory paradigm + sleep) and offset, theta center frequency, and beta center frequency were statistically significant in neonates. Findings suggest higher baseline power of the signal across the frequencies, as well as higher aperiodic-adjusted center frequencies of theta and beta oscillations during the auditory + sleep vs. sleep alone paradigm (**Table 17**).

Table 17. Effects of condition (sleep/auditory paradigm + sleep) on center frequency values in neonates from Study III.

		NEONATES (STUDY III)			
Outcome variable	**Predictor**	**Estimate**	**SE**	**t value**	**p value**
Offset (EEG)	Condition	0.04	0.01	3.63	0.001
Center frequency of the theta (4–8 Hz) frequency band (EEG)	Condition	0.22	0.08	2.74	0.008
Center frequency of the beta (12.5–30 Hz) frequency band (EEG)	Condition	0.25	0.12	2.15	0.035

Table 17 footnote | Abbreviations: EEG = electroencephalography; SE = standard error.

Summary

Results revealed higher baseline power of the signal as well as aperiodic-adjusted theta and beta center frequencies during auditory stimuli + sleep compared to sleep alone data, reflecting changes in electrophysiological activity between these two conditions.

5.8 Effects of early life stressors

5.8.1 Prematurity (Study II)

Negative association with exponent (in fMRI BOLD signal) in neonates:

Prematurity was negatively associated with the exponent indicating overall smaller exponents in infants born preterm compared to term-born infants (**Table 18** and **Figure 11**).

Nearly statistically significant association with offset (in fMRI BOLD signal) in neonates:

Prematurity was nearly statistically significantly associated with offset. This indicates overall smaller offsets in preterm infants compared to term-born infants. Furthermore, the interaction effect of prematurity and ROI was statistically significant, indicating that the effect of prematurity on offset was even weaker in precentral gyri (**Table 18** and **Figure 11**).

Table 18. Effects of prematurity on aperiodic exponent & offset in neonates from Study II.

NEONATES (STUDY II)

Outcome variable	Predictor	Estimate	SE	t value	p value
Exponent (BOLD)	Prematurity	-0.17	0.08	-2.11	0.036
Offset (BOLD)	Prematurity	-0.09	0.05	-1.91	0.057
	Prematurity x ROI	0.06	0.03	1.98	0.048

Table 18 footnote | ROI = region of interest; BOLD = blood-oxygen-dependent; SE = standard error.

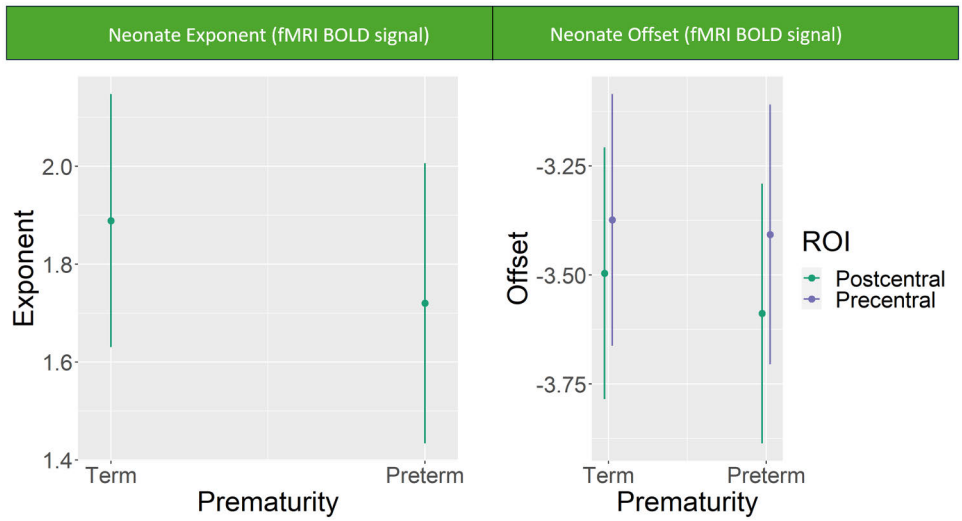

Figure 11. Prematurity-related differences in exponent and offset values in fMRI BOLD signal in pre- and postcentral gyri from Study II. Vertical lines present 95% confidence intervals around the average predicted value for each group. ROI = region of interest. Modified from Study II, which is licensed under a Creative Commons Attribution–NoDerivatives International License (https://creativecommons.org/licenses/by-nd/4.0/).

Summary

Results indicate smaller exponents and, tentatively, smaller offsets in preterm neonates compared to term-born neonates. These changes may reflect maturational changes during pregnancy (increasing neuronal firing rate, synaptic changes), which were interrupted by the early birth.

5.8.2 Prenatal maternal depressive symptoms (Study I)

Mismatch Responses:

The mean mismatch response amplitude values differed significantly from 0 μV for each emotional stimulus category in each time window (**Table 19**).

Table 19. Results of the two-tailed one-sample t-tests from Study I. N = 58.

Type of mismatch response	Mean (μV)	SD	95 % CI	t value	p value
EARLY TIME WINDOW					
happy	-1.68	3.59	-2.62…-0.73	-3.55	0.001
sad	-2.97	2.81	-3.71…-2.24	-8.07	< 0.001
angry	-1.45	3.24	-2.30…-0.60	-3.41	0.001
INTERMEDIATE TIME WINDOW					
happy	-3.24	4.73	-4.49…-2.00	-5.22	< 0.001
sad	-2.00	4.82	-3.27…-0.73	-3.16	0.003
angry	-1.89	4.03	-2.95…-0.83	-3.57	0.001
LATE TIME WINDOW					
happy	-2.28	5.48	-3.72…-0.84	-3.17	0.002
sad	-3.50	4.65	-4.72…-2.28	-5.73	< 0.001
angry	-5.25	4.65	-6.48…-4.03	-8.60	< 0.001

Table 19 footnote | Abbreviations: SD = standard deviation; CI = confidence interval.

Mismatch response amplitude for happy sounds decreases (early time window):

Maternal depressive symptoms were positively associated with the mismatch response amplitudes of the child, indicating less negative (decreasing) amplitude of mismatch response for happy sounds as maternal depressive symptoms increase (**Table 20A** and **Figure 12A**).

Emotion condition-related differences (early and intermediate time windows)

Angry emotion condition was positively associated with mismatch response amplitudes in early and intermediate time windows, suggesting weaker mismatch responses in the angry condition compared to other conditions (**Table 20A & B**).

Table 20. Results of the linear mixed-effects regression model from Study I in A) early time window (80–120 ms); B) intermediate time window (240–280ms); C) late time window (350–450 ms). DF = 162.

A. EARLY TIME WINDOW

Outcome variable	Predictor	Estimate	SE	t value	p value	Adjusted p-value
Mismatch response	EPDS	0.21	0.09	2.30	0.023	0.067
	Angry	1.73	0.70	2.46	0.015	0.044
	Angry x EPDS	-0.20	0.10	-1.92	0.056	0.168
	Sad x EPDS	-0.25	0.10	-2.37	0.019	0.057
B. INTERMEDIATE TIME WINDOW						
Mismatch response	Angry	2.34	0.96	2.44	0.016	0.047
C. LATE TIME WINDOW						
Mismatch response	EPDS	0.29	0.15	1.92	0.057	0.171
	Angry x EPDS	-0.32	0.14	-2.33	0.021	0.063

Table 20 footnote | Abbreviations: SE = standard error. EPDS = Edinburgh Postnatal Depression Scale.

Nearly statistically significant association with mismatch responses for happy sounds (late time window):

A nearly statistically significant positive association between maternal depressive symptoms and mismatch response amplitudes of the child was found. If true, this would indicate less negative (decreasing) amplitude of mismatch response as maternal depressive symptoms increase (**Table 20C** and **Figure 12B**).

Negligible effects on mismatch responses in other emotional conditions (early and late time windows)

In the early time window, the statistically significant negative interaction effect between sad emotion category "sad" as well as "angry" were found, but the effect sizes were negligible and none of the results survived from Bonferroni correction.

Furthermore, the negative interaction effect between maternal depressive symptoms and the emotion category "angry" existed, indicating more negative (increasing) mismatch response amplitudes for angry sounds as maternal depressive symptoms increase. However, the effect size was negligible, and results did not survive Bonferroni correction. Additionally, when outlier values of the model (N = 2) were removed, the association weakened below statistical significance.

Summary

The findings revealed diminished mismatch negative amplitudes in response to positive stimuli during the early time window, suggesting attenuated neural responses among children born to mothers with higher prenatal depressive scores.

However, these results did not withstand Bonferroni correction, prompting a cautious interpretation of our findings.

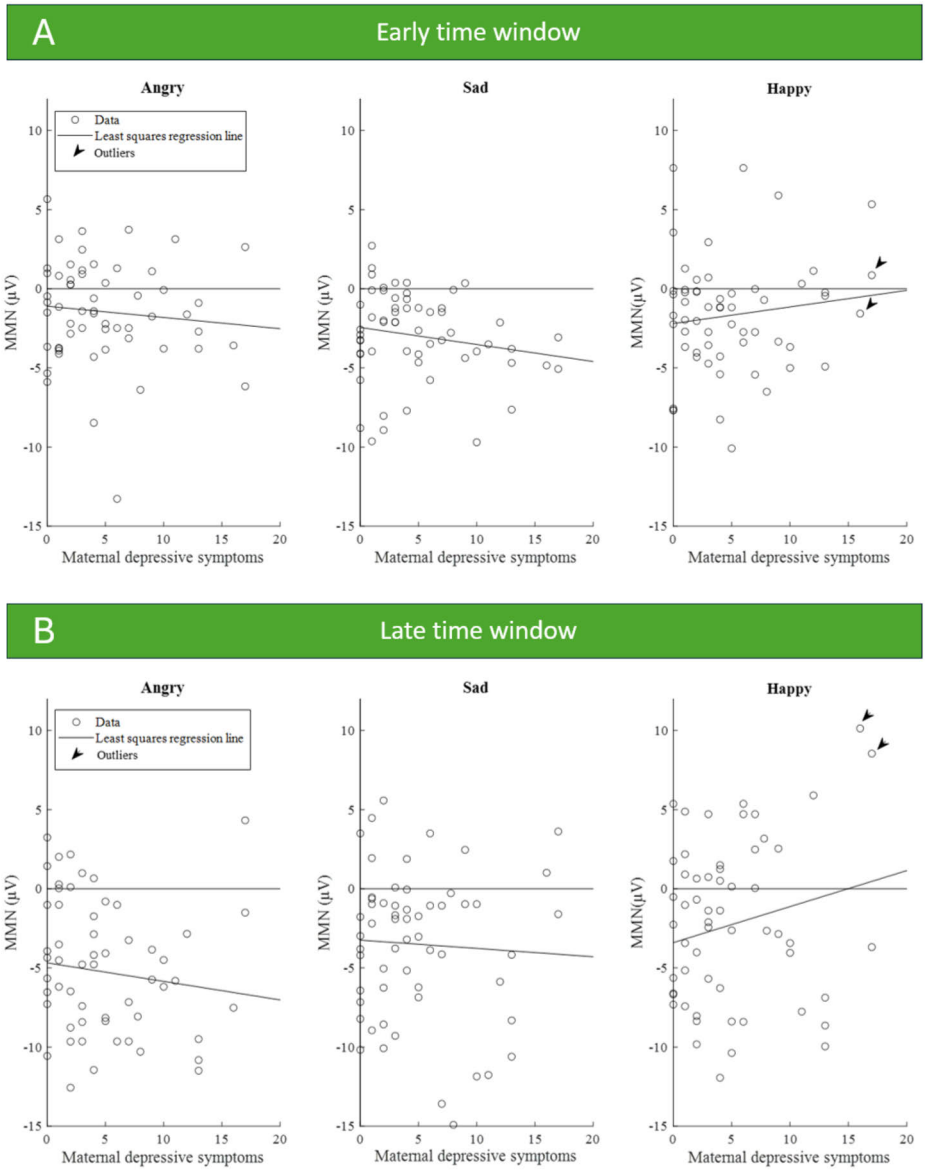

Figure 12. Scatterplots of maternal depressive symptoms and the mismatch response amplitudes (μV) of the children in A) the early time window (80–120 ms) and B) the late time window (350–450 ms). Of note, the lines are least-squares regression lines fitted across the data points, not the results of the mixed-effects models. Reference lines at 0μV are also presented in the figure. Outliers = subjects with the mismatch response amplitude > 7 μV in the emotion category "Happy" (N = 2). Modified from Study I, which is licensed under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

6 Discussion

6.1 Gestation- and age-related changes in aperiodic and periodic activity (Study II and III)

Our findings from Studies II and III demonstrate the developmental changes of aperiodic activity across early life. Specifically, we observed an increase in aperiodic exponents in EEG as a function of gestational duration, as well as higher offsets and, depending on the brain region, also higher exponents in the fMRI BOLD signal as a function of postmenstrual age. This association between a steeper slope of the EEG power spectrum was observed also in 3-year-olds. During the postnatal period, these effects appear to reverse, as indicated by a decrease in aperiodic exponents of the fMRI BOLD signal, as well as in aperiodic offsets and theta center frequencies in EEG observed in neonates. It could be that this pattern forms a reverse U-shaped curve from prenatal period across early life, with birth potentially marking a critical timepoint in this process.

Aperiodic activity and gestational duration/postmenstrual aging

In Study II, we found that higher postmenstrual age in the neonatal recordings correlates with elevated fMRI BOLD signal offsets in pre- and postcentral gyri and higher exponents in postcentral (somatosensory) gyri. Study III revealed a positive association between gestational duration and exponent values in toddler & neonatal EEG but not, interestingly, between gestational duration and offset. Higher exponents reflect a steeper distribution of signal power across the frequencies, i.e., more pronounced low-frequency fluctuations of the signal. Increase of offset refers to a uniform shift of the spectral power towards the higher power, which has been shown to correlate with neuronal populational spiking, and further, asynchronous signals have been identified as a principal source of BOLD responses (Manning et al., 2009; Miller et al., 2012). Taking this into account, our results could reflect the increasing neuronal firing rate in pre- and postcentral gyri during the prenatal period. In turn, the changes in exponent are proposed to reflect the balance between excitatory and inhibitory activity (Gao et al., 2017). Considering that, we propose that the offset and exponent could serve as markers for neurodevelopmental

processes during gestation, possibly reflecting, for example, the rapid synaptogenesis and increasing neuronal firing rates in the developing brain.

Interestingly, we observed different associations with aperiodic parameters based on gestational duration and postmenstrual age: in Study II, we found a positive association between neonate offsets (fMRI BOLD signal) and postmenstrual age, while in Study III, we observed a positive association between neonate and toddler exponents (EEG signal) and gestational duration. Several factors may explain this discrepancy, including the differing postnatal ages of the neonates between the studies (mean age in Study II: 2.5 weeks; Study III: 1.5 days), regional differences in the recordings (Study II: somatosensory and motor brain areas; Study III: global brain aperiodic activity), and variations in temporal and spatial accuracy between the imaging methods (fMRI vs. EEG). We suggest that future studies explore these differences, potentially by combining EEG and fMRI recordings, although we acknowledge the technical challenges of doing so, especially with our age group.

Our findings support that the effects of gestational duration, even in primarily term-born or early term-born children (gestational age > 36 weeks), can be seen as higher exponents as late as in 3-year-olds and this association is stronger than in neonates. While this difference may reflect differences in signal-to-noise ratio between neonate and toddler datasets or the cumulative modulatory effects of postnatal environmental factors in toddlers, it is also possible that the effect of the gestational duration becomes more prominent during early life.

Periodic activity and gestational duration

In Study III, a quadratic relationship between gestational duration and beta center frequencies in neonates was found, with a positive association until approximately 40–41 weeks of gestation, after which relationship turned negative. This quadratic effect may reflect shifts in neural activity during a period near late gestation and typical time of birth, as transition from discrete, spontaneous EEG activity to more continuous high-frequency activity is essential for cognitive functions (Vasung et al., 2019). Also, increasing beta frequencies can reflect the rapid growth of the brain, as gray matter volume reaches up to 50% of the total brain volume during the gestational weeks 29 and 41 (Hüppi et al., 1998). Also, changes in sleep state patterns in late gestation (Coons & Guilleminault, 1982; Ficca et al., 2000; Louis et al., 1997) as well as the onset of synaptic pruning (Tau & Peterson, 2010) may explain our findings. Our enticing finding needs future research to confirm the non-linear association and elucidate both typical patterns and their developmental underpinnings.

Aperiodic activity in preterm neonates

Prematurity was associated, in Study II, with overall lower exponents in pre- and postcentral gyri and, tentatively, lower offsets in postcentral gyri compared to term born neonates. This could simply reflect the shorter duration of gestation in preterm compared to term-born neonates. Before this thesis (Study III), aperiodic activity during gestation, as far as we know, remained unstudied. However, our findings on prematurity and aperiodic activity are in line with the previous fMRI BOLD signal study showing altered low-frequency fluctuation amplitudes, mostly in the motor and primary sensor cortices in preterm compared to term newborns (Wu et al., 2016).

Aperiodic activity and postnatal age

Postnatal age was negatively associated with the exponent values in neonate fMRI BOLD signal (Study II) and with the offsets in neonatal EEG (Study III). This indicates that the distribution of the BOLD signal baseline power would flatten across the frequencies as postnatal age increases, which could reflect the emergence of more widespread or global neural processes during aging. Our findings of decreasing exponent values as a function of postnatal age are congruent with the current body of literature, including electrophysiological studies in infants, children, adolescents, and young adults (Cellier et al., 2021; Clark et al., 2024; Hill et al., 2022; McSweeney et al., 2023; Rico-Picó et al., 2023; Schaworonkow & Voytek, 2021; Stanyard et al., 2024; Tröndle et al., 2022). However, this association may not be linear across the lifespan, as McSweeney et al. (2023) have found non-linear age-related relationships in 4–12-year-old children. Also, Wilkinson et al. (2024) have reported opposite findings with increasing aperiodic exponent and offset during the first years of life, especially rapid before the age of one year. As the exponent has been related to synaptic currents and, especially, to E-I balance, our results may indicate a shift of the global E-I balance toward excitation as neural circuits mature. This seems to be crucial to typical brain development, as aperiodic exponent and disrupted E-I balance have been implicated in pathology in attention deficit hyperactivity disorder (ADHD) and autistic traits (Carter Leno et al., 2022; Karalunas et al., 2022; Robertson et al., 2019). Correspondingly, treatment with medication has been shown to lead to the “normalization” of E-I balance (reflected by exponent) in ADHD children (Robertson et al., 2019). Our finding with a decrease in offset, i.e., baseline power of the neonatal EEG across frequencies, contradicts earlier results by Wilkinson et al. (2024). We propose that reduction in baseline aperiodic activity would reflect the shift in the neonatal brain from more spontaneous electrophysiological activity towards sensory-driven activity, which occurs approximately around gestational week 42 as circuits with sensory-driven activity develop (Vasung et al., 2019).

As discussed earlier, aperiodic activity has often been linked to changes in neuronal processes, such as neuronal firing rates or the balance between excitatory and inhibitory activity. However, recent research has also suggested alternative interpretations. Schmidt et al. (2024) demonstrated in adults that aperiodic activity originates from multiple physiological sources. They showed that changes in aperiodic parameters, which have been previously predominantly interpreted as reflecting neuronal activity, can also be explained by heart rate variability recorded via electrocardiogram. During early postnatal life, the transition from a low-sensory intrauterine to an extrauterine environment requires rapid adaptation across multiple organ systems. These include changes both in the nervous system as well as dramatic cardiovascular adjustments following separation from placental circulation, such as the closure of the foramen ovale, ductus arteriosus, and ductus venosus. (Morton & Brodsky, 2016). Considering this knowledge, it is possible that our findings are, at least partially, influenced by other physiological factors beyond pure neuronal changes. Investigating these questions further in future research could provide deeper insights into the origins of aperiodic activity. Key future directions are to perform multimodal measurements including EEG, fMRI, and heart rate in a single measurement across variable gestational and postnatal ages.

Periodic activity and postnatal age

Finally, we found that the center frequency of EEG theta oscillation was negatively associated with postnatal age in neonates, showing an age-related shift towards lower frequencies during the first days of life. One possible explanation for this observation could be changes in sleep architecture, occurring soon after birth, where active sleep is relatively more replaced with quiet sleep, which is characterized by slow oscillations (Coons & Guilleminault, 1982; Ficca et al., 2000; Louis et al., 1997).

Summary

The findings from our studies reveal a significant decrease in the aperiodic exponent (in fMRI BOLD signal, as well as in the aperiodic offset and theta center frequency (in EEG) as a function of postnatal aging in neonates. These results predominantly align with existing literature, likely reflecting early maturational changes driven by adaptation to the extrauterine environment and changes in sleep architecture. Interestingly, we did not observe postnatal age-related changes in toddlers, but only in neonates.

However, it's essential to consider the nuances within our findings. While the exponent and offset in Study III represent global electrophysiological signal parameters averaged across all electrodes, in Study II these parameters originate

more locally, from the pre- and postcentral gyri BOLD-signal power. Therefore, interpretations of our findings should be contextualized within the developmental age of the participant, the neuroimaging method used, and the specific brain region under investigation.

6.2 Sex-related differences in aperiodic and periodic activity (Study II and III)

Aperiodic activity in female vs. male neonates

In Study II, we demonstrated that female neonates had higher offsets but smaller exponents in fMRI BOLD signal. However, in Study III, no sex-related differences in aperiodic parameters were found. These differences in findings might be related to, for example, the different postnatal age of neonates between studies (mean postnatal age 2.5 weeks in Study II and 1.5 days in Study III), or the regional differences, as while Study III was focused on global brain aperiodic activity, Study II was focused only on somatosensory and motor brain areas, major cortical hubs during the neonatal period, maturing among the earliest brain regions (Thomason, 2020). Considering that, our results could support a faster pace of brain maturational processes during gestation in females, where lower exponents in females were observed in Study II but not in Study III, which could reflect either faster postnatal maturational processes in females or earlier, more "postnatal-like" maturation of somatosensory and motor brain areas in females during the pregnancy.

Higher beta center frequencies in female toddlers

In Study III, aperiodic-adjusted beta center frequencies were positively correlated with sex, indicating higher beta center frequencies in female toddlers compared to males. Similar phenomena have been demonstrated in prior research (Wilkinson et al., 2024). Beta frequencies are thought to originate at the cortical network level and are linked to various cognitive functions such as decision-making and working memory (Spitzer & Haegens, 2017). Interestingly, we observed sex-related changes only in toddlers, not in neonates. The discrepancy may reflect the more mature cortical-level neural networks in females compared to males at this developmental stage. Longitudinal studies across early life would provide valuable insights into the developmental trajectories underlying these differences.

Summary

Our findings revealed sex-specific changes in aperiodic exponent and offset in neonates, likely reflecting earlier brain maturational processes in females during pregnancy. During the toddlerhood, female neonates have also higher beta center frequencies compared to males, which may reflect more mature cortical-level neural networks at this developmental stage. However, in the context of aperiodic activity, sex-related differences remain largely unstudied. Electrophysiological findings from adolescents support that in early adolescence, males would have higher offsets and exponents compared to females, but in later adolescence, these roles seem to reverse (McSweeney et al., 2021). The effects of sex on aperiodic activity remain controversial, and further studies, especially in neonates and young children, are required.

6.3 Regional changes in aperiodic and periodic activity (Study II)

Higher offsets in precentral versus postcentral gyri

In Study II, we observed higher offset values in the precentral (motor) compared to the postcentral (somatosensory) gyri, particularly prominent in preterm-born infants. This suggests a greater power of the BOLD signal in the precentral gyri, indicating heightened neural activity compared to postcentral gyri, especially in preterm infants. Interestingly, this regional difference disappeared as postnatal age approached approximately 20 weeks, which aligns with the estimated date of delivery for neonates in our study.

Exponent & postmenstrual age in postcentral gyri

Additionally, we found that the exponent increased in the postcentral gyri as postmenstrual age increased, while there was no considerable change in exponent values in the precentral gyri. This indicates that aperiodic activity distribution across frequencies steepened in the postcentral gyri with increasing postmenstrual age. Considering that the flattening of the power spectrum has been associated with postnatal aging in previous studies (Cellier et al., 2021; Hill et al., 2022; Schaworonkow and Voytek, 2021; Tröndle et al., 2022) and discussed as potentially reflecting changes in myelination, brain volume, and cortical thickness (McSweeney et al., 2023), our findings suggest earlier development of precentral (motor) gyri compared to postcentral (somatosensory) gyri during gestation. Although previous research (Fogliarini et al., 2005) has generally supported earlier maturation of

somatosensory areas, our results align with an earlier diffusion tensor imaging study of preterm newborns, which found higher functional anisotropy and lower diffusivity in motor tracts compared to the sensory tracts, reflecting earlier white matter maturation of the motor system compared to sensory pathways (Berman et al., 2005).

Asymmetry in aperiodic activity

Moreover, we observed asymmetry in aperiodic activity, with slightly higher offset values in the right hemisphere compared to the left hemisphere, indicating greater broadband power of the BOLD signal in the right hemisphere. This aligns with findings from previous studies suggesting earlier maturation of the right hemisphere, as evidenced by cortical folding occurring earlier in the right hemisphere in fetuses and general functional dominance (except for linguistic stimuli) of the right hemisphere in fetuses, neonates, and preterm-born infants (Bisiacchi and Cainelli, 2022).

Summary

Findings from Study II likely reflect region-dependent maturational differences, suggesting earlier maturation of the precentral gyri during the prenatal period. While partially contradicting previous literature, parallel results have also been described. Future studies are needed to further investigate this issue and clarify the underlying mechanisms driving these observed differences.

6.4 Effects of maternal prenatal distress on mismatch responses of EEG (Study I)

Weaker mismatch responses to happy stimuli in children of mothers with higher prenatal depressive symptoms

In Study I, using mismatch responses as an electrophysiological correlate of automatic auditory perception, we observed a positive association between maternal prenatal depressive symptoms and mismatch response amplitude to happy auditory stimuli in an early time window. This indicates that children exhibit reduced mismatch response amplitudes as maternal depressive symptoms increase. This finding is consistent with previous research in neonates within our research group, where Lavonius et al. (2020) similarly found decreased ERP amplitudes for happy auditory stimuli associated with higher maternal sleep problems during pregnancy, another dimension of prenatal distress. Together, these results support the hypothesis that deficiencies in maternal well-being during pregnancy may lead to children

exhibiting weaker responses to happy stimuli, potentially extending from the neonatal period into early childhood.

While studies specifically examining prenatal maternal depressive symptoms in our age group are lacking, findings from studies related to prenatal anxiety symptoms suggest stronger reactions to fearful emotional auditory stimuli in infants or increased attention to neutral versus unpleasant pictures in children (Otte et al., 2015; van den Heuvel et al., 2018). Previous research into depressive symptomology during pregnancy indicates potential effects on infant relative frontal EEG asymmetry, with even subclinical levels of prenatal depression potentially impacting offspring's EEG activity more than postnatal or concurrent depression (Goodman et al., 2021; Gustafsson et al., 2018). However, the effects of maternal prenatal distress on offspring brain functioning remain debated, necessitating further studies across various age groups.

The mechanisms underlying the association we have identified can only be speculated upon, as EEG does not allow for precise localization of brain areas of unraveling the neural basis of the findings. Nonetheless, emotion perception activates a network of brain regions, including the amygdala, insula, and orbitofrontal cortex (Lindquist et al., 2012). Volume-specific changes in the amygdala, a crucial structure for emotional processing, have been linked to prenatal maternal depressive symptoms in children (Acosta et al., 2020; Wen et al., 2017) and newborns (Lehtola et al., 2020). These findings are partly controversial and show sex-specific differences, reporting smaller volumes in newborn boys, overall smaller amygdala volumes in 4-year-olds, but stronger in boys, and larger volumes in 4.5-year-old girls was maternal prenatal depressive symptom scores increase. Finally, functional connectivity-related changes also suggest negative associations between prenatal distress and the stability of frontoparietal connections, supporting that frontal areas are especially sensitive to prenatal stress exposure (Tuulari et al., 2024). One possible explanation for our findings could be that, in children of depressed mothers, happy sounds may not capture attention as effectively, or that these children may have reduced exposure and experience to happy sounds.

Summary

Our findings indicate that children of mothers who experienced prenatal depressive symptoms exhibit weaker responses to happy sounds. This may reflect reduced attention in children of depressive symptomatic mothers when reacting to happy versus other emotional category sounds in children of mothers with depressive symptoms. However, investigations into the mechanisms underlying this association, as well as studies investigating possible sex-modulated effects with larger sample sizes, are required. Future research should also consider the influence

of genetic factors, or indirect (postnatal) environmental factors correlated with maternal prenatal depressive symptoms. Furthermore, the long-term developmental implications of prenatal distress-induced changes remain unclear and require longitudinal studies for elucidation of the potential practical implications of the findings.

6.5 Strengths and Limitations

In this thesis, we utilized two different functional neuroimaging techniques, EEG and fMRI, to explore gestational duration- and age-related changes in two age groups, neonates and toddlers. Unlike previous research, we applied spectral power analysis also to fMRI data, providing, to our best knowledge, the first such study in neonates. This approach allowed us to capture both the rapid temporal dynamics of power spectra with EEG's high temporal resolution (Study III) and the more precise localization of neural activity with fMRI (Study II). Notably, this thesis encompasses multiple novel studies investigating gestational duration-related associations with aperiodic activity.

However, several limitations should be acknowledged. First, our assessment of the study outcomes was cross-sectional in all studies, limiting our ability to infer true longitudinal changes in neural activity. Nevertheless, the large sample size in Study II supports the generalizability of our findings to a broader population. Larger sample sizes in Studies I and III could have improved statistical power, helping to detect small effects that might otherwise be masked by random variability. However, it is notable that studies in toddlers are scarce, primarily due to challenges in behavioural measures (Putkinen et al., 2012). In the context of aperiodic signals, neonate/infant studies are rare and show even smaller sample sizes than ours (for example, Schaworonkow & Voytek, 2021).

Second, our reliance on auditory paradigm data (neonates and toddlers, Study III) for estimating power spectra presents limitations. Although prior electrophysiological studies have typically utilized resting state data (Hill et al., 2022), it is important to notice that our sensitivity analyses in Study III revealed condition-related (sleep/auditory) interactions only in the beta center frequency model in neonates, supporting the generalizability of our age-related group-level findings.

Third, the lack of information regarding the sleep state of neonates (active/quiet sleep) in Studies II and III complicates the interpretation of our results. Among newborns, sleep-wake patterns undergo rapid evolution during the first few months after birth, transitioning from relatively active to structured non-rapid eye movement and rapid eye movement sleep phases (Coons & Guilleminault, 1982; Ficca et al., 2000; Louis et al., 1997). Around postmenstrual age of 34 weeks, EEG exhibits

longer periods of continuity but remains relatively discontinuous, showing similar patterns during awake and active sleep, while periods of discontinuity are observed during quiet sleep. Eventually, EEG becomes consistently continuous around postmenstrual age 44 weeks. (Louis et al., 2016). The uncertainty surrounding the wakefulness/sleep state during measurement has been shown to complicate the interpretation of fMRI data (Scheinost et al., 2023). Given the inherent difficulty in distinguishing sleep states in this age group, we cautiously attribute observed changes in aperiodic parameters to factors such as aging, premature birth, and sex of the neonates. Also, it is important to note that while neonates were sleeping during the recording in Study III, toddlers were awake. Therefore, caution is required when interpreting these results.

Fourth, we encountered some restrictions regarding the variability for our predictor variables. In Study I, our dataset included many mothers who scored zero (no depressive symptoms) on the EPDS questionnaire and their children exhibited a variance in mismatch responses similar to those whose mothers had higher EPDS scores. Caution is thus required when interpreting our findings from associations between maternal EPDS scores and children's responses. Similar issues have been reported in prior research (Mostert et al., 2016). Future studies should explore the factors underlying this variance, e.g., by analyzing biological samples or investigating other prenatal exposures. Further, in Study II, the variation of postnatal age in neonates was low due to the decision to perform scans close to birth. Consequently, this led to a highly skewed distribution of infant age data. However, upon visually inspecting the diagnostics of the linear regression models, they were found to be acceptable, and indeed linear models are robust to skewed distributions against general perceptions (Ernst & Albers, 2017).

Fifth, it is important to acknowledge that our results in Study I did not survive Bonferroni correction, underscoring the preliminary nature of our findings. Increasing the number of trials per condition–or reducing the number of different conditions to increase the number of trials per condition–could have improved the precision in measuring mismatch responses, potentially leading to stronger statistical conclusions. Despite this, the use of a multifeatured MMN paradigm allowed for measuring multiple deviants concurrently within a short timeframe, maintaining child engagement and minimizing movement artifacts. When interpreting our results, it is important to note that the Bonferroni correction can be conservative, which may make it harder to detect real effects, especially with a small sample size or when the effects are small. Additionally, the emotional stimuli varied not only in valence but also in other sound properties like intensity and duration. It remains uncertain if the observed late-time window mismatch responses (350–450 ms) were specifically elicited by the second syllable of the pseudoword "ta-ta" or resulted from differences in acoustic properties. Nevertheless, acknowledging the challenge in

isolating such effects, we cautiously attribute changes in mismatch response amplitude to the emotional valence of the stimuli.

Sixth, it is important to note that in Study III, the multiple comparison correction was not conducted for the neonate multilevel regression model (sleep / sleep + auditory paradigm). Thus, the condition-related difference that we observed in beta center frequency in neonates, should be considered preliminary.

Seventh, factors such as the alertness level of toddlers prior to EEG recording (Study I & III) and the absence of information on their potential disorders (such as autism spectrum disorder) or medication status could influence variations in mismatch response amplitudes.

Eighth, our samples in Study III included both late preterm (born at 36 weeks of gestation) and term children (born at 37 weeks of gestation or later) to ensure the sample size remained as large as possible. Although these age groups are often treated separately in research, the effects of gestational age seem to follow a continuum (Engle, 2011), which suggests that our findings may be generalized to a broader population.

Ninth, we cannot be certain whether the prematurity-related results in Study II are best explained by prematurity itself (i.e., the early transition from the intrauterine to the extrauterine environment) or by the underlying causes of prematurity (such as maternal distress, inflammatory conditions, etc.). More research is needed to identify potential mediating factors linking prematurity to later developmental outcomes.

Finally, in Study II, the cross-validated test performance indicates a strong generalization ability of the model. However, it's crucial to acknowledge that training performances are notably superior, suggesting potential overfitting despite model regularization. This can lead to unreliable feature weights, complicating model interpretation (Nielsen et al., 2020). Additionally, research has shown that functional connections strongly associated with age exhibit higher intercorrelation than expected by chance, resulting in redundant information and unreliable weights (Pathania et al., 2021). Although our study employed BOLD signal parameters as features instead of functional connections, similar limitations may affect the interpretability of our analysis.

6.6 Future Directions

Our findings revealed developmental changes in both aperiodic and periodic activity across early life. Specifically, we observed an increase in aperiodic exponents in EEG as a function of gestational duration, along with higher offsets and exponents in the fMRI BOLD signal related to postmenstrual age. Changes in the slope of the EEG power spectrum due to gestational duration were observed even at 3 years of age. However, these effects seem to reverse after birth as indicated by decreases in

aperiodic exponents in the fMRI BOLD signal, as well as reductions in aperiodic offsets and theta center frequencies in EEG observed in neonates. Prematurity was linked to a flatter distribution of spectral power across frequencies when compared to term-born neonates. Additionally, we found an association between prenatal maternal depressive symptoms and the later neural activity of offspring.

While our studies were cross-sectional, longitudinal research design would be ideal for investigating other age-related, individual-level changes in neural activity. Such studies, involving repeated EEG measurements from childhood through adulthood, could provide deeper insights. The FinnBrain Birth Cohort study (Karlsson et al., 2018) presents an excellent opportunity for future research, with its potential for multidisciplinary data analysis, including distress measurements, biological samples, and neuropsychological assessments. Moreover, large longitudinal neuroimaging projects exploring the developmental trajectories of the brain, such as the Adolescent Brain Cognitive Development Consortium (ABCD; Volkow et al. (2018) or The HEALthy Brain and Child Development Study (Volkow et al., 2024) give valuable possibilities to explore these questions further.

While we have successfully employed two distinct brain imaging methods (fMRI, EEG) in separate studies to investigate the aperiodic activity of the developing brain, it would be interesting in the future to integrate these techniques to study age-related changes in a multimodal fashion within the same sample and measurement point. This would allow us to leverage the advantages of both imaging modalities: capturing the rapid temporal dynamics of power spectra with EEG's high temporal resolution and achieving precise localization of neural activity with fMRI's superior spatial resolution. Such an integrated approach could yield a more comprehensive understanding of brain function.

Furthermore, recent studies in both children and adults (Ibarra Chaoul & Siegel, 2021; Manyukhina et al., 2022; Thuwal et al., 2021) have demonstrated the potential of magnetoencephalography (MEG) in capturing aperiodic aspects of neural activity. Like EEG, MEG offers excellent temporal resolution but, unlike EEG, is not significantly distorted by tissues. Additionally, MEG provides direct information about neural activity, unlike fMRI. Given these advantages, MEG could prove to be a valuable tool for studying aperiodic activity in future research.

Flattening of the power spectrum across postnatal aging is becoming a 'well-known phenomenon' and has predominantly been interpreted as changes in neuronal activity. However, the recent study by Schmidt et al. (2024) demonstrates in adults that aperiodic parameters are also linked to the cardiac activity (electrocardiogram). This kind of study has not yet been done in younger children or adolescents, and this would be interesting to address in future research.

As demonstrated in Study II, prematurity appears to correlate with a general reduction in aperiodic activity among neonates, likely reflecting disrupted neural

maturation processes ex-utero due to the shorter gestation duration compared to term-born peers. It is also possible that the observed changes in aperiodic activity are linked to the underlying causes of prematurity itself. This question could be best explored further in sibling datasets, such as in the study by Kuula et al. (2022), where genetic and environmental and confounders can be accounted for. While the long-term effects of these changes in aperiodic activity on neurodevelopmental outcomes remain uncertain, there is a consensus regarding the role of prematurity in increasing the risk of various neurodevelopmental conditions (Allen, 2008; Taine et al., 2018). This underscores the importance of preventive interventions. Interventions utilizing bedside facilitation of mother-infant emotional connection have been shown to have potential beneficial effects on preterm babies' brain development (Yrjölä et al., 2022).

We also found an association between maternal prenatal depressive symptoms and toddler neural responses to happy sounds. Future studies could focus on possible underlying mechanisms in associations of this kind by exploring the possible mediators, such as maternal hair cortisol, or genetic variations in this relationship. In future measurement points, controlling the child's own stress symptoms will be important as well. Furthermore, other potential moderating postnatal factors, such as parental caregiving quality, social support, or socioeconomic status, should be taken into account (Nolvi et al., 2020). The impact of the prenatal distress on child future outcomes remains poorly understood, as low to moderate levels of prenatal distress may serve adaptive roles for offspring (Fatima et al., 2017). However, as higher amounts of distress seem to be unfavorable for later offspring neurodevelopmental outcomes (Räikkönen et al., 2011; Tuovinen et al., 2021; Van den Bergh et al., 2020), the studies focusing on preventing interventions for prenatal distress are needed. A promising example could be maternal mindfulness during pregnancy (van den Heuvel et al., 2015) or increase in prenatal physical activity (Na et al., 2022). Also, the role of the postnatal environment seems promising, as factors like high-quality caregiving, socioeconomic status, and social support may modulate the relationship between prenatal stress and child brain development (Nolvi et al., 2023).

7 Conclusions

The major findings of the studies are as follows:

I. Maternal prenatal depressive symptoms are associated with weaker mismatch responses to happy auditory stimuli. This may reflect that in children of depressed mothers, happy sounds may not capture attention as effectively, or these children may have reduced exposure and experience to happy sounds.

II. Preterm birth, postmenstrual age, and postnatal age are associated with aperiodic activity in fMRI BOLD signal in neonates. Findings suggest increasing aperiodic activity during gestation, followed by a decrease during the postnatal period. Results likely reflect maturational changes during brain development, with birth marking a critical checkpoint in this process.

III. Gestational duration is associated with electrophysiological activity, suggesting a steeper distribution of spectrum power across the frequencies in toddlers as well as in neonates with longer duration of gestation. Findings suggest that gestational duration may have significant and relatively long-lasting effects on brain physiology.

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