Zentralinstitut für Seelische Gesundheit

Direktor: Prof. Dr. Andreas Meyer-Lindenberg

Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters

Direktor: Prof. Dr. Dr. Tobias Banaschewski

The Effect of Maternal Prenatal Smoking on Brain Activity in Childhood, Adolescence, and Young Adulthood and Its Association with Behavioral and Cognitive Development Using Data from Longitudinal Cohort Studies

Inauguraldissertation

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Karina Janson

aus Astana (Kasachstan)

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Dekan: Prof. Dr. med. Sergij Goerdt

Referent: Prof. Dr. med. Dr. rer. nat. Tobias Banaschewski

„Der Erkenntnisvorgang ist nicht die bloße Wiedergabe des Gegebenen, sondern immer auch ein Verstehen, das vom Vorverständnis geleitet wird.“

Gadamer, H.-G. – Wahrheit und Methode, 1960

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PREFACE

This publication-based cumulative dissertation includes two previously published papers.

The first publication, "Association of Maternal Smoking During Pregnancy With Neurophysiological and ADHD-Related Outcomes in School-Aged Children" (section 2.1 of the dissertation), of which I am the sole first author, was published in the International Journal of Environmental Research and Public Health (impact factor: 4.614) in 2022. For this original research, I contributed 80% of the conceptual design, 90% of the literature research, and 100% of the data analysis and interpretation of results. I also contributed 90% of drafting and revising the manuscript. I was not involved in ethics approval or data collection for this study. The data were obtained as part of a large longitudinal cohort study, with all analyses and results originating from my own work.

The second publication, "Long-Term Impact of Maternal Prenatal Smoking on EEG Brain Activity and Internalizing/Externalizing Problem Symptoms in Young Adults" (section 2.2 of the dissertation), of which I am the sole first author, was published in Addictive Behaviors (impact factor: 3.7) in 2024. For this research, I contributed 80% of the conceptual design, 100% to data analysis, 90% each to the literature research and interpretation of results, and 90% to the drafting of the manuscript. The data were again obtained from a longitudinal cohort study, and I was not involved in the ethics application for the study.

Detailed information on my contributions can also be found in the attached form below.

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LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
AUDIT	Alcohol Use Disorders Identification Test
DISPYPS	Diagnostik-System für Psychische Störungen im Kindes- und Jugendalter (Diagnostic System for Mental Disorders in Childhood and Adolescence)
EEG	Electroencephalography
EOG	Electrooculography
ERP	Event-Related Potential
FBB-ADHS	Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (External Rating Scale for ADHD)
FFT	Fast-Fourier transformation
(f)MRI	(Functional) Magnetic-resonance imaging
GAMM	Generalized Additive Mixed Models
ICA	Independent component analysis
IDS	Intelligence and Development Scales
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
QEEG	Quantitative Electroencephalography
RNA	Ribonucleic Acid
SPSS	Statistical analysis toolbox
YASR	Young Adult Self-Report

Darstellung der Eigenleistung der Doktorandin/des Doktoranden

bei kumulativen Dissertationen

Name der Doktorandin/des Doktoranden Karina Janson

Titel der Dissertation

The effect of maternal prenatal smoking on brain activity in childhood and young adulthood and association with behavioral and cognitive development using data from longitudinal cohort studies

Betreut durch Prof. Dr. Dr. Tobias Banaschewski

☐ Ich möchte eine kumulative Dissertation einreichen und bitte den Promotionsausschuss zu prüfen, ob die vorgeschlagenen Publikationen quantitativ und qualitativ ausreichen, um die Anforderungen an eine kumulative Dissertation zu erfüllen.

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Publikation 1

Jansone, K.; Eichler, A.; Fasching, P.A.; Kornhuber, J.; Kaiser, A.; Millenet, S.; Banaschewski, T.; Nees, F.; The IMAC-Mind Consortium. Association of Maternal Smoking during Pregnancy with Neurophysiological and ADHD-Related Outcomes in School-Aged Children. Int. J. Environ. Res. Public Health 2023, 20, 4716. https://doi.org/10.3390/ ijerph20064716

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Publikation 2

2. Zusammenfassung des Beitrags der Doktorandin/des Doktoranden zu der in jedem Manuskript berichteten Arbeit

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Beide der oben genannten Publikationen habe ich als alleinige Erstautor*in verfasst, ohne Beteiligung einer gemeinsamen Erstautorenschaft

4. Ich bestätige hiermit, dass dies eine wahrheitsgetreue Darstellung des Beitrags der Doktorandin/des Doktoranden zu den aufgeführten Publikationen ist.

1 INTRODUCTION

Early stages of prenatal development are critical period for the child's development, involving the foundation for both physical and psychological health throughout life. While genetic factors play a foundational role, prenatal exposures such as maternal tobacco smoking and alcohol consumption have been consistently associated with adverse neurodevelopmental and behavioral outcomes in offspring (M. Ekblad et al., 2015; Hackshaw et al., 2011). These exposures can disrupt key developmental processes, particularly in the brain, which undergoes rapid growth and differentiation during gestation but also contribute to long-term behavioral and cognitive outcomes. Therefore, exploring risk factors for later cognitive, emotional, and behavioral challenge difficulties requires an understanding of how prenatal exposures impact child and adolescent development (Abraham et al., 2017; Button et al., 2007).

The following chapter will provide an overview of how prenatal exposures, particularly maternal tobacco smoking, act as significant risk factors influencing child and adolescent development. Particular focus will be on neurodevelopmental changes which can be affected by early exposures as well as pathways through which behaviors of the mother during pregnancy can influence the developmental process.

1.1. DEVELOPMENT ACROSS THE EARLY LIFE SPAN

A vast range of biological, psychological, and environmental factors impact the complex process of child and adolescent development (Dahl, 2004; Miller et al., 2011; Shiner & Caspi, 2003). From the earliest stages of prenatal life all the way through adolescence, individuals progress through rapid changes that set the groundwork for future health, behavior, and mental well-being (Dorn et al., 2019). These changes are guided by genetic predispositions and shaped by the family environment, cultural norms, and socioeconomic contexts (Dodge & Pettit, 2003; Maggi et al., 2010).

During infancy, children acquire fundamental abilities such as basic motor coordination, language comprehension, and problem-solving (Keen, 2011; Siregar & Lubis, 2023). As they enter middle childhood, these initial skills are refined further by increasingly complex academic challenges and peer relationships (Siregar & Lubis, 2023). By the time adolescence begins, hormonal shifts related to puberty come into play, intertwining with questions of personal identity, greater independence, and changing social expectations (Pfeifer & Allen, 2021). Meanwhile, the ongoing maturation of the adolescent brain contributes to both the potential for high-level reasoning and the tendency toward more impulsive decision-making (Dahl, 2004).

Recognizing how these developmental stages interact with genetic, family, and cultural factors is key to supporting positive outcomes. It sheds light on the risks that might disrupt healthy development — such as continuous stress, inadequate social support, or harmful environmental exposures — as well as on the resources that strengthen resilience (Walsh, 2016). In the pages that follow, this chapter will outline the major developmental transitions from prenatal life through adolescence, exploring how immediate surroundings, genetic factors, and broader social forces collectively shape both short-term well-being and the path toward adulthood.

1.1.1. From the Prenatal Phase to Childhood, Adolescence, and Young Adulthood

Neurodevelopment is a continuous, dynamic process that begins well before birth and extends into the early years of adulthood. During this prenatal period, the foundation for the nervous system is laid down as neurons are generated, migrate to their appropriate locations, and establish rudimentary connections (Gibb & Kovalchuk, 2018; ten Donkelaar et al., 2023). During this stage, the fetus is particularly sensitive to a variety of influences, such as maternal health, nutritional intake, and exposure to environmental risk factors (Gibb & Kovalchuk, 2018). These prenatal experiences can have lasting effects on cognitive, emotional, and behavioral outcomes.

Following birth, the brain undergoes notable structural and functional changes. Infancy and early childhood are marked by rapid synaptogenesis — when neurons establish a vast network of connections — followed by a period of synaptic pruning, which refines these connections based on a child’s experiences and environment (ten Donkelaar et al., 2023). Myelination, or the formation of a protective sheath around nerve fibers, further enhances the efficiency of neural communication. These maturational processes allow young children to develop foundational skills in language, motor coordination, and social interaction at a remarkable pace.

During middle childhood, ongoing neurodevelopment supports increasingly complex cognitive tasks, such as problem-solving and logical reasoning. During this phase, the interplay of genetic predispositions, family dynamics, and cultural context becomes even more pronounced, influencing not only cognitive growth but also emotional regulation and social behavior. By adolescence, hormonal changes linked to puberty interact with shifts in neural architecture — particularly in regions responsible for decision-making and impulse control — contributing to both the exploration and vulnerabilities common to the teenage years (Sturman & Moghaddam, 2011). Research suggests that the adolescent brain's heightened plasticity allows for rapid skill acquisition and adaptability, but it can also magnify the impact of stress or maladaptive behaviors.

Although some areas of the brain appear largely mature by the end of adolescence, certain regions, particularly in the frontal cortex, continue to refine their connectivity into early adulthood (Arain et al., 2013). These ongoing changes affect higher-order functions such as planning, self-regulation, and long-term goal setting. Recognizing this extended timeline underscores the importance of supportive environments and interventions that cater to the evolving capacities of children and adolescents as they transition into adulthood.

In the subsequent subsections, each major developmental phase — ranging from prenatal and perinatal periods (1.1.1.1) to childhood (1.1.1.2) and adolescence (1.1.1.3) — will be explored in detail in order to demonstrate how early foundations and later environmental experiences intertwine to shape cognitive development, social behavior, and overall mental health.

1.1.1.1. The Prenatal Phase as a Foundation for Development

The importance of the prenatal and perinatal stages of development are extremely complex. Prenatal development is a sequential process that consists of highly defined stages through which the growth and differentiation of cells, tissues, and organ systems takes place (Blackburn, 2007). This highly ordered process from conception to birth is approximately nine months long. For instance, period consists of three trimesters, each characterized by important developmental milestones and vulnerabilities (ANEF et al., 2019; Hack & Glanc, 2023). The first trimester is often seen as the most critical phase, as it encompasses the embryonic period (weeks 1–8) during which organogenesis occurs (Blackburn, 2007; Connolly & Valsiner, 2002). Key milestones include the development of the neural tube (precursor to the central nervous system), the heart (which begins beating by week 4), and the initial formation of limbs and facial features. The zygote's cells divide, implant in the uterine lining, and acquire the necessary components to sustain life during the first trimester (Connolly & Valsiner, 2002). The brain and spinal cord, as well as the infant's primary organs, grow during the five weeks that the baby is known as an embryo (3 to 9 weeks). Around the third week of pregnancy, the neural plate forms and folds into the neural tube, marking the beginning of the earliest stage of neurodevelopment. The brain and spinal cord are derived from this tube. The brain's building blocks, billions of neurons, are created during an intense phase of neuronal proliferation that lasts from the second to the fifth month of pregnancy (Kostović et al., 2021; ten Donkelaar et al., 2023). With the help of radial glial cells' structural framework and chemical cues, these neurons move to particular areas. Six weeks after fertilization, brain waves can be captured. By week eight, the kidneys are functioning and the liver is producing blood. Additionally, the muscles, digestive tract, backbone, and ribs start to form. This period also sees the formation of several exterior bodily structures, including the face, arms, hands, fingers, legs, feet, and toes (Karaca, 2022).

During the second trimester, rapid fetal growth and functional maturation dominate. The infant is referred now to as a fetus at nine weeks (Karaca, 2022). This stage is mostly referred to as the finishing and growing phase. The muscles, organs, brain, and spinal cord start to cooperate and arrange themselves (Tan & Lewandowski, 2019). The brain undergoes a surge of neuronal proliferation and migration, establishing the basic architecture of the cerebral cortex (Kostović et al., 2021). The fetus may move and behave because of these connections. At this point, an ultrasound may reveal mouth opening, thumb sucking, arm and hand motions, and kicking. With the exception of the immune system, every bodily system in the fetus is functioning by 12 weeks (Tan & Lewandowski, 2019).

The third trimester focuses on preparing the fetus for independent life. The fetus's growing size and functional development are the main goals of development throughout this trimester. The brain keeps expanding. The cerebral cortex, frequently referred to as the brain's thinking region, enlarges. The grooves and convolutions (folds and wrinkles) characteristic of an adult brain start to deepen at this stage of brain development. Because of this, the brain may grow in size and volume without the skull growing larger (Kostović et al., 2021). The brain undergoes extensive synaptogenesis and myelination, processes critical for sensory processing, motor coordination, and cognitive function. Beginning in the second trimester, synaptogenesis — the process by which neurons develop synaptic connections — peaks in the third trimester. Neural networks that process information through motor, sensory, and cognitive processes are built on these connections (Kostović et al., 2021). Concurrently, the third trimester marks the start of myelination, a process that improves signal transmission by coating axons with a fatty sheath. This process continues after birth. Supporting these activities requires adequate maternal consumption of important fatty acids, such as omega-3s (Li et al., 2016). With increasing synapse density and electrical activity, the brain starts to establish functional networks at the end of the second and third trimesters (Kostović et al., 2021). For example, the embryonic brain begins to exhibit basic electrical oscillation patterns, which are necessary for the integration of senses and motor skills. These early networks can be upset by environmental variables including stress, exposure to toxins, and maternal health, which may have an impact on later emotional control and cognitive development. Epigenetically, neurodevelopment is also controlled by processes such as histone modification and DNA methylation (Podobinska et al., 2017). Neurodevelopment is also regulated epigenetically, through mechanisms like DNA methylation and histone modification (Dall'Aglio et al., 2018). These processes influence gene expression without altering the DNA sequence, allowing the fetal brain to adapt to environmental inputs. However, adverse exposures such as maternal tobacco smoking or malnutrition can induce maladaptive epigenetic changes, potentially predisposing offspring to neuropsychiatric disorders and altered stress responses.

Prenatal development occurs within a complex interplay of genetic, epigenetic, and environmental factors. While the tightly regulated sequence of growth generally leads to healthy outcomes, the developing fetus is particularly vulnerable to disruptions during critical periods of organogenesis and functional maturation.

1.1.1.2. Neurodevelopment in Childhood: Brain Maturation and Cognitive Growth

Neurodevelopment is a dynamic process that extends beyond the prenatal period, continuing through childhood, adolescence, and into adulthood. This process leads to rapid changes in brain morphology, connectivity, and function that are also influenced by genetic, epigenetic, and environmental factors.

During the early childhood, brain is marked by fast synaptogenesis, i.e., the formation of new connections between the neurons at a much faster rate. This "synaptic bloom" is necessary for sensory processing, motor regulation and for the development of supporting cognitive and affective abilities. Studies utilizing advanced neuroimaging techniques, such as magnetic resonance imaging (MRI), have revealed significant growth of brain volume between the first few years of life and specifically, in brain regions that underlie sensory and motor processes (Rivkin, 2000; Vo Van et al., 2022). These changes support the brain’s remarkable capacity for neuroplasticity during this period, enabling adaptation to environmental stimuli and new learning experiences.

As the child matures, the phase of synaptogenesis transitions to synaptic pruning, where redundant or underutilized connections are selectively eliminated (Abbott & Burkitt, 2023). This process enhances the efficiency of neural networks, allowing for more specialized and streamlined brain activity. Synaptic pruning is particularly pronounced in the prefrontal cortex, the region responsible for executive functions such as attention, planning, and decision-making (Sakurai & Gamo, 2019). The balance between synapse formation and pruning is crucial for healthy neurodevelopment; disruptions in this process, such as those caused by early adversity or trauma, have been linked to long-term cognitive and emotional difficulties (Malave et al., 2022; Zonuzirad, 2024).

During childhood, the brain undergoes increasing functional specialization. Regions responsible for specific tasks, such as language (Broca’s and Wernicke’s areas), memory (hippocampus), and problem-solving (prefrontal cortex), become more distinct and interconnected (Zonuzirad, 2024). This period also sees a rise in myelination, the process by which axons are coated with a protective myelin sheath. Myelination improves the speed and efficiency of neural transmission, allowing for more coordinated and complex cognitive processes (Nickel & Gu, 2018). The maturation of white matter pathways, such as the corpus callosum, is particularly important for integrating information across hemispheres, contributing to higher-order cognitive functions like reasoning and abstract thinking (Paul, 2011).

Neurodevelopment in childhood is not a uniform process; different brain regions mature at different rates. For example, primary sensory and motor areas develop earlier, while association areas responsible for complex thought and emotion mature later (Zonuzirad, 2024). This sequential pattern reflects the brain's prioritization of immediate survival and learning needs in early childhood, followed by the refinement of higher cognitive functions as the child grows older.

The childhood brain is highly plastic, making it particularly sensitive to environmental inputs. Positive experiences, such as a secure attachment with caregivers, access to education, and a stimulating environment, can enhance neural development and foster resilience. Conversely, adverse exposures — such as chronic stress, malnutrition, or exposure to environmental toxins — can disrupt neurodevelopmental trajectories. These effects are mediated by epigenetic mechanisms, including DNA methylation and histone modification, which alter gene expression in response to environmental factors (Ogunjobi et al., 2024). For example, studies have shown that chronic stress during childhood can dysregulate the hypothalamic-pituitary-adrenal (HPA) axis, leading to long-term changes in brain regions such as the amygdala and prefrontal cortex, which are involved in emotion regulation and executive function (Raymond et al., 2018). Neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), often emerge during early childhood, reflecting disruptions in typical brain maturation processes. Research suggests that atypical patterns of synaptogenesis, pruning, or myelination may underlie these disorders, leading to difficulties in attention, social communication, or emotional regulation (Dow-Edwards et al., 2019; Marsh et al., 2008).

1.1.1.3. Neurodevelopment in Adolescence: Changes in Brain Function and Structure

During adolescence, the brain continues to mature through extensive synaptic pruning and myelination processes. Adolescence marks a second critical phase of neurodevelopment, driven by hormonal, social, and cognitive changes. This period is characterized by the extensive pruning of synaptic connections and the continued myelination of axons, both of which enhance the brain's processing efficiency. MRI studies have shown that gray matter volume, reflecting synaptic density, peaks during early adolescence before declining as pruning occurs. Meanwhile, white matter volume, associated with myelinated axons, increases steadily, supporting faster and more efficient neural communication (Nave, 2010). The prefrontal cortex undergoes substantial maturation during adolescence, playing a key role in executive functions such as decision-making, impulse control, and emotional regulation. However, its development lags behind that of the limbic system, which processes emotions and rewards, contributing to the heightened risk-taking behaviors often observed during this stage (Romer et al., 2017). Functional MRI (fMRI) studies have demonstrated that the connectivity between the prefrontal cortex and other brain regions strengthens during adolescence, supporting the integration of higher-order cognitive functions (Sakurai & Gamo, 2019). Adolescence is also a sensitive period for social and emotional learning. Neural networks involved in social cognition, including the medial prefrontal cortex and superior temporal sulcus, become more specialized, enabling adolescents to navigate increasingly complex social environments. However, this heightened plasticity also makes the adolescent brain vulnerable to environmental stressors, such as substance abuse or chronic stress, which can disrupt developmental trajectories and increase the risk of neuropsychiatric disorders.

During the transition to adulthood, brain development slows down, but significant changes still occur, particularly in the areas of cognition and memory. Functional plasticity remains intact, but the brain becomes less malleable compared to childhood and adolescence. In adulthood, neurodevelopment continues at a slower pace, with a focus on maintaining and optimizing brain function rather than rapid growth or reorganization. Functional plasticity remains a hallmark of adult neurodevelopment, allowing the brain to adapt to new learning and experiences, albeit less robustly than during childhood or adolescence. Research has shown that adult cognitive processes become more efficient due to increased network integration and functional specialization. For example, studies using EEG and MRI techniques have demonstrated that adult brains exhibit refined neural pathways that support complex cognitive abilities, such as abstract reasoning and problem-solving (Mustafa & Rashid, 2023; Yen et al., 2023). These changes reflect the brain's ability to streamline activity in established networks while maintaining flexibility for learning. Nevertheless, the adult brain is not immune to decline. Aging is associated with volume reductions in the prefrontal cortex and hippocampus, areas critical for memory and executive function. These changes can contribute to age-related cognitive decline (Persson et al., 2006). However, neuroplasticity persists, enabling adults to form new synaptic connections and adapt to environmental challenges, albeit at a slower rate compared to earlier stages. Cognitive enrichment through activities like learning, physical exercise, and social engagement has been shown to mitigate some of these age-related declines.

In addition to these general trajectories of brain development, it is important to consider a complex interplay of genetic factors, early environmental exposures, and ongoing maturation. Genetic factors influence baseline developmental trajectories, while epigenetic processes such as DNA methylation and histone modification mediate the interaction between genes and the environment. These epigenetic mechanisms enable the brain to adapt dynamically to environmental conditions, ensuring developmental flexibility. Adverse environmental exposures, such as maternal stress, malnutrition, or toxin exposure during pregnancy, can disrupt these processes, leading to maladaptive epigenetic changes. Such alterations may predispose individuals to neuropsychiatric disorders, cognitive impairments, or altered stress responses later in life. Conversely, positive environmental inputs, such as enriched learning environments or secure attachments, can promote resilience and optimize developmental outcomes.

1.1.2. Behavioral Development from Infancy through Childhood, Adolescence, and Young Adulthood

Behavioral development in childhood involves a complex interplay of biological predispositions, early family relationships, cultural norms, and broader social contexts (Cicchetti, 2016; Little, 2017). Even in the first months of life, infants begin to display individual differences in temperament, such as how easily they are calmed or how intensely they react to stimuli (Thomas et al., 2017; Trevarthen, 1993). As these infants grow into toddlers, interactions with parents and caregivers become increasingly important in shaping emotional expression and self-regulation. For example, caregivers who respond consistently and sensitively to a child's signals often reinforce positive social and emotional outcomes (Trevarthen, 1993).

One key area of concern in childhood behavioral development is the emergence of externalizing problems, which include behaviors like aggression, defiance, and hyperactivity (Kimonis et al., 2019). These outwardly directed behaviors not only strain relationships in settings such as home and school but also raise the risk of continued difficulties later in life (Kimonis et al., 2019). Although genetic factors can predispose certain children to externalizing tendencies, stressful environments — characterized by harsh discipline, parental conflict, or economic adversity — can heighten the likelihood of persistent behavior problems (Burt, 2022). Conversely, research shows that stable routines, clear expectations, and supportive adult–child relationships can mitigate or even prevent the progression of early behavioral challenges (Burt, 2022; Kimonis et al., 2019).

Within the realm of externalizing behaviors, Attention-Deficit/Hyperactivity Disorder (ADHD) warrants particular attention. Children with ADHD commonly exhibit sustained inattention, impulsivity, and often hyperactive behavior that may interfere with daily functioning at school or home (Efron, 2019; Saylor & Amann, 2016). While studies of twins and adoption samples demonstrate a substantial genetic component, environmental exposures — ranging from prenatal tobacco use to inconsistent parenting — can further influence the severity and presentation of ADHD symptoms (Tistarelli et al., 2020). Teachers and parents frequently notice the signs once academic or social demands become more challenging, as children struggle to stay focused in class or control impulses during peer interactions (Efron, 2019). Collectively, these findings highlight how early environmental influences, familial factors, and individual dispositions can shape a child's behavioral trajectory (Tistarelli et al., 2020). Yet, behavior does not emerge in isolation; it is closely linked to the maturation of neural systems. In the next section will be explored how ongoing brain development and behavioral patterns continually interact, shedding further light on the dynamic processes that guide children's growth into adolescence and beyond.

1.1.3. Interaction between Neurodevelopment and Behavioral Development from Infancy to Young Adulthood

Children's behavioral patterns emerge in tandem with the development of the brain, creating a dynamic loop in which biology and experience continuously shape one another (Dow-Edwards et al., 2019). From infancy through adolescence, the maturation of neural circuits underpins key abilities, such as attention, emotion regulation, and self-control (Nigg, 2017). At the same time, the child's environment — family relationships, peer interactions, and educational settings — can either support or hinder these underlying neural processes (Osher et al., 2021).

Research shows that responsive caregiving and predictable routines can help children develop secure emotional bonds (Julian et al., 2017). These positive experiences boost the growth of brain regions linked to stress regulation and executive function (Julian et al., 2017; O'Connor, 2017). Conversely, prolonged exposure to chaos or conflict may alter neural pathways in ways that contribute to externalizing behaviors, such as aggression or impulsivity (Puiu et al., 2018). Children who face these circumstances often struggle to adapt, especially when the demands of social or academic life become more complex (McKernan & Lucas-Thompson, 2018).

Neuroimaging studies provide concrete evidence for this interplay. For example, atypical patterns of neural activity have been associated with externalizing behavior and attentional challenges (Sonuga-Barke et al., 2016). Other work suggests that children’s individual differences in neural development can influence how they respond to their environment, highlighting the role of both genetic and epigenetic factors (Gartstein & Skinner, 2018; Tooley et al., 2021). Findings from prior studies further illustrate that variations in brain activity are linked to behavioral measures in areas such as ADHD symptomatology and internalizing or externalizing problem behaviors (Barch et al., 2021).

During childhood and adolescence, the brain exhibits a notable capacity for change, allowing well-designed interventions to reinforce adaptive pathways and alleviate potential risks (Mastorci et al., 2024; Osher et al., 2021). At the same time, external forces — including family context, socioeconomic factors, and broader societal pressures — can interact with neurodevelopment in ways that either foster resilience or heighten susceptibility to difficulties in cognition, emotion, or behavior (Osher et al., 2021). Recognizing these intricate connections underscores the importance of examining the earliest possible influences on a child’s developmental trajectory.

In the following chapters, the discussion shifts toward environmental exposures during the prenatal period. It will be explored how various prenatal risk factors, including tobacco exposure, may set the stage for both neurodevelopmental processes and subsequent behavioral patterns.

1.2. ENVIRONMENTAL EXPOSURES DURING THE PRENATAL PERIOD

The prenatal environment significantly influences lifelong health and development, where early exposures can potentially show enduring consequences on behavior, cognition, and mental health. These influences can include maternal health behaviors, such as tobacco smoking, alcohol consumption, and drug use, as well as socioeconomic factors, maternal stress, and exposure to environmental toxins. In the following chapter, the specific effects of maternal tobacco exposure will be explored on neurodevelopment and behavior, particularly how these early exposures relate to children's/adolescents' development.

1.2.1. Overview of Prenatal Exposures and Their Impact on Child Development

Numerous epidemiological studies have investigated the connections between unfavorable prenatal circumstances and heightened susceptibility to illnesses, health issues, and psychological consequences in later life. Smoking during pregnancy is one of the leading causes for adverse pregnancy outcomes (Crume, 2019). Maternal cigarette smoking is a common and potentially hazardous environmental exposure during pregnancy, with over 4,000 chemicals in cigarette smoke, including benzo(a)pyrene, nicotine, and carbon monoxide, and over 40 of these chemicals being known carcinogens (Thielen et al., 2008; Wang, 2024). Nicotine crosses the placenta, and fetal concentrations of nicotine can be 15% higher than maternal concentrations (Lambers & Clark, 1996). Therefore, prenatal cigarette smoking is associated with increased risk for spontaneous abortion, preterm delivery, respiratory disease, immune system difficulties, and cancer later in life. Placental complications, including alterations to the development and function of the placenta, are also linked to prenatal exposure to cigarette smoke. Additionally, carbon monoxide reduces oxygen availability to the fetus, potentially leading to hypoxia, which is further associated with lower birth weights, cognitive delays, and increased susceptibility to behavioral disorders (Kleinman, 2020).

Globally, there are wide regional variations in the prevalence of mother smoking during pregnancy; industrialized countries and some low- and middle-income countries tend to have greater rates. Around one in ten pregnant women worldwide smoke, according to estimates from the World Health Organization (WHO), with significant regional and national variations. Prenatal smoking rates have typically decreased over the previous few decades in high-income nations including the US, Canada, and portions of Europe. This may be because tobacco control laws have been put into place, smoking cessation programs have been successful, and people are more aware of the health consequences. However, there are still notable regional variations throughout Europe. For example, due to cultural norms, a lack of tools for quitting smoking, and a high frequency of smoking in general, Eastern European nations like Serbia and Bulgaria report maternal smoking rates during pregnancy reaching 25%. On the other hand, because of their strong public health campaigns and more stringent tobacco laws, Northern and Western European nations like Iceland, Sweden, and Norway often have substantially lower rates, frequently below 10%. Figure 1 illustrates data from a cross-sectional study involving pregnant women and new mothers across 15 European countries (Smedberg et al., 2014). It highlights regional differences in the extent of smoking during pregnancy, categorizing smokers by daily cigarette consumption. Notably, a higher proportion of heavy smokers (≥11 cigarettes per day) was observed in Eastern Europe (47.7%), compared to Northern (21.6%) and Western Europe (30.7%). A recent large-scale study involving 21,472 pregnancies (Voutilainen et al., 2024) further underscores the impact of smoking on pregnancy outcomes. It found that while 74% of women ceased smoking during pregnancy, approximately 20% of pregnancies were still exposed to maternal tobacco smoking.

The descriptive review (Banderali et al., 2015) highlights how prenatal tobacco exposure impacts both short-term and long-term health outcomes. On physiological level, prenatal tobacco exposure has been linked to an increased risk of bronchitis, asthma, wheezing, airway hyperresponsiveness, and lung impairment (Cheraghi & Salvi, 2009). According to a recent systematic review and meta-analysis (Burke et al., 2012), tobacco smoking during pregnancy is linked to a higher risk of wheeze and asthma in children and adolescents up to the age of 18, with the largest influence on asthma incidence in children under the age of two. There is increasing concern that perinatal exposure to harmful chemicals, such as those from maternal tobacco smoking, may contribute to the rising prevalence of obesity and metabolic disorders (Ino, 2010; Leary et al., 2006). A meta-analysis of 17 studies found that children of mothers who smoked during pregnancy faced a higher risk of obesity by around age 9 compared to children of non-smoking mothers (Ino, 2010). According to Leary et al., (2006) smoking by the mother at any point during pregnancy has been linked to increased total fat mass (assessed by Dual-energy X-ray absorptiometry) in the kids at a mean age of 9.9 years.

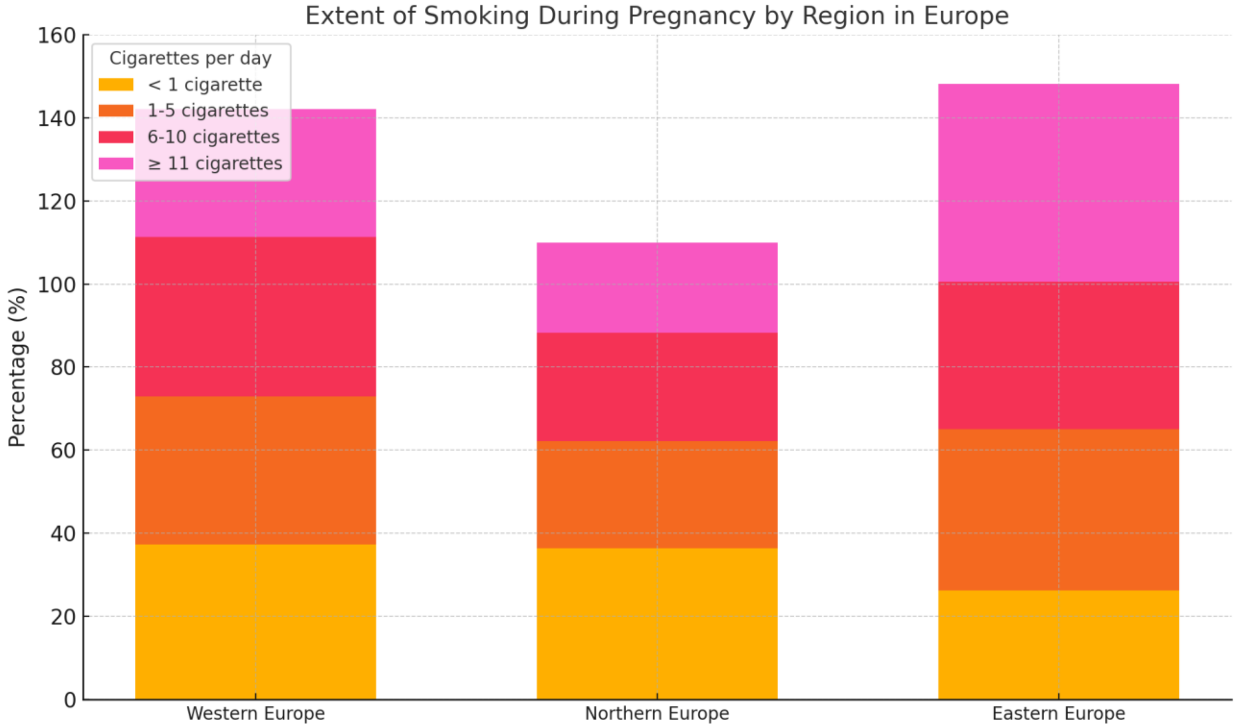

Figure 1 Extent of smoking during pregnancy by region in Europe.
Note: Total *N*=770; Western Europe includes Austria, France, Italy, Switzerland, the Netherlands, United Kingdom; Northern Europe includes Finland, Iceland, Norway, Sweden; Eastern Europe includes Croatia, Poland, Russia, Serbia, Slovenia; created using data from (Smedberg et al., 2014)

Despite the advice to abstain throughout pregnancy, alcohol exposure occurs during many pregnancies. Among women of reproductive age, alcohol has been and continues to be the most often used drug. Globally, the prevalence of alcohol use during pregnancy is estimated to be approximately 9.8% (95% CI = 8.9–11.1) (Popova et al., 2017). Specifically, according to a systematic review and meta-analysis by Popova et al. (2017), the five countries with the highest estimated prevalence of alcohol use during pregnancy were: Ireland (60.4%, 95% CI: 42.8–76.8), Belarus (46.6%, 42.4–50.7), Denmark (45.8%, 30.9–61.2), United Kingdom (41.3%, 32.9–49.7), Russia (36.5%, 18.7–56.4). Compared to other regions of the world, these nations have noticeably greater rates of alcohol consumption during pregnancy. On the other hand, the WHO Eastern Mediterranean Region (EMR), which includes Oman, Saudi Arabia, the United Arab Emirates, Qatar, and Kuwait, had the lowest prevalence (around 0%). Prior large cohort study (Lees et al., 2020) explored the effects of prenatal alcohol exposure on various outcomes in children. This study involved over 9,700 children aged 9-10, with approximately 25.9% reporting prenatal alcohol exposure. Key findings indicated that even low levels of prenatal alcohol exposure were associated with higher risks for psychological and behavioral problems in children, including attention deficits, impulsivity, and greater likelihood of psychopathology. Additionally, the study highlighted differences in brain structure, with children exposed to alcohol showing increased cerebral and regional brain volumes as well as larger surface areas in certain brain regions compared to unexposed children. The effects of prenatal alcohol consumption on newborn mental development, as measured by the Mental Development Index (MDI), were investigated through a meta-analytic analysis (Testa et al., 2003) in the field of neurobehavioral repercussions. Ten studies examined the effects of three levels of average daily exposure during pregnancy: less than one drink per day, one to one and a half drinks per day, and two or more drinks per day. Only four studies indicated low consumption, compared to five that reported moderate usage. The meta-analysis's authors discovered that among children aged 12 to 13 months, all three intake levels were linked to noticeably reduced MDI scores. Significant adverse effects were evident even at the lowest level of exposure, and increasing exposure was linked to bigger impairments.

Illicit substance exposure during pregnancy, including cocaine and opiates, can also have a significant impact on development. Exposure to cocaine interferes with the prenatal oxygen flow, resulting in neurobehavioral abnormalities. According to Patrick et al. (2012), neonatal abstinence syndrome (NAS), which is prevalent in infants exposed to opioids, frequently leads to extended hospital admissions and developmental problems. Fetal brain development can be disrupted by maternal malnutrition, which includes shortages in folate, iron, and critical fatty acids. Folate deficiency is strongly linked to neural tube defects, while insufficient omega-3 fatty acids are associated with impaired neurogenesis and cognitive function in offspring (Smithers et al., 2008). On the other hand, obesity and metabolic diseases in the progeny have been linked to excessive prenatal weight increase. Maternal stress and anxiety during pregnancy can affect the developing fetus via alterations in the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels in utero. This dysregulation has been linked to increased risk for anxiety, depression, and behavioral disorders in childhood (O’Donnell et al., 2017). Stress-related epigenetic modifications, such as changes in DNA methylation of glucocorticoid receptor genes, may mediate these long-term effects. By altering the hypothalamic-pituitary-adrenal (HPA) axis, maternal stress and anxiety during pregnancy can have an impact on the growing fetus and raise cortisol levels in utero. A higher risk of anxiety, depression, and behavioral disorders in children has been associated with this dysregulation (O'Donnell et al., 2017). These long-term effects could be mediated by stress-related epigenetic changes, such as variations in the DNA methylation of glucocorticoid receptor genes.

1.2.2. Prenatal Tobacco Exposure as a Distinct Risk Factor for Childhood and Adolescent Development

Previous chapter has demonstrated that prenatal tobacco has a negative impact on the health of the offspring, like preterm birth, fetal growth restriction, low birth weight. Additionally, prenatal tobacco exposure can modulate fetal brain development and function. Here maternal tobacco smoking has long been associated with adverse neurodevelopmental outcomes in children, including cognitive impairments, behavioral disorders, and delayed developmental milestones. The following chapter will demonstrate key findings from research studies on the neurodevelopmental effects of prenatal tobacco exposure.

Nicotinic acetylcholine receptors (nAChRs), are also ligand-activated neurotransmitter receptors, and play essential role in both the central and peripheral nervous systems. From the research on animal studies, it has been shown that thenAChR is functioning early in fetal development, at the time the neural tube is being formed (Atluri et al., 2001). The most significant physiological feature of nicotine from the perspective of nervous system development is its capacity to activate the nAChR and set off neurodevelopmental processes that are typically attributed to acetylcholine's effect. Acetylcholine has been shown to play a very active part in brain development in animal models, where it is in charge of the proliferation, maturation, and differentiation of several brain cell types (Role & Berg, 1996). Nicotine exposure influences the intensity and timing of brain cell development and the programming of neurodevelopmental events on a cellular level. Therefore, the ordered mechanisms by which neurons multiply and differentiate into functional neuronal cells are changed when the timing of these events is perturbed. Nicotinic AChRs are present in the human brain and spinal cord from the first trimester in and play important role throughout early brain development (Hellström-Lindahl et al., 1998). Chronic in utero nicotine exposure has been shown to disrupt neuronal architecture, alter nAChR expression, and affect the functionality of various neurotransmitter systems. Nicotine's activation of nAChRs can prematurely trigger developmental processes, such as cholinergic signaling, which drives neurons to shift from replication to differentiation. This prenatal exposure has been associated with apoptotic cell death and reduced cell size in several brain regions. Additionally, nicotine's influence on nAChRs disrupts the proper development of critical neurotransmitter systems, including dopamine (DA), norepinephrine (NE), and serotonin (5-HT). These disruptions can lead to long-term changes in neurobehavioral outcomes, such as locomotor hyperactivity, depressive behaviors, and altered sensitivity to nicotine and other stimulants. Consequently, prenatal nicotine exposure significantly impacts neuroanatomy, nAChR function, and neurotransmitter systems, resulting in lasting effects on neurobehavioral trajectories. It has been demonstrated that nicotine exposure during pregnancy alters the differentiation and replication of brain cells, affecting to changes in brain structure.

Most previous studies examining the impact of maternal smoking during pregnancy (MSDP) on brain structure and function have been conducted using animal models. Findings from these studies show a strong link between prenatal nicotine exposure and an increase in nicotinic acetylcholine receptors (nAChRs) across various brain regions as early as the first trimester. This upregulation of nAChRs inhibits DNA synthesis, disrupting brain cell replication and differentiation (Slotkin, 1998). Prenatal nicotine exposure has also been linked to imbalances in cholinergic, catecholaminergic, serotonergic, and other neurotransmitter systems. Building on these findings, the following section will explore how advanced imaging techniques, such as magnetic resonance imaging (MRI), have been used to study the brain development of children exposed to maternal smoking (Zou et al., 2022). Prior review study (Bublitz & Stroud, 2012) highlighted significant effects of maternal smoking during pregnancy on offspring brain structure and function. Structural imaging has linked tobacco exposure to reduced brain volumes in areas like the frontal lobe, lateral ventricular system, cerebellum, cortical gray matter, and corpus callosum. Adolescents exposed to MSDP also showed cortical thinning in frontal, temporal, and parietal regions, along with altered white matter microstructure, which have been tied to cognitive impairments, auditory issues, social difficulties, and ADHD. Functional studies associate prenatal tobacco exposure with increased auditory brainstem response (ABR) rates in infants, which may disrupt auditory processing and speech/language development. Adolescent fMRI studies revealed inefficient activation of brain regions like the temporal lobe, hippocampus, and cerebellum during tasks involving attention, memory, and response inhibition. Additionally, maternal smoking appeared to amplify the effects of adolescent smoking on temporal lobe activation. However, structural findings did not show additive effects of prenatal and current smoking exposure on white matter microstructure. Despite these findings, limitations in the existing research point to areas for improvement. The literature is small, with overlapping samples across studies, and most rely on retrospective maternal reports without biochemical verification of smoking exposure. Few studies assessed dose-response relationships or fully accounted for socioeconomic status, a significant confounding factor (Holz et al., 2014; Lees et al., 2020). There are also gaps in the timeline of research. Studies focus on fetal/infant stages or adolescence, leaving a critical lack of data on the impact of maternal smoking during early and middle childhood — a period when cognitive, attention, and behavioral deficits often emerge. Moreover, existing research focuses mainly on cognitive, auditory, and attention tasks, overlooking other outcomes like externalizing behaviors and emotional regulation, which are tied to altered brain regions like the amygdala and orbitofrontal cortex.

In contrast to the relatively robust body of literature utilizing MRI and fMRI to examine the effects of maternal smoking during pregnancy (MSDP), there has been far less research employing electroencephalography (EEG) to study neurodevelopmental outcomes in tobacco-exposed children. EEG is one of the most widely used and cost-effective neuroimaging techniques for noninvasive brain research, offering high temporal resolution and the ability to capture real-time neural activity. Its advantages make it especially valuable for studying functional brain dynamics in younger populations, including infants and children, where tolerance for longer imaging protocols like MRI may be limited. Despite its potential, studies using EEG to investigate the effects of prenatal tobacco exposure remain sparse. Existing findings suggest that MSDP is associated with altered neural oscillatory patterns, including atypical activity in key frequency bands that underpin cognitive and behavioral functioning. For example, prenatal tobacco exposure was associated with decreased EEG power in higher-frequency bands (beta and gamma), particularly in cases of continuous exposure throughout pregnancy (Pini et al., 2024). The Safe Passage Study (Shuffrey et al., 2020) explored how prenatal tobacco exposure (PTE) affects newborn brain activity using EEG during active sleep. The results showed that PTE impacted higher-frequency brain waves, specifically beta and gamma frequencies, in the right-central and right-parietal regions. Infants whose mothers smoked at low levels or quit during pregnancy had increased beta and gamma power compared to unexposed infants. However, infants exposed to moderate or high levels of continuous smoking had reduced beta and gamma power compared to both unexposed infants and those whose mothers smoked less or quit. Quitting smoking during pregnancy did not completely normalize EEG activity, but it was linked to better outcomes compared to continued moderate or heavy smoking. These findings suggest a dose-dependent effect of PTE on newborn brain development and highlight the benefits of smoking cessation during pregnancy in reducing harm to the baby’s brain activity.

Prenatal tobacco exposure and behavioral development

Maternal smoking not only impacts physiological processes but also profoundly influences behavioral and psychological outcomes in offspring. The interplay between prenatal exposure to harmful substances like nicotine and postnatal environmental factors can shape a child’s developmental trajectory, influencing cognitive, emotional, and behavioral domains. Numerous studies highlight how maternal smoking during pregnancy contributes to harmful consequences, including heightened susceptibility to attention deficits, impulsivity, and emotional regulation difficulties (Cornelius et al., 2012; Holz et al., 2014; Huijbregts et al., 2007).

A number of studies have suggested that maternal tobacco smoking exposure during pregnancy contributes to the attention-deficit/hyperactivity disorder (ADHD) of the fetus (Han et al., 2015; Lin et al., 2021; Minatoya et al., 2019; Tiesler & Heinrich, 2014). As described in previous chapters smoking is known to affect physiological processes that may increase hazards related to the genesis of ADHD, a childhood-onset neurodevelopmental condition, it is physiologically probable. The key characteristics of (ADHD) are inattention and/or hyperactivity symptoms that interfere with developmentally appropriate functioning and last for at least six months in a variety of contexts (Wolraich et al., 2019). Although the exact origins of ADHD are still unknown, environmental and genetic factors have been demonstrated (Cortese, 2012; Franke et al., 2012; Swanson et al., 2007; Thapar et al., 2013). It should be mentioned that the results are not consistent, since correlations between case-control and epidemiologic samples that account for potentially confounding factors have been shown, supporting a dose-dependent relationship in which risk rises as cigarette consumption increases. Dong et al. (2018) conducted an extensive meta-analysis that included data from 27 eligible original articles with a total of 3076173 subjects and found that prenatal exposure to maternal smoking during pregnancy or smoking cessation during first trimester was significantly associated with childhood ADHD. Higher maternal smoking levels were linked to a higher incidence of ADHD, according to the analysis's dose-dependent pattern (Dong et al., 2018).

On behavioral level, significant long-term effects of prenatal cigarette smoke exposure on the behavior problems and smoking behavior were shown by 22-year-old offspring (Cornelius et al., 2012). The results demonstrated that prenatally tobacco exposed young adults had significantly higher scores on the externalizing, internalizing, aggression, and somatic scales (measured with ASR questionnaire) and were more likely to have a history of arrests (Cornelius et al., 2012). Maternal smoking during pregnancy has been also linked to the development of severe antisocial behaviors in offspring, including aggression and conduct disorders (Wakschlag et al., 2002). The comprehensive review explored the potential links between prenatal tobacco exposure and these behavioral outcomes. The authors highlight how prenatal smoking may disrupt fetal brain development by altering neurotransmitter systems and neural pathways critical for emotional regulation and impulse control and therefore increase the risk for severe behavioral problems in children. Furthermore, the study underscores the potential for interaction between biological vulnerabilities and environmental factors. For example, children exposed to tobacco in utero may be more sensitive to adverse postnatal environments, such as high-stress households or inconsistent parenting. As the result of those adverse environments, children might develop antisocial tendencies. It should be noted that these behaviors are not solely attributable to prenatal exposure; genetic predispositions and socioeconomic factors likely play a role (Wakschlag et al., 2002).

However, recent evidence challenges the assumption of a direct causal relationship between prenatal smoking and ADHD (Thapar et al., 2009). In order to distinguish between genetic and environmental factors, Thapar et al. (2009) conducted a novel design that compared mother-child pairs that were genetically related and unrelated. The results suggest that hereditary factors, rather than the direct biological consequences of smoking, are primarily responsible for the observed link between prenatal smoking and ADHD symptoms. Specifically, maternal smoking was more significantly associated with ADHD symptoms among genetically related pairings. This suggests that the association may be explained by shared genetic predispositions between mother and child. This perspective emphasizes how complicated the etiology of ADHD is and how future studies and public health initiatives must take genetic-environment interactions into account.

Similarly, another prior study (Thapar et al., 2003) explored the link between maternal smoking during pregnancy and ADHD symptoms in children, considering both genetic and environmental influences. The researchers examined whether the observed association between prenatal smoking and ADHD symptoms is a direct causal relationship or the result of shared familial and genetic factors. Maternal smoking during pregnancy was consistently associated with higher levels of ADHD symptoms in children. However, the study highlighted the complexity of disentangling direct causal effects from confounding variables, such as shared genetic predispositions and environmental influences. A comparison of children exposed to prenatal smoking and unexposed siblings in the same family showed that the association between maternal smoking and ADHD symptoms weakened when familial factors were controlled. This suggests that genetic or familial environmental factors might play a significant role in the observed relationship.

1.3. HYPOTHESES

The primary aim of this dissertation is to examine the long-term effects of prenatal tobacco exposure on neurophysiological and behavioral outcomes in childhood and young adulthood. Specifically, this research investigates how prenatal tobacco exposure influences brain activity (as measured by EEG) and ADHD-related behaviors.

1.3.1. Prenatal Tobacco Exposure Leads to Alterations in Brain Development in Children

It has been demonstrated that prenatal tobacco exposure has influence on neurodevelopment, with evidence suggesting alterations in brain activity, especially in regions involved in cognitive functions such as attention, memory, and emotional regulation. The neurophysiological effects of prenatal smoking have been frequently associated with changes in EEG frequency bands, particularly in the slower frequencies such as delta and theta waves. While theta waves are linked to working memory, emotional control, and cognitive flexibility, delta waves are linked to deep sleep, memory consolidation, and concentration. Based on previous literature, we assume that individuals who were exposed to tobacco prenatally will demonstrate different brain activity patterns, particularly in the delta and theta frequency bands, in comparison to individuals with no prenatal tobacco exposure.

1.3.2. Prenatal Tobacco Exposure Associated with Behavioral Problems in Childhood and Adolescence

Numerous studies (Minatoya et al., 2019; Tiesler & Heinrich, 2014; Y et al., 2020) have demonstrated a strong association between prenatal tobacco exposure and the development of behavioral problems in childhood and adolescence, including externalizing behaviors such as attention problems, impulsivity, hyperactivity, and delinquency. Given the previous findings, we hypothesize that prenatal exposure to tobacco will predict higher levels of ADHD-related symptoms in children. In particular, individuals who were prenatally exposed to tobacco are expected to report higher levels of attention problems and hyperactivity, compared to individuals with no prenatal tobacco exposure. These findings would further support the notion that prenatal tobacco exposure has enduring effects on behavioral regulation and could increase the risk for developing antisocial or disruptive behaviors in adulthood.

1.3.3. Moderating Effects of Familial Factors on Prenatal Tobacco Exposure and Behavioral Outcomes

Research has consistently shown that behavioral outcomes in children and young adults are influenced not only by prenatal exposures but also by genetic predispositions and environmental factors such as maternal mental health and the child’s own behavior (Thapar et al., 2003). The presence of maternal psychopathology (e.g., depression, anxiety, or substance use) during pregnancy has been shown to moderate the effects of prenatal exposures on child development, and substance use during adolescence and adulthood can amplify these vulnerabilities. Therefore, we hypothesize that the behavioral outcomes of prenatal tobacco exposure will be moderated by familial factors, particularly maternal psychopathology and the child’s substance use.

The relationship between prenatal tobacco exposure and externalizing behaviors is expected to be stronger in individuals with a history of maternal psychopathology and in those with higher levels of substance use during young adulthood. This moderation effect would suggest that the combination of prenatal tobacco exposure and these familial and behavioral factors results in compounded risks for behavioral difficulties in young adulthood.

1.3.4. Dose-Dependent Relationship between Prenatal Tobacco Exposure and Neurophysiological and Behavioral Outcomes

Given that the amount of tobacco smoked during pregnancy can vary considerably, we hypothesize that there will be a dose-dependent effect, such that greater levels of maternal smoking during pregnancy will lead to more pronounced alterations in brain activity and more severe behavioral outcomes. Previous research has indicated that higher levels of prenatal tobacco exposure are associated with greater neurodevelopmental risks, including cognitive and behavioral deficits. Therefore, we predict that individuals exposed to higher amounts of tobacco (e.g., more than five cigarettes per day) during pregnancy will exhibit more substantial disruptions in EEG patterns (particularly in delta and theta bands) and will report higher levels of externalizing behaviors.

1.3.5. Mediation of Brain Activity in the Relationship between Prenatal Tobacco Exposure and ADHD-Related Behaviors

Given that prenatal tobacco exposure has been linked to alterations in brain activity, it is hypothesized that brain activity might mediate the relationship between prenatal tobacco exposure and ADHD-related behaviors. Previous research has demonstrated that brain activity in specific frequency bands (delta and theta) is associated with ADHD symptoms such as hyperactivity and impulsivity (Aldemir et al., 2018; Saad et al., 2018). This mediation effect would suggest that changes in brain activity due to prenatal smoking could be a mechanism through which prenatal exposure influences ADHD-related behaviors in childhood. This hypothesis connects brain activity with behavioral outcomes while considering the mediation effect, adding insights to the investigation of how prenatal tobacco exposure impacts both neurophysiological and behavioral development.

2 EMPIRICAL STUDIES

2.1 STUDY 1: Association of Maternal Smoking during Pregnancy with Neurophysiological and ADHD-Related Outcomes in School-Aged Children

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2.1.1 Abstract

Objective: Data of a longitudinal cohort study were analyzed to explore the association between prenatal tobacco exposure with the electroencephalographical (EEG) power spectrum in healthy, school-aged children and whether this relates to attention deficit hyperactivity disorder (ADHD)-related symptoms of impulsivity, attention deficit and hyperactivity in the offspring.

Methods: Maternal smoking was assessed with a self-report questionnaire, and in children (aged 6.7 to 9.9 years), resting state EEG activity was measured during eyes open and eyes closed conditions, and ADHD symptoms with the behavioral difficulties questionnaire. Group comparisons (exposed vs. non-exposed) and generalized additive mixed model analyses were performed using the amount of exposure were applied to test whether prenatal tobacco exposure was associated with brain activity and ADHD symptoms (impulsivity, attention deficit and hyperactivity). Factors of child's sex, child's age, maternal age, and maternal smoking habit before pregnancy, alcohol consumption during pregnancy, gestation age and maternal psychopathology were considered as covariates.

Results: We found significant effects of maternal smoking during pregnancy on EEG delta and theta frequency bands in central and posterior regions and on hyperactivity in children, where tobacco exposure compared to non-exposed children showed higher brain activities in both frequency bands as well as higher hyperactivity scores. While the effects on brain activity were independent of the considered covariates, but related to the amount tobacco exposure, effects on hyperactivity significantly depended on maternal age and alcohol consumption during pregnancy, but not on the amount of exposure.

Conclusion: While smoking during pregnancy affects resting-state brain activity in children, when it comes to ADHD-related behavior, socio-demographic confounding factors like alcohol consumption and age of the mother come into play.

Keywords: EEG, maternal smoking, pregnancy, ADHD, hyperactivity, resting-state brain activity

2.1.2 Introduction

Pregnancy is a period that is vital for the physiological and psychological development of a child. Health-related risk behaviors of the mother during this period can therefore have highly relevant consequences for the child (Banderali et al., 2015; Rogers, 2019). A growing body of literature over the past decades provides evidence that specifically maternal smoking during pregnancy results in an increased risk for adverse neurodevelopmental and health outcomes during childhood and adolescence (e.g., Modabbernia et al., 2021; Orleans et al., 2000).

Tobacco smoke contains thousands of known toxic components including nicotine and carbon monoxide, which, in pregnancy, do not only affect the mother, but can also induce early-life changes at the level of enzymes, hormones. As well as on expression of genes, micro RNAs, and proteins in the child (Braun et al., 2020). Prenatal smoking leads to deleterious effects on cognitive (Clifford et al., 2012) and neurobehavioral developmental processes (Laucht & Schmidt, 2004) during childhood, including externalizing behaviors of oppositional defiant problems, hyperactivity, inattention (Melchior et al., 2015), and impairments in intellectual functioning associated with auditory processing, reading, and language development (Weitzman et al., 2002). In this respect, several review articles (Dong et al., 2018; Neuman et al., 2007) have also described an association between maternal smoking and diagnoses of mental disorders, pointing to higher rates of conduct disorder and ADHD in prenatally tobacco exposed compared to non-exposed children (D'Onofrio et al., 2008; Sciberras et al., 2017; Tarver et al., 2014). Nevertheless, some studies suggest that exposure to maternal cigarette smoking in pregnancy might only be indirectly linked to ADHD symptoms, and rather reflect an interaction with factors related to socioenvironmental load like family-related ones of parental psychopathology, including an additional involvement of genetic factors in case of parental ADHD (Thapar et al., 2009). Another study of Langley et al. (2012) compared risks of maternal smoking during pregnancy with those of paternal smoking during pregnancy on offspring ADHD and demonstrated that ADHD symptoms were significantly associated with exposure to both maternal and paternal smoking during pregnancy, also when paternal smoking was examined in the absence of maternal smoking, associations remained significant. While a significant risk of prenatal tobacco exposure on lower birth weight remain also when controlling for genetic or household-level factors, for ADHD those control factors co-determine the exposure-related effects.

It is also important to note that prior studies found prenatal smoking exposure to affect brain growth. For instance, prenatal tobacco exposure was associated with a volume decrease in cortical areas such as regional thinning of the superior frontal, superior parietal, lateral occipital, and precentral cortices (Derauf et al., 2012; El Marroun et al., 2014), and in white matter (Paus et al., 2008), as well as in subcortical regions such as the amygdala, cerebellum, and the corpus callosum of the newborn brain (M. Ekblad et al., 2015). Those structural changes were also observed to be accompanied by functional and behavioral alterations, for instance changes in the cerebellum were found to relate to emotional, impulse control, and attentional processes (M. Ekblad et al., 2010).

Importantly, those early changes in the brain and alterations in behavior and psychopathology might persist into adolescence and adulthood. For example, Holz et al. (2014) showed that maternal smoking is associated with changes in brain regions related to behavioral response inhibition, together with ADHD symptomatology. The results of the study indicated an inverse relationship between inferior frontal gyrus activity and ADHD symptoms in prenatally tobacco exposed children. Besides fMRI, some studies on maternal smoking during pregnancy also used electroencephalography (EEG) as a measure of brain functions. Due to its non-invasive nature and high millisecond temporal resolution EEG represents a specifically valid measure not only with respect to brain development (Baillet et al., 2001; Brown & Jernigan, 2012), but also as an indicator of behavioral control (Bridwell et al., 2018). The few available data on EEG and maternal smoking during pregnancy stem from investigations in the neonatal period. In a prospective cohort study, Shuffrey et al. (2020) found significantly increased right-central beta (19-24 Hz), low gamma (28-36 Hz) and increased right-parietal low gamma (28-36 Hz) and high gamma (37-45 Hz) EEG power in prenatally tobacco exposed neonates compared to non-exposed infants. Such negative effects of fetal exposure to parental tobacco smoking might further cumulate negatively with smoking during lactation and with second-hand smoking exposure (Banderali et al., 2015). Investigations of the influence of prenatal smoking on electrical brain activity, assessed with EEG, in the offspring are therefore limited so far, and did not investigate effects into childhood.

Nevertheless, previous studies indicate associations between behavioral symptoms of ADHD with EEG power spectra (Barry et al., 2009; Karakaş, 2022; Machado et al., 2015). School aged children diagnosed with ADHD show increases in theta activity and the theta/beta ratio, increased frontal delta, reduced global alpha and frontal beta activity during an eyes-closed resting condition (Clarke et al., 2011) compared to healthy controls. Frontal theta activity correlated with inattention, the theta/beta ratio correlated with hyperactivity-impulsivity. Similarly, the results of the study of Rodríguez-Martínez et al. (2020) observe an increase in delta power and decreased beta power in children and adolescents with ADHD compared to control subjects.

In the present study, we aimed to a) examine the influence of prenatal smoking on EEG brain activity in school-aged children taking into consideration the amount of smoked cigarettes during pregnancy and b) analyze its relations to ADHD-associated behaviors. For ADHD, particularly higher rates in hyperactive and impulsive behavior might be related to prenatal smoking as indicated by earlier work (Tarver et al., 2014). Moreover, ADHD is also characterized by functional changes in brain regions that were found to be affected by prenatal tobacco exposure in the newborn brain, including reduced delta power in fronto-central and parietal regions (Shuffrey et al., 2020). So, we hypothesize main changes in these brain regions in our adolescent sample as well. Because of previous findings (Langley et al., 2008, 2012; Thapar et al., 2009), maternal psychopathology and alcohol consumption during pregnancy as well as child's sex, child's age, maternal age, and maternal smoking habit before pregnancy, and gestation age were included in the analysis as additional cofounds in order to investigate the true risk effect of prenatal tobacco exposure.

2.1.3 Methods

We used data from the longitudinal Franconian Maternal Health Evaluation Studies (FRAMES, Erlangen, Bavaria, Germany; see Reulbach et al., 2009) and the follow-up Franconian Cognition and Emotion Studies (FRANCES, Erlangen, Bavaria, Germany; see Eichler et al., 2017). The FRAMES data were obtained in the years 2005 till 2007 and the total sample on the baseline assessments consisted of 1,100 pregnant women older than 18 years. Perinatal maternal health data were collected at the Department of Obstetrics and Gynecology (Hein et al., 2014; Reulbach et al., 2009). From the baseline sample, 618 women were contacted again via telephone for participation in the follow up FRANCES assessments, from whom 253 families agreed to participate

(41%). These assessments took place at the Department of Child and Adolescent Mental Health in Erlangen, Germany, where parents filled out the questionnaires and children were tested for cognitive abilities and EEG measurements were performed. Inclusion and exclusion criteria were pre-determined by the project and were checked prior to study enrolment. For participation in the study women had to be aged ≥ 18 years with at least 30 full weeks of gestational age. The studies are consistent with the Declaration of Helsinki and were approved by the Local Ethics Committee of the University Hospital Erlangen (no. 4596). Before participation, all subjects received detailed information about the study and gave their written informed consent.

2.1.3.1 Data acquisition

2.1.3.2 Assessment of maternal smoking

Maternal smoking was assessed with a retrospective self-report screening questionnaire that involved questions about the frequency and the amount of cigarettes woman weekly smoked during each of the three trimesters. Moreover, women were asked about their smoking behavior before pregnancy as well as during lactation. In addition, information about passive smoking were collected, with items on the quantity of weekly smoked cigarettes of the father at home (during pregnancy).

2.1.3.3 Assessment and pre-processing of resting-state EEG activity

Participants completed 2.5 min of eyes-open and 2.5 min of eyes-closed resting-state EEG. During the eyes open resting-state, participants fixated on a point in front of them and were encouraged to minimize ocular and other movements. EEG activity was recorded from 25 sites (10–20 system plus additional midline electrodes and mastoid electrodes; recording reference: Fcz, ground electrode: CP2), with standard electrode caps with sintered Ag/AgCl electrodes (Easycap, Herrsching, Germany). The raw EEG data were inspected, pre-processed, and analyzed offline using BrainVision Analyzer (Version 2.2.0). Filter bandwidth was set to 0.016–120 Hz; the sampling frequency was 500 Hz. The resistance of the electrodes was kept below 20 kΩ.

For pre-processing, the following steps were applied: downsampling to 250 Hz, filtering; removal of artifacts (i.e. eye blinking, heart beating, muscles etc. or due to loose/broken electrode) using rejection techniques, like filtering, in order to enable more sensitive and reliable analyses: low pass filtering was set up to 0.1 Hz (the basic cortical rhythms that underlie higher brain functions); high pass filtering to 70 Hz. In order to attenuate artifacts caused be external devices, like electrical power supply of devices in the recording room, we used a notch filter of around 50 Hz. After artifact rejection, frequency analysis was performed in order to explore the EEG data gathered during the two resting state conditions “eyes open” and “eyes closed”. Ocular (blinks and saccades) and any other remaining artifacts like muscular or cardiac effects were isolated and rejected by independent component analysis (ICA) on continuous data. Components for rejection were selected manually. Using a Hanning window with 10% taper length, fast Fourier transformations were conducted with non-overlapping 2.048 s epochs of corrected data. By using a built-in algorithm in Brain Vision Analyzer, Fast Fourier Transform (FFT) has been applied to transform the time-domain EEG epochs into equivalent frequency-domain epochs. Afterwards, the obtained FFT values of delta, theta, alpha, and beta were extracted using the FFT band export option. After artifact detection and rejection, the averaged data consisted of 74% of good segments by eyes open resting-state condition and 68% of good segments by eyes closed condition (Kaiser et al., 2021).

Finally, we averaged the participants’ data individually across the epochs for each electrode site and for the frequency bands (delta, theta, alpha, beta) and the mean absolute power was computed, and exported in the form of text files. Participants were only included if their EEG data contained at least 50% of artifact-free segments. The recorded activity was divided into 3 regions using an average value for each region. The posterior region represented averaged activity in electrodes T5, P3, O1, P2, T6, P4, O2; the frontal region averaged activity from Fp1, Fp2, F3, F7, FCz, Fz, F4, F8, and the average of T3, C3, Cz, T4 and C4 electrodes was used as indicator of the central area. For both resting-state conditions, “eyes open” and “eyes closed”, the absolute power was obtained for four frequency bands: theta (0.5-3.5 Hz), delta (3.5-7.5 Hz), alpha (7.5-12.5 Hz) and beta (12.5-30 Hz).

2.1.3.4 Assessment of ADHD-related behavioral difficulties

For behavioral difficulties, we regressed to the German screening instrument Parent-assessment ADHD (DISPYPS-II, Fremdbeurteilungsbogen ADHS, FBB-ADHD, Breuer & Döpfner, 2008), a 20 items questionnaire that captures the following three dimensions: inattention, impulsivity, and hyperactivity. It includes an assessment of the severity and perceived burden of each dimension and the sum of all dimensions represents the total score of ADHD.

2.1.3.5 Statistical Analysis

Statistical analyses were performed using SPSS 27.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and R using “mgcv” package (Version 1.8–28; Wood, 2004, 2011). In the first step, we performed analyses for the sample characteristics with respect to smoking-exposed vs. non-exposed children, including correlations between our outcome variables (EEG power spectrum and ADHD-related symptoms). For the main hypotheses, we then examined a) the effects of prenatal smoking as a dichotomous variable (prenatally tobacco exposed vs. unexposed) on EEG power spectrum and FBB-ADHD scales of impulsivity, attention deficit, and hyperactivity, and b) in the children who experienced prenatal tobacco exposure, we explored linear and nonlinear associations between the estimated averaged amount of weekly smoked cigarettes of the mother during pregnancy and brain frequencies as well as ADHD-relates outcomes. We used a series of generalized additive mixed models (GAMMs) (Baayen et al., 2017; C. Chen, 2000), adjusting for fixed and random effects (spline models) (C. Chen, 2000). Here, 1.5% winsorization was applied to convert extreme outliers. This approach follows prior studies on the effects of prenatal alcohol exposure on psychological, behavioral, and neurodevelopmental outcomes in children (e.g., Lees et al., 2020). For all analyses, we run covariate-unadjusted and -adjusted models, using for the adjusted models the following covariates: child’s sex, maternal age, maternal psychopathology, maternal smoking before pregnancy, maternal alcohol drinking during pregnancy and week of pregnancy at birth.

2.1.4 Results

The FRANCES cohort included 248 parents and children each. For our data analyses, we only used full datasets, which resulted in a final sample of *N* = 142 parents and children each, with mothers aged 19 to 41 (*M* = 32.68, *SD* = 4.32), fathers aged 23 to 52 (*M* = 35.25, *SD* = 5.50) and children aged 6 to 9 years (*M* = 7.73, *SD* = .67). Subject characteristics are described as frequency, mean and standard deviation (see Table 1). None of the children had a history of clinically significant developmental or intellectual disorders or clinically significant somatic abnormalities. The information on parental psychopathology was obtained with trained psychologists. According to maternal responses, 34 mothers reported the presence of at least one psychiatric diagnosis.

Table 1 Sample characteristics with children divided into two groups of tobacco non-exposed and prenatal tobacco exposed children

Characteristic	Tobacco Unexposed Children (n=116)		Children With Prenatal Tobacco Exposure (n=26)		
Youth Variables					
	n	%	n	%	*p*
Sex					.434
male	59	50.9	11	42.3	
female	57	49.1	15	57.7	
Prenatal alcohol exposure					.562
No	95	81.9	20	76.9	
Yes	21	18.1	6	23.1	
	Mean	SD	Mean	SD	*p*
Age (years)	7.72	0.65	7.76	0.74	.781
Gestational age	39.41	1.33	39.23	1.45	.533
Birth weight	3453.91	494.28	3370.77	520.34	.446
Intelligence quotient*	104.23	10.25	104.31	7.18	.972
Parent Variables					
Age at giving birth	32.86	4.12	31.88	5.15	.299
	n	%	n	%	*p*
Marital status					.068
married	113	97.4	23	88.5	
single parent	3	2.6	3	11.5	
Maternal Psychopathology					.536
No	68	58.6	17	65.4	
Yes	29	25.0	5	19.2	
Unknown	19	16.4	4	15.3	
Paternal Psychopathology					.461
No	92	79.3	20	76.9	
Yes	12	10.3	2	7.7	
Unknown	12	8.3	4	15.3	

Note: *intelligence quotient was assessed with Intelligence and Development Scales (IDS) test battery (Grob, Meyer, 2013)

For the mean values of the maternal smoking behavior and the amount of weekly smoked cigarettes for active and passive smoking (for illustration see Table 2), we found that, in total, 26 women smoked during pregnancy and 101 women were in the non-smoker group. Thereby, 35 women from the non-smoker group reported passive smoking during pregnancy. For the main data analyses, we used the mean value of three obtained values from each trimester with respect to the averaged quantity of cigarettes smoked per week during pregnancy.

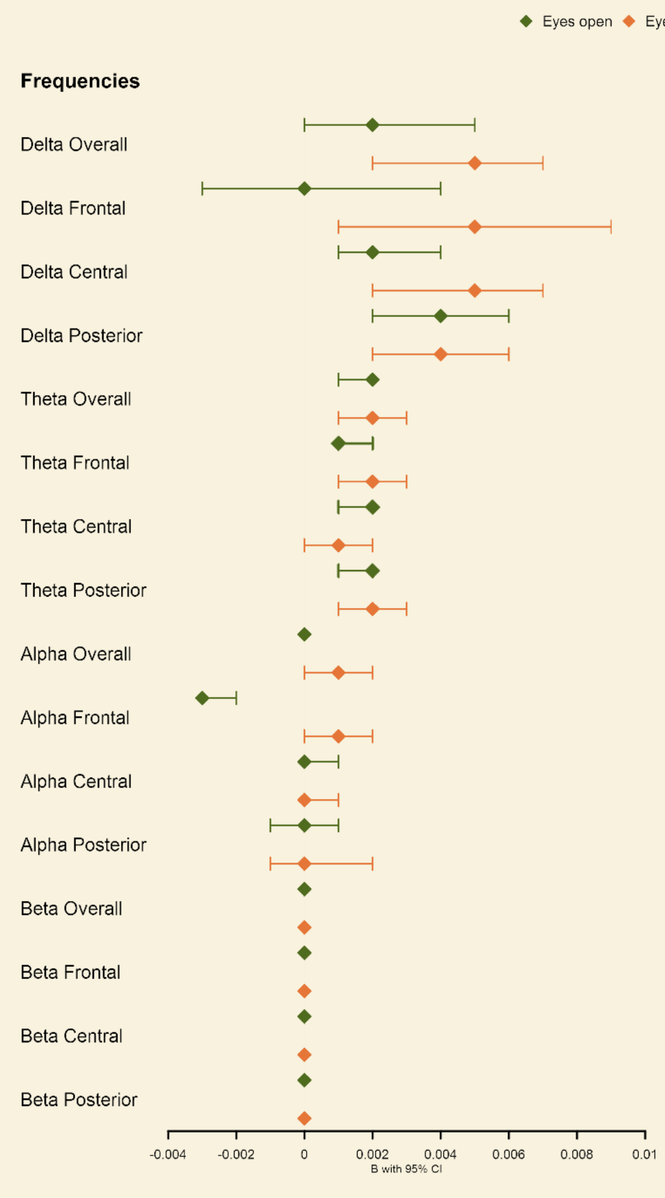
Table 2 Detailed information on maternal smoking behavior

	Smoked	Did not smoke	Did not answer	Passive smoking
	n (%) *[Min, Max]* *M (SD)*	*n* (%)	*n* (%)	*n* (%) *[Min, Max]* *M (SD)*
Before pregnancy	40 (28.2) [2,300] 25.21 (50.72)	100 (70.4)	2 (1.4)	33 (32.4) [3, 210] 102.39 (57.44)
1.Trimester	26 (18.3) [2,140] 5.25 (19.28)	102 (71.8)	14 (9.9)	40 (34.5) [4, 210] 98.16 (57.09)
2.Trimester	24 (16.9) [2, 140] 5.07 (19.25)	104 (73.2)	14 (9.9)	37 (31.4) [4,210] 99.05 (56.39)
3.Trimester	24 (16.9) [2, 140] 4.83 (19.01)	104 (73.2)	14 (9.9)	35 (29.7) [4, 210] 99.00 (56.48)
During pregnancy	26 (18.3) [2, 140] 5.09 (19.23)	101 (63.6)	15 (10.6)	35 (30.2) [4, 210] 100.51 (55.27)

2.1.4.1 Effects of prenatal tobacco-exposure on brain activity

Exposure vs. non-exposure. For the covariate-unadjusted models, we found significant effects of maternal smoking during pregnancy on delta central, posterior and overall in frontal, posterior and overall theta as well as on frontal, central and overall alpha brain activity in eyes closed resting-state condition (see Tables S3 in the supplement). Here, the prenatally exposed group obtained significantly higher brain activity. In eyes open resting-state condition significant effect were shown in frontal, central, posterior and overall theta as well as in central alpha (see Tables S3 in the supplement) brain activity, with prenatally tobacco-exposed children compared to non-exposed children also showing significantly higher brain activity in these areas. When adjusting for the covariates (child's sex, child's age, maternal age; maternal psychopathology; maternal smoking before pregnancy; maternal alcohol drinking, week of pregnancy at birth), the effects for the delta and theta frequency bands in both eyes open and eyes closed conditions remained significant (see forest plot in Figure 2; for effects of included covariates see Table S5 in the supplement).

Linear and non-linear associations. For the covariate-unadjusted models, we found both linear and nonlinear associations were observed between the estimated averaged amount of weekly smoked cigarettes during pregnancy and brain activity, with linear associations for delta central and nonlinear associations for theta posterior, theta central, theta overall, and delta posterior. These associations remained significant when adjusting for covariates (see spline models in Figure 3).



Frequencies	B	CI lower	CI upper	p-value	R^2adjusted	R^2(%)
Delta Overall	0.002	0	0.005	0.25	0.1	19
	0.005	0.002	0.007	0.08	0.13	22
Delta Frontal	0	−0.003	0.004	0.9	0.04	13
	0.005	0.001	0.009	0.25	0.14	23
Delta Central	0.002	0.001	0.004	0.17	0.08	17
	0.005	0.002	0.007	0.03	0.08	17
Delta Posterior	0.004	0.002	0.006	0.05	0.15	24
	0.004	0.002	0.006	0.09	0.11	20
Theta Overall	0.002	0.001	0.002	0.02	0.08	17
	0.002	0.001	0.003	0.12	0.08	17
Theta Frontal	0.001	0.001	0.002	0.08	0.05	14
	0.002	0.001	0.003	0.12	0.14	23
Theta Central	0.002	0.001	0.002	0.02	0.06	15
	0.001	0	0.002	0.44	0.04	14
Theta Posterior	0.002	0.001	0.002	0.02	0.11	20
	0.002	0.001	0.003	0.1	0.04	13
Alpha Overall	0	0	0	0.98	0.06	16
	0.001	0	0.002	0.49	0.06	15
Alpha Frontal	−0.003	−0.003	−0.002	0.99	0.11	20
	0.001	0	0.002	0.15	0.11	20
Alpha Central	0	0	0.001	0.55	0.05	15
	0	0	0.001	0.54	0.07	16
Alpha Posterior	0	−0.001	0.001	0.77	0.03	13
	0	−0.001	0.002	0.86	0.04	13
Beta Overall	0	0	0	0.72	0	10
	0	0	0	0.96	−0.05	4
Beta Frontal	0	0	0	0.3	0.05	14
	0	0	0	0.95	−0.03	7
Beta Central	0	0	0	0.91	−0.03	7
	0	0	0	0.93	−0.06	3
Beta Posterior	0	0	0	0.73	−0.04	6
	0	0	0	0.38	−0.01	9

Figure 2. Association of prenatal tobacco exposure (exposed vs. non-exposed) with EEG activity among school aged children

Note: adjusted for covariates: child's sex, child's age, maternal age; maternal psychopathology; maternal smoking before pregnancy; maternal alcohol drinking, week of pregnancy at birth.

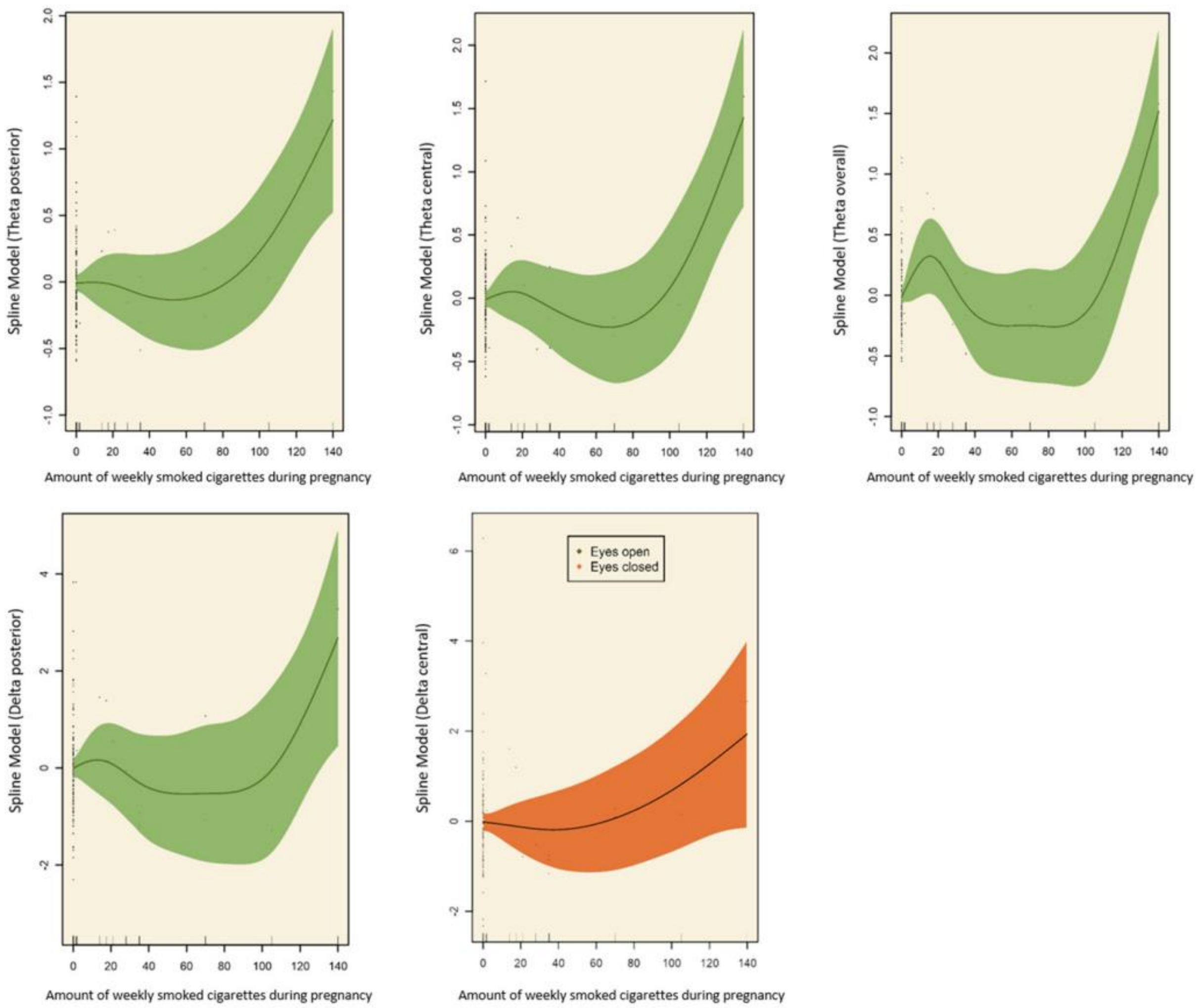


Figure 3 Spline models demonstrating a significant relationship between the estimated number of smoked cigarettes of the mother during pregnancy and offspring brain activity (delta and theta frequency bands)

Note: adjusted for covariates: child's sex, child's age, maternal age, maternal psychopathology, maternal smoking before pregnancy, maternal alcohol drinking, week of pregnancy at birth.

2.1.4.2 Effects of prenatal tobacco-exposure on ADHD

Exposure vs. non-exposure. For the unadjusted models, we observed a significant effect of maternal smoking during pregnancy on hyperactivity scores of the children where prenatally exposed children (M = 5.33, SD = 1.45) showed higher rates on hyperactivity compared to prenatally unexposed (M = 4.75, SD = 2.28) children (see Table S3 in the supplement). No significant effects were observed for impulsivity and attention deficits. When adjusting for the covariates, the effect on hyperactivity did not survive (see Table S4 in the supplement).

Linear and non-linear associations. For both covariate-adjusted and -unadjusted models, we did not observe any significant associations between the estimated number of smoked cigarettes of the mother and ADHD-related symptoms.

2.1.4.3 Interaction of prenatal tobacco exposure, brain activity and ADHD symptoms

With respect to associations between the outcome variables, brain activity and ADHD-related symptoms, in eyes open condition, we found significant partial correlations between impulsivity and frontal (r = .21, p < .05), central (r = .22, p < .05) alpha brain activity, central (r = .31, p < .05), frontal (r = .20, p < .05), posterior (r = .20, p < .05), overall delta (r = .32, p < .05) frequency power and frontal (r = .21, p < .05) theta brain activity. Hyperactivity and the total ADHD-score were significantly associated with frontal (r = .25, p < .01; r = .22, p < .01), central (r = .33, p < .01; r = .31, p < .01), posterior (r = .23, p < .01; r = .21, p < .01) and overall (r = .34, p < .01; r = .30, p < .01) delta brain activity. No significant correlation was observed between attention deficit and any of the frequencies in eyes open condition. In eyes closed condition significant correlations were observed between central delta frequency power and impulsivity (r = .22, p < .05), hyperactivity (r =.22, p < .05), and the total ADHD-score (r = .20, p < .05). Posterior delta frequency power was also significantly associated with the total ADHD-score (r = .21, p < .05). As for the eyes open condition, no significant correlation was observed between attention deficit and any of the frequencies in eyes closed condition (see Figure S1 in the supplement).

Since brain activity in alpha, delta and theta frequencies were positively associated with ADHD-related symptoms (hyperactivity, impulsivity, total ADHD-score), mediation analysis was performed in order to test whether brain activity mediated associations between prenatal maternal smoking and behavioral outcomes (FBB-ADHD scales) in covariate-adjusted models. Here, differential mediation was observed, where prenatal smoking was significantly associated with brain activity (alpha, delta and theta frequencies) and brain activity (alpha and delta frequencies) was significantly associated with impulsivity. Whereas, brain activity did not mediate the relationship between prenatal smoking and ADHD-related behavior (see Tables S6-S11 in the supplement).

2.1.5 Discussion

In the present study, we aimed to investigate the influence of prenatal smoking on a) EEG brain activity, b) ADHD-related symptoms in school-aged children and c) their interaction, taking into account the amount of smoked cigarettes during pregnancy, as well as considering potential confounding factors including child's sex, child's age, maternal age, maternal psychopathology, maternal smoking before pregnancy, maternal alcohol drinking, week of pregnancy at birth.

Previous studies have shown that maternal smoking during pregnancy is a major prenatal risk factor for child development: excessive prenatal tobacco exposure was related to adverse behavioral outcomes, including hyperactivity and impulsivity, to deficits in cognitive abilities, such as auditory and visual attention performance accuracy, and to changes in the brain`s structure, such as a significant reduction in cortical gray matter, in young children (Albers et al., 2018; Dong et al., 2018; Rivkin et al., 2008). With respect to changes in the brain, the majority of these studies has so far focused either on fetal structural and functional brain development or on brain correlates in newborn (Bridwell et al., 2018; Havlicek et al., 1977; Loffe et al., 1984), mainly using MRI (Holz et al., 2014; Jacobsen et al., 2007; Rivkin et al., 2008). Moreover, studies were so far partly restricted by relatively small sample sizes (Havlicek et al., 1977; Loffe et al., 1984; Shuffrey et al., 2020), and proximal risk factors like socio-demographical characteristics may have co-determined or masked effects (e.g., Cornelius & Day, 2009).

Capitalizing on EEG, behavioral and clinical data, with socio-demographical relation, like maternal psychopathology, from a larger sample of mothers and their children, we found significant changes in resting-state EEG as a response to prenatal tobacco, with increased delta and theta brain activity in resting-state EEG in school aged exposed compared to non-exposed children. Brain activity in these frequency bands was also significantly related to the amount of cigarettes smoked. This is in line with previous studies that reported an association between prenatal tobacco exposure and changes in the brain of newborn and young children. In our study, we also see that these effects are independent of potential confounding covariates - both the covariate-unadjusted and -adjusted models were significant. This adds information to the previous literature highlighting that there might be some single specific effects that are rather independent of proximal risk factors. However, we then also looked at the effects of prenatal maternal smoking on behavior and clinical symptoms. For ADHD-related symptoms, effects of prenatal maternal smoking were only significant in the unadjusted models with including potential confounding factors, when controlling for covariates, the effects did not remain significant. This indicates the need to take into account proximal risk factors particularly when it comes to effects of prenatal tobacco exposure on behavior and clinical symptoms. Some previous studies have also made this point, highlighting that association of ADHD with prenatal tobacco exposure symptoms might not be directly affected, but might rather covary with intra-household related factors (Langley et al., 2012). Rice et al (2018) stated that the negative causal link between maternal smoking and physiological characteristics such as child birth weight seems to be a rather direct effects (Rice et al., 2018), consistent across various study designs (Abraham et al., 2017; Langley et al., 2012), however, when it comes to children`s psychopathology a broader set of risk factors including socioeconomic status (e.g., income conditions), parental psychopathology, maternal stress (Rice et al., 2018) and maternal age (Gustavson et al., 2017) come into play. This has also been indicated by data from a large prospective birth cohort study that the association between prenatal tobacco exposure and offspring ADHD was significantly related to confounding factors and did not reflect causal intrauterine effects (Moylan et al., 2015).

These and our findings raise several questions for future studies, for example whether or to which degree these are divergent pathways, and at which point during development factors might strongly interact. Associations between prenatal smoking exposure during pregnancy and behavior problems might not be simply direct or causal (see e.g., Langley et al., 2012).

In the present study, we also observed significant partial correlations between impulsivity and hyperactivity and frontal alpha (for impulsivity only) as well as frontal, central, posterior and overall delta frequencies (also for the total ADHD-score). Such association shave also been reported previously, for example increased alpha and theta activity (Kitsune et al., 2015; Machado et al., 2015; Tye et al., 2014) as well as increased delta activity (Kitsune et al., 2015) has been found in children and ADHD diagnosis compared to typically developing children. This underlines not only brain-behavior interactions, but those may contribute, together with socio-demographic and psychosocial, to a rather complex developmental pathway of prenatal tobacco exposure. Since the present study involved typically developing children without ADHD diagnosis, this might have an effect even at lower rates of ADHD symptoms.

The present study needs to be seen in the light of some limitations. First, we assessed smoking behavior during pregnancy retrospectively with a self-report questionnaire. This could have resulted in a bias, for example in that parents might underreport smoking during pregnancy due to social desirability. Second, the ADHD-scores in our sample were rather low. While on the one hand one could argue that this may dampen the generalizability of the findings, on the other hand, we could provide add on insights into a low-risk sample, which are also interesting with respect to brain-related associations.

In summary, to the best of our knowledge, this is one of the first studies that examined effects of maternal smoking during pregnancy on brain activity assessed with EEG and behavioral and While smoking during pregnancy affects resting-state brain activity in children, independent of socio-demographic factors and thus indicating rather long-lasting effects on brain development, for effects on ADHD-related behavior, socio-demographic confounding factors such as maternal alcohol consumption and age of the mother significantly come into play. Future should investigate effects of maternal smoking on oscillatory power in offspring at frequent intervals in order to characterize the developmental changes to disorder specificity in EEG profiles and also consider different ADHD symptom scores and ADHD diagnosis longitudinally as well as more deeply disentangle and integrate socio-demographic and cultural circumstances.

2.2 STUDY 2: Long-Term Impact of Maternal Prenatal Smoking on EEG Brain Activity and Internalizing/Externalizing Problem Symptoms in Young Adults

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2.2.1 Abstract

Objective**:** The objective of this study was to investigate the impact of smoking during pregnancy on the development of the child. While previous research has established its detrimental effects during early childhood, understanding potential long-term consequences into adulthood remains limited. This study specifically aimed to explore the influence of prenatal smoking exposure on brain activity and whether internalizing and externalizing symptoms are influenced by prenatal smoking exposure in a cohort of young adults.

Methods**:** Utilizing data from 176 participants (mean age *M*=24.68, *SD*=0.49) and their mothers enrolled in a longitudinal risk study (MARS), we employed Generalized Additive Mixed Models (GAMMs) to analyze electroencephalography (EEG) power at rest and behavioral outcomes derived from the Young Adult-Self-Report (YASR) scales. Both covariate-unadjusted and -adjusted models were used, taking into account participant variables such as sex and age, as well as maternal factors like psychopathology and alcohol consumption, in addition to smoking and alcohol intake by the participants themselves.

Results**:** The study revealed a significant impact of prenatal smoking on delta and theta band power, indicating decreased slower brain activity in prenatally exposed individuals compared to unexposed counterparts. Additionally, individuals exposed to prenatal smoking exhibited significantly higher levels of externalizing behavior. While this association was strongly influenced by maternal psychopathology, the child's gender, and the child's own substance use, the effect on delta power band remained after adjusting for covariates.

Conclusion**:** The findings suggest that prenatal smoking exposure may have enduring effects on brain activity patterns in young adulthood. Conversely, the influence on externalizing behaviors depended on familial factors (maternal psychopathology) and the lifestyle of the individual (substance use).

Keywords: prenatal smoking, EEG, brain development, externalizing behavior, internalizing behavior

2.2.2 Introduction

The prenatal period represents a critical developmental phase where various risk factors, including maternal health-related behavior, can significantly impact the physiological, cognitive, behavioral, psychological, and neurobiological development of the offspring (Abraham et al., 2017; Button et al., 2007; M. Ekblad et al., 2015, 2017; Hackshaw et al., 2011). Notably, maternal smoking emerges as a key factor in this context (M. O. Ekblad et al., 2023; Y et al., 2020). Maternal smoking has been associated with the development of mental disorders and related behaviors in offspring (M. O. Ekblad et al., 2019; Froggatt et al., 2020; Liu et al., 2010). For instance, Dolan et al., (2016) explored the potential causal effects of maternal smoking on the behavioral patterns of 3-year-old twins and found a significant impact on externalizing behavior problems, including aggression, overactive behavior, and withdrawn behavior. Beyond early childhood, studies consistently demonstrate an association between prenatal tobacco exposure and higher rates of conduct disorder as well as attention deficit hyperactivity disorder among children (Dong et al., 2018; Neuman et al., 2007).

This association has been supported by a longitudinal birth cohort study (Brannigan et al., 2022), which investigated the links between maternal smoking, maternal stress during pregnancy, and offspring psychiatric disorders during development. The results indicated an increased risk of offspring mental disorders, including mood, anxiety, and psychotic disorders due to smoking during pregnancy. Additionally, genetic factors, such as parental psychopathology, and socioenvironmental factors, including negative parenting behavior such as permissiveness, punishment or emotional overreaction and levels of emotional support or disciplinary approaches, may contribute to these effects (Langley et al., 2007; Muñoz-Silva et al., 2017).

In a prior study (Jansone et al., 2023), we examined the effects of prenatal maternal smoking on ADHD symptoms and symptom-related behaviors. Here, we found no significant effect of prenatal smoking when considering covariates such as maternal age and psychopathology. However, while existing research has primarily focused on maternal smoking effects on behavioral trajectories in children, there is a gap in evidence for its impact on adulthood. Moreover, besides these findings on effects of prenatal tobacco exposure and clinical symptoms and changes in symptom-relevant behaviors, consequences of prenatal smoking have also been reported for neurodevelopmental changes in brain activity. Here, prior studies have mainly used electroencephalography (EEG) to investigate the effects of maternal smoking during pregnancy on brain activity patterns in children (Jansone et al., 2023; Shuffrey et al., 2020). EEG is a non-invasive technique that provides exceptional temporal resolution in the millisecond range and is widely used for investigation of neurodevelopmental patterns. So far, effects of maternal smoking on brain activity have been identified in very early years, in newborns (Shuffrey et al., 2020). In a sample of 1739 newborns, the authors showed that even low levels of tobacco exposure were associated with changes in offspring brain development. Specifically, newborns with moderate or high continuous tobacco exposure showed decreased 19-to 24-Hz right-central EEG power compared to those with no tobacco exposure. Similar effects of maternal smoking during pregnancy on brain development were also identified in children with increasing age. Here, significant changes in resting-state EEG, with increased delta and theta brain activity in school-aged children who were exposed to prenatal tobacco compared to non-exposed children (Jansone et al., 2023). Importantly, these effects were found to be independent of various covariates, including child's sex, age, of maternal factors (age, smoking habit before pregnancy, and alcohol consumption during pregnancy, gestation age, and psychopathology). Together, these studies underscore the impact of cigarette smoking during pregnancy on child's neurodevelopmental patterns assessed through EEG. Nevertheless, existing research has so far primarily focused on investigating the immediate and early childhood consequences, and there is still a substantial gap in understanding the potential long-lasting effects of maternal smoking in adulthood for both neurodevelopmental patterns and clinical symptom relevant behavior patterns.

Therefore, this study aims to explore the long-term consequences of maternal smoking during pregnancy on brain activity and behavioral patterns (internalizing and externalizing problem behaviors) during early adulthood. Using resting-state EEG data from participants aged 24-27 years exposed to different levels of maternal smoking during gestation, we seek to elucidate potential dose-dependent effects of maternal smoking on brain function. Previous studies (e.g., Holz et al., 2014) have found respective changes in inhibitory control and behavioral trajectory in adulthood with respect to the amount of smoking exposure, including a specific effect for doses of more than 5 cigarettes compared to less than 5 cigarettes per day. In our study, we have also used this dose-dependent differentiation. Moreover, in the present study, we used the same variables as in our previous study Jansone et al. (2023) examining now another sample with respect to age. This allows to link of our previous findings to those from the current paper and through this also increase the understanding of potential long-term effects, which then also strengthens the understanding of prenatal smoking exposure on outcomes during adulthood.

2.2.3 Methods

For the present paper, we used data from the Mannheim Study of Children at Risk, a continuous epidemiological cohort investigation focusing on the long-term effects of early risk factors (for details, refer to (Esser & Schmidt, 2017; Holz et al., 2020; Laucht et al., 1997). The MARS cohort underwent 11 assessment waves, at the ages of 3 months, 2 years, 4.5 years, 8 years, 11 years, 15 years, 19 years, 22 years, 23 years, and 25 years. Each wave of MARS included detailed evaluations of developmental risk factors, encompassing prenatal, perinatal, and psychosocial adversities. Data collection involved a combination of standardized questionnaires, clinical interviews, and direct behavioral assessments. The ethics committee of the University of Heidelberg granted approval for the study, and written consent was acquired from all participants after providing them with detailed information. The MARS cohort initially comprised 384 children, representing the original sample. Resting state EEG data was collected at the age of 25, and this assessment was used to explore the long-term effects of maternal smoking during pregnancy on the children. For the analyses presented in this paper, the sample consisted of 176 participants. These participants were selected because complete data were available for both EEG assessments at age 25 and the Youth Self-Report (YASR) questionnaire subscales, as well as for the smoking behavior of mothers during pregnancy, and the included covariate variables.

2.2.3.1 Assessment and Pre-Processing of Resting-State EEG Activity

Participants were instructed to complete 2.5 minutes of eyes-open and 2.5 minutes of eyes-closed resting-state EEG. During the eyes-open resting state, participants were asked to fixate on a point in front of them and minimize both ocular and bodily movements. EEG data were recorded using 60 Ag–AgCl electrodes placed on the scalp according to the International 10–20 system (Brain Products GmbH), and mastoid electrodes. To monitor ocular movements and eye blinks, electro-oculographic (EOG) signals were simultaneously recorded using two surface electrodes. The raw

EEG data underwent inspection and pre-processing using MNE Python (Gramfort et al., 2014). A filter bandwidth of 0.00-250 Hz and a sampling frequency of 500 Hz were employed. The electrode impedance was maintained below 20 kΩ. The pre-processing steps involved various procedures such as filtering and the removal of artifacts caused by eye blinking, heartbeats, or muscle movements. Independent component analysis (ICA) was utilized on the continuous data to isolate and reject components associated with ocular movements (blinks and saccades) and any remaining artifacts, such as muscular or cardiac effects. The selection of components for rejection was done manually. Filtering with a low-pass filter of 0.1 Hz and a high-pass filter of 70 Hz to capture the basic cortical rhythms underlying higher brain functions. Additionally, a notch filter around 50 Hz was used to attenuate artifacts originating from external devices such as the electrical power supply in the recording room. Following artifact rejection, frequency analysis was conducted to explore the EEG data obtained during the two resting state conditions: "eyes open" and "eyes closed." Fast Fourier transformations were performed on the corrected data, and the FFT values of delta, theta, alpha, and beta bands were extracted using the FFT band export option. After the artifact detection and rejection process (Kaiser et al., 2021), the averaged eyes-open resting-state condition yielded an average of 68.36% (*SD* = 26.63) good segments, while the eyes-closed condition resulted in an average of 66.2% (*SD* = 27.96) good segments.

Finally, the participants' data were individually averaged across the epochs for each electrode site and frequency band (delta, theta, alpha, beta). Only participants with EEG data containing at least 50% artifact-free segments were included in the analysis. The recorded EEG activity was divided into three regions based on the average values of each region. The posterior region represented the averaged activity of electrodes O1, O2, Oz, PO9, PO10, PO1, PO2, OI1, OI2. The parietal region included P3, P4, P5, P6, P7, P8, Pz, TP7, TP8, Iz. The frontal region encompassed F3, F4, F5, F6, F7, F8, Fp1, Fp2, Fz, AFz, FT7, FT8, FT9, FT10. The central area was indicated by the average of the C3, C4, Cz, CP1, CP2, CP3, CP4, CP5, CP6, FC1, FC2, FC5, FC6, and FCz electrodes. For both resting-state conditions, "eyes open" and "eyes closed", the absolute power was calculated for four frequency bands: theta (1–4 Hz), delta (4–8 Hz), alpha (8–13 Hz), and beta (13–30 Hz).

2.2.3.2 Assessment of Emotional and Behavioral Symptoms

In the study, we utilized the Young Adult Self-Report (YASR; Achenbach*,* 1997) questionnaire to assess the emotional and behavioral problems of the participants. The YASR questionnaire covers a wide range of symptoms and behaviors, allowing for a comprehensive evaluation. The questionnaire includes problem scales that provide scores for various domains, including withdrawal, somatic complaints, anxiety and depression, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior, self-destructive behavior, and total problem behaviors (T-scores). T-scores have a mean of 50 and a standard deviation of 10, enabling a comparison of individual scores with population norms. T-scores below 50 indicate fewer problems than the average population, scores around 50 indicate average levels, and scores above 50 indicate more problems compared to the average population.

2.2.3.3 Assessment of Maternal Prenatal Smoking

Maternal smoking was evaluated three months after giving birth through a standardized interview conducted with the mothers. The smoking amount was assessed via interview, and the responses were categorized into the following groups: non-smoker, 1-5 cigarettes per day, more than 5 cigarettes per day, and about 20 cigarettes per day. However, since there were no women in the mothers' group who smoked about 20 cigarettes per day, this category was not used in the final analysis. Among the 176 mothers who participated in the study, 118 (65.2%) were identified as nonsmokers, while 15 (8.3%) reported smoking 1 to 5 cigarettes per day, and 43 (23.8%) reported smoking more than 5 cigarettes per day. The same question was also asked by participants themselves at the age of 25 years. In the participants' group, only one person reported smoking about 20 cigarettes per day. To maintain consistency in group sizes for the analyses, this individual was included in the group of those smoking more than 5 cigarettes per day (see Table 1).

2.2.3.4 Statistical analyses

The statistical analyses were conducted using R software, specifically utilizing the "mgcv" package (Version 1.8-28) for generalized additive modeling. This approach enabled the consideration of potential nonlinear effects of predictor variables on EEG measures and a comprehensive set of YASR questionnaire subscales encompassing various domains of behavioral and emotional problems. In all analyses, the false discovery rate was used to correct for multiple comparisons, and the adjusted p values are reported. The analyses involved comparing sample characteristics among three groups: non-smokers, mothers smoking 1 to 5 cigarettes per day, and mothers smoking more than 5 cigarettes per day. The categorization of maternal smoking was based on evidence suggesting differential effects of low and higher levels of prenatal tobacco exposure on fetal development. Specifically, previous research (Holz et al., 2014) has indicated that smoking more than 5 cigarettes per day is associated with significantly higher risks of adverse fetal outcomes compared to lighter smoking (e.g., 1-5 cigarettes per day). This classification aligns with findings in the literature demonstrating that heavier smoking leads to markedly different and more severe developmental impacts on the fetus (Sharma et al., 2008; Sun et al., 2023). The study focused on investigating the effects of prenatal smoking on the EEG power spectrum and the aforementioned YASR scales. To account for potential confounding factors, generalized additive mixed models (GAMMs) with fixed and random effects (spline models) were employed. Covariate-unadjusted and -adjusted models were conducted, considering covariates such as participant's sex, age, maternal psychopathology (assessed through a question in the clinical interview with dichotomous self-rating), maternal alcohol consumption during first three month after giving birth, week of pregnancy at birth, as well as the smoking habits of participants and alcohol intake. In the context of comparisons among the three groups, the non-smoker group served as the reference. This means that the effects of smoking (1 to 5 cigarettes per day and more than 5 cigarettes per day) were assessed in relation to the non-smoker group. The coefficients associated with the smoking groups indicated the difference in the outcome variables compared to the non-smoker group, providing insights into the impact of different levels of maternal smoking on EEG power spectrum and behavioral/emotional problems measured by YASR questionnaire subscales. It is important to note that this analysis was conducted in accordance to the prior study by Jansone et al. (2023), which focused on a school-age cohort of children from a different study but with similar variables. The analyses in the present paper were conducted using the same design, as in Jansone et al. (2023), including the same covariates and outcomes, however now capitalizing on data from a different sample and different age period. Conducting these parallel analyses on distinct samples strengthens the validity and robustness of findings, and provides understanding of the long-term effects of prenatal smoking across different developmental stages.

2.2.4 Results

In our data analysis, the mothers' ages ranged from 18 to 41 years (*M* = 27.70, *SD* = 4.77) at the time of their child's birth, while the fathers' ages ranged from 19 to 48 years (*M* = 31.07, *SD* = 5.77) at the child's birth. The children included in the study were aged between 23 and 26 years (*M* = 24.68, *SD* = 0.49). Descriptive statistics such as frequencies, means, and standard deviations for subject characteristics are presented in Table 3. None of the children had a documented record of significant developmental or intellectual disorders. In contrast, regarding maternal psychopathology, 24 (13.64%) of the mothers acknowledged having been diagnosed with at least one psychiatric condition.

Table 3 Sample characteristics with children divided into three groups of tobacco non-exposed and prenatal tobacco exposed children

Characteristic	Unexposed (n=118)		1-5 cigarettes/d (n=15)		>5 cigarettes/d (n=43)		
Youth Variables							
	n	%	n	%	*n*	%	*p*
Sex							.235
male	56	47.5	7	46.7	14	32.6	
female	62	52.5	8	53.3	29	67.4	
Smoking habit							.073
nonsmoker	99	83.1	12	80.0	27	62.8	
1-5 cig./d	5	4.2	3	20.0	8	18.6	
>5 cig./d	15	12.7	-	-	8	18.6	
			-	-	-	-	
	Mean	SD	Mean	SD	M	SD	*p*
Age (years)	24.70	0.51	24.58	0.46	24.69	0.47	.714
Gestational age	38.67	2.60	39.13	2.23	37.79	3.22	.129
Birth weight	3013.47	647.72	3156.67	683.81	2736.05	689.81	.032
Intelligence quotient	105.84	15.37	106.90	8.17	99.61	14.57	.050
Alcohol intake (AUDIT Score)	54.96	5.23	56.40	4.88	54.53	5.01	.486
Parent Variables							
Age at giving birth	28.72	4.63	25.60	3.20	25.65	4.85	.000
	n	%	n	%	n	%	*p*
Maternal alcohol consumption*							.769

never	26	22.0	5	33.3	11	25.6	
rarely	83	70.4	6	53.4	27	62.8	
frequently	9	7.6	2	13.3	5	11.6	
Maternal Psychopathology							.349
No	105	89.0	12	80.0	35	81.4	
Yes	13	11.0	3	20.0	8	18.6	
Paternal Psychopathology							.160
No	112	96.6	11	84.6	31	93.9	
Yes	4	3.4	2	15.4	2	6.1	

Note: *alcohol consumption during first three month after giving birth

2.2.4.1 *Effects of Prenatal Tobacco Exposure on Brain Activity*

The results from the covariate unadjusted GAMMs revealed significant differences in the EEG power spectrum between nonsmoking mothers and mothers who smoked different quantities of cigarettes (see Tables 1, 2 in the Supplementary Materials). In the delta frequency band, significant effects were observed in the frontal region, where both categories of prenatal smoking habits (1-5 cigarettes/day and >5 cigarettes/day) showed a decreased brain activity in exposed children. Similarly, for the theta frequency band, significant effects were observed in the frontal region, where both categories of prenatal smoking habits showed negative associations.

The results from the covariate adjusted GAMMs revealed same significant differences in the EEG power spectrum between nonsmoking mothers and mothers who smoked different quantities of cigarettes (see Table 4). Specifically, comparisons were made between mothers who smoked 1-5 cigarettes per day and those who smoked more than 5 cigarettes per day. In the delta frequency band, both the frontal and posterior regions exhibited significant differences where the >5 cigarettes/day group demonstrated negative coefficients, indicating a decreased brain activity in the exposed groups compared to the non-exposed group (Figure 4). Additionally, marginal significant differences were observed in the frontal theta and parietal delta, suggesting a potential impact of cigarette consumption on decreased brain activity as well. In the alpha frequency band, no significant differences were found across the different brain regions. Similarly, in the beta frequency band, no significant differences were found across the brain regions.

Table 4 Results of covariate* adjusted GAMMs for EEG power spectrum during eyes open (EO) condition in relation to prenatal smoking habits

Frequency band		*1-5 cigarettes/day* B	SE	*p*	*>5 cigarettes/day* B	SE	*p*	R^2(%)	R^2adj
Delta	Central	-0.26	0.16	0.097	-0.24	0.10	**0.024**	27.5	0.20
	Frontal	-0.45	0.22	0.090	-0.34	0.15	**0.025**	28.9	0.21
	Parietal	-0.38	0.22	0.090	-0.29	0.15	**0.054**	26.9	0.19
	Posterior	-0.42	0.25	0.089	-0.34	0.16	**0.040**	27.1	0.19
Theta	Central	-0.12	0.08	0.133	-0.06	0.05	0.270	26.9	0.19
	Frontal	-0.16	0.08	0.104	-0.09	0.05	0.194	30.4	0.23
	Parietal	-0.18	0.12	0.127	-0.02	0.08	0.760	24.5	0.16
	Posterior	-0.22	0.14	0.127	-0.03	0.09	0.760	23.6	0.16
Alpha	Central	-0.09	0.10	0.372	0.01	0.07	0.875	18	0.10
	Frontal	-0.08	0.06	0.272	-0.03	0.04	0.575	23.7	0.16
	Parietal	-0.24	0.21	0.271	0.09	0.14	0.517	18.4	0.11
	Posterior	-0.31	0.28	0.270	0.05	0.19	0.791	17.9	0.11
Beta	Central	-0.03	0.03	0.316	-0.02	0.02	0.443	23.6	0.16
	Frontal	-0.04	0.03	0.224	-0.02	0.02	0.443	27.7	0.21
	Parietal	-0.07	0.05	0.224	-0.03	0.03	0.389	26	0.19
	Posterior	-0.10	0.06	0.224	-0.05	0.04	0.390	27.3	0.20

Note: *participant's sex, age, maternal psychopathology (assessed through an interview question with dichotomous self-rating), maternal alcohol consumption during first three month after giving birth, week of pregnancy at birth, smoking habits of participants and alcohol intake; *B* represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

The results of covariate adjusted GAMMs for eyes closed condition in Table 5 represent the differences in the EEG Power Spectrum between mothers who smoked different quantities of cigarettes (1-5 cigarettes per day and more than 5 cigarettes per day) compared to non-smoking mothers. In the delta frequency band, in contrast to the eyes open condition, there were no statistically significant differences in the central region between the groups. Regarding the theta frequency band, there were also no statistically significant differences between groups. Similarly, in the alpha and beta frequency band, there were no statistically significant differences observed.

Table 5 Results of Covariate* Adjusted GAMMs for EEG Power Spectrum during eyes closed (EC) condition in Relation to Prenatal Smoking Habits

Frequency band		*1-5 cigarettes/day*			*>5 cigarettes/day*				
		B	**SE**	***p***	**B**	**SE**	***p***	**R2 (%)**	**R2 adj**
Delta	Central	-0.16	0.13	0.184	-0.13	0.08	0.244	23.7	0.17
	Frontal	-0.27	0.16	0.184	-0.10	0.11	0.341	25.5	0.19
	Parietal	-0.28	0.18	0.275	-0.20	0.12	0.138	26.1	0.18
	Posterior	-0.28	0.21	0.178	-0.20	0.14	0.142	24	0.17
Theta	Central	-0.07	0.06	0.241	-0.05	0.04	0.211	26	0.18
	Frontal	-0.10	0.06	0.220	-0.06	0.04	0.316	29.2	0.22
	Parietal	-0.10	0.09	0.275	-0.06	0.06	0.323	25	0.17
	Posterior	-0.10	0.09	0.275	-0.07	0.06	0.813	25.4	0.18
Alpha	Central	-0.04	0.07	0.554	-0.00	0.04	0.963	17.9	0.01
	Frontal	-0.04	0.04	0.543	-0.02	0.03	0.816	24	0.17
	Parietal	-0.11	0.12	0.341	0.04	0.08	0.619	16.7	0.09
	Posterior	-0.15	0.15	0.341	0.05	0.10	0.651	14.7	0.07
Beta	Central	-0.02	0.02	0.395	-0.01	0.02	0.704	25.3	0.18
	Frontal	-0.03	0.03	0.295	-0.01	0.02	0.704	29	0.22
	Parietal	-0.04	0.04	0.294	-0.01	0.02	0.631	24.7	0.18
	Posterior	-0.05	0.04	0.294	-0.02	0.03	0.635	25.4	0.18

Note: *participant's sex, age, maternal psychopathology (assessed through an interview question with dichotomous self-rating), maternal alcohol consumption during first three month after giving birth, week of pregnancy at birth, smoking habits of participants and alcohol intake; *B* represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

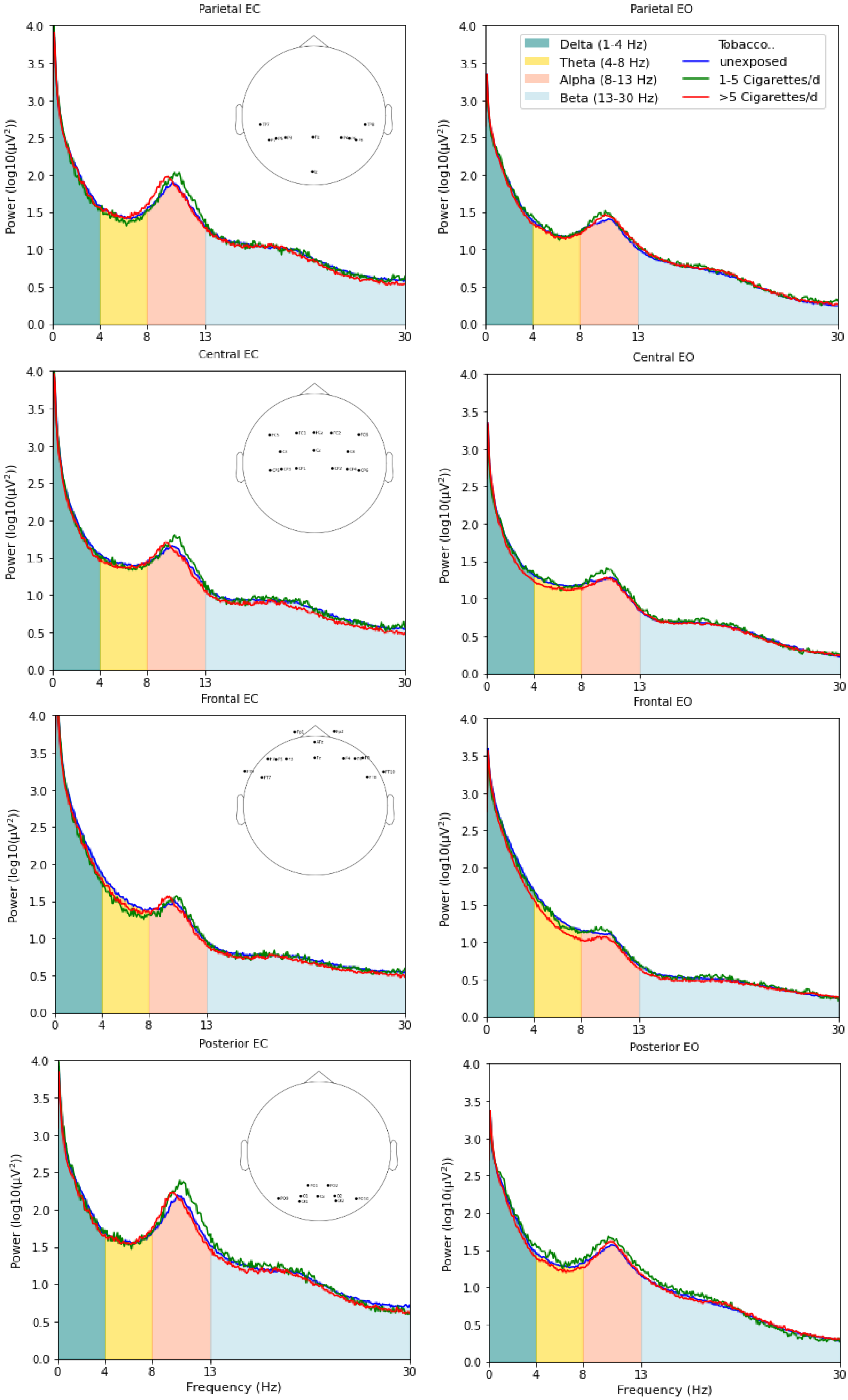

Figure 4 Average Log10-Transformed Absolute Spectral Power in Different Frequency Bands for Prenatally Unexposed Children (blue), Maternal Smoking: 1-5 Cigarettes/Day (green), and Maternal Smoking: >5 Cigarettes/Day (red).

2.2.4.2 *Effects of Prenatal Tobacco Exposure on Behavioral Patterns*

The results of the YASR questionnaire were analyzed and presented in the form of T-scores for each subscale. As could be seen in Figure 5, descriptive statistics revealed distinct patterns of group differences in emotional and behavioral problems among young adults based on their mothers' smoking habits, where maternal smoking was associated with higher levels of emotional and behavioral problems in their young adult children.

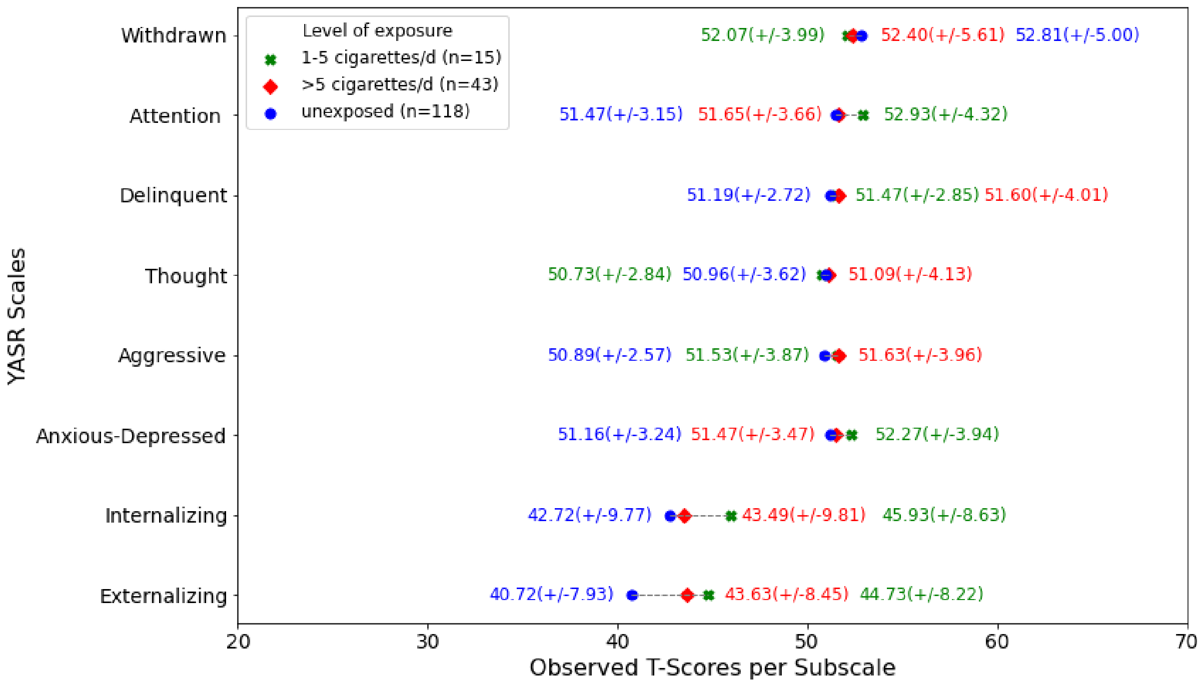

Figure 5 Descriptive statistics of the YASR subscales, M(+/-SD)

In the unadjusted models, significant group differences were found in relation to maternal prenatal smoking and child´s externalizing behavior symptoms (see Table 3 in the Supplementary Materials). Here, only the group of prenatally exposed children whose mothers smoked more than 5 cigarettes per day, significantly differed from non-exposed children (B = 4.01, SE = 2.12, p = 0.045).

However, after including the covariates, significant factors such as maternal psychopathology, gestation age, child´s gender and their own substance consume emerged as influential factors and no significant group difference could be identified (see Table 6).

Table 6 Results of Covariate* GAMMs for YASR scales in Relation to Prenatal Smoking Habits

	1-5 cigarettes/day			*>5 cigarettes/day*				
YASR Scales	**B**	**SE**	***p***	**B**	**SE**	***p***	**R2**	**R2 adj**
Anxious	1.14	0.60	0.606	0.34	0.59	0.970	19.9	0.12
Withdrawn	-1.13	1.41	0.848	-0.36	0.93	0.702	10.7	0.03
Thought	-0.57	1.07	0.875	-0.02	0.71	0.972	3.13	0.05
Attention	1.52	0.94	0.606	0.07	0.62	0.972	11.2	0.04
Delinquent	0.13	0.81	0.875	0.38	0.54	0.474	19.7	0.13
Aggressive	0.23	0.84	0.875	0.32	0.58	0.563	16.3	0.09
Internalizing	3.04	2.69	0.260	0.61	1.78	0.731	10.7	0.03
Externalizing	3.16	2.24	0.261	2.84	1.49	0.116	14.9	0.07

Note: *participant's sex, age, maternal psychopathology (assessed through an interview question with dichotomous self-rating), maternal alcohol consumption during first three month after giving birth, week of pregnancy at birth, smoking habits of participants and alcohol intake; *B* represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

2.2.5 Discussion

This study investigated the long-term effects of maternal smoking during pregnancy on brain activity and internalizing and externalizing behavior symptoms in young adults. The research builds upon existing studies that focused on prenatal tobacco exposure in infants and school-aged children. The present study explored potential dose-dependent effects on both resting-state EEG power spectrum and YASR scales during adulthood by comparing three groups – non-smoking mothers, those who smoked 1-5 cigarettes daily, and those who smoked more than 5 cigarettes daily.

The results showed an influence of smoking during pregnancy on the power bands of delta and theta in the brain, suggesting reduced slower brain activity in individuals exposed to prenatal smoking compared to those who were not exposed. However, after accounting for covariates, this impact was persistent only in the delta power band. Moreover, adults with prenatal smoking exposure demonstrated higher levels of externalizing behavior. Although this link was strongly affected by factors such as maternal psychopathology, the child's gender, and the child's substance use, the influence on the delta power band persisted even after adjusting for these covariates. Our findings are consistent with previous studies (Pini et al., 2024; Shuffrey et al., 2020), and particularly our recent study in children (Jansone et al., 2023), which identified significant effects in resting-state EEG power bands (delta and theta) as direct effects, independent of potential covariates such as child's sex, age, maternal age, smoking habits before pregnancy, alcohol consumption during pregnancy, gestation age, and psychopathology.

The prior study reported increased delta and theta brain activity in school-aged participants prenatally exposed to tobacco. Similarly, we found significant differences in delta and theta frequency bands between prenatally exposed and unexposed children. However, unlike in school-aged children, this study observed decreased brain activity in prenatally smoking exposed adults in the delta and theta (frontal) frequency bands, suggesting developmental stage-dependent effects. These differences align with prior research indicating a consistent decrease in delta and theta bands from childhood to late adolescence (Mason et al., 2022; Zhong & Chen, 2020). The persistence of delta power band alterations despite controlling for covariates underscores the potential long-term neurophysiological impact of prenatal smoking. Delta waves are typically associated with deep sleep and restorative processes (Knyazev, 2012), and reduced activity in this band could indicate disruptions in these functions, potentially leading to deficits in cognitive performance and emotional regulation. It could therefore be related to cognitive processes such as attention, memory, and executive function (Harmony, 2013), which are critical during development (Thompson & Steinbeis, 2020) and also for several psychopathologies including ADHD (Breteler et al., 2012), autism spectrum disorder (Coben et al., 2008) and mood disorders (Armitage et al., 2001). Further investigation are needed to elucidate the respective mechanisms and how these changes manifest in adulthood using task-based assessments.

The second aim of the study was to explore the long-term effects of prenatal tobacco exposure on behavioral patterns in adults. Behavioral assessments revealed significant associations between prenatal smoking and increased externalizing behavioral problems in prenatally tobacco exposed adults. However, after adjusting for covariates, such as maternal psychopathology, and child's substance use, these effects became non-significant. This suggests that maternal smoking during pregnancy did not directly affect behavioral development, but that it might be driven by psychosocial factors.

While factors like maternal psychopathology and additional risk behaviors may contribute to behavioral problems, the study suggests that the influence of maternal smoking on brain activity has a more direct and lasting effect. The complex interplay between genetic predisposition and environmental influences highlighted in prior studies emphasizes the intricate relationship between prenatal environmental factors and psychiatric vulnerability. This interplay is evident in neurodevelopmental disorders such as ADHD, where maternal smoking in pregnancy might not be causally linked to offspring ADHD, but rather influenced by shared inherited liability and genetic risk variants for both nicotine dependence and ADHD (D’Onofrio et al., 2008; Thapar et al., 2009).

Moreover, findings from sibling studies (D’Onofrio et al., 2003; Lambe et al., 2006) further underscore the complexity of these relationships . Examining siblings discordant for exposure to smoking in pregnancy suggests that maternal smoking in pregnancy might be indexing unmeasured familial risk not captured by conventional confounders. Siblings not exposed to smoking in pregnancy but from families where the mother smoked in another pregnancy show increased attentional, behavioral, and scholastic problems (D’Onofrio et al., 2003; Lambe et al., 2006). Therefore, when considering results from all these designs collectively, a consistent pattern of findings emerges, suggesting that the association between maternal smoking in pregnancy and offspring ADHD, in contrast to offspring neurophysiological development, might not be entirely causal. The shared inherited liability between maternal smoking in pregnancy and offspring ADHD symptoms also raises the possibility that there are genetic risk variants that confer susceptibility to both nicotine dependence and ADHD.

Recognizing certain limitations, such as sample size discrepancies and the absence of paternal smoking data, future longitudinal studies with larger and diverse samples are essential for further unraveling the complex relationships between maternal smoking, brain activity, and behavioral development across different age groups. Another limitation is related to the assessment of maternal psychopathology. In our study, maternal psychopathology was evaluated using a binary "yes/no" classification to control for the presence or absence of maternal psychopathology in general, rather than specifying particular types of psychiatric disorders (see also Jansone et al., 2023). Future research with a larger sample of children exposed to maternal smoking could involve categorizing psychopathological conditions more precisely to further specify the observed effects in relation to the presence of a mental diagnosis in the mother.

Additionally, it is important to note that the smoking assessment did not capture the exact number of cigarettes smoked. Instead, smoking habits were categorized into groups (according to Holz et al., 2014). Although, we had clear hypotheses based on the previous studies with respect to the present categorization, it still limits the possibility of distinguishing further dose-dependent effects or of effects of smoking exposure in general, independent of the dosage, compared to no-exposure at all. To additionally examine potential general effects of smoking exposure versus non-exposure, we conducted an add on analysis comparing two groups, those who were exposed to maternal smoking (combining the groups of mothers who smoked 1-5 cigarettes daily, and those who smoked more than 5 cigarettes daily) versus those who were not exposed to maternal smoking. The results of this two-group comparison are presented in the supplementary materials (see Supplemental material, Tables S4-S9). When comparing the two (prenatally tobacco exposed vs. unexposed) and three group (group of non-smoking mothers, mothers who smoked 1-5 cigarettes daily, and those who smoked more than 5 cigarettes daily) analyses, the unadjusted analyses of the EEG power spectrum during the eyes open condition in the three-group approach revealed significant differences in the delta and theta frequency bands, while the two-group approach showed significant differences in the theta and alpha frequency bands. Specifically, the exposed group exhibited lower theta and alpha power across various brain regions compared to the unexposed group in the two-group analysis. After adjusting for covariates, the significant differences in theta and alpha power observed in the unadjusted models were no longer significant in both approaches, though the significant effect in the delta band remained in the adjusted models in the three-group approach. In the eyes closed condition, the three-group analysis revealed no significant differences in the unadjusted or adjusted models, whereas the two-group analysis showed significant differences in the theta and alpha frequency bands in the unadjusted model, which also became insignificant after adjusting for covariates. For the YASR subscales, the three-group analysis showed significant differences in externalizing behavior in the unadjusted models, which became insignificant after adjusting for covariates. In contrast, the two-group analysis revealed significant differences in several factors, including anxious, withdrawn, thought, internalizing, and externalizing behaviors in the unadjusted models, with these differences becoming insignificant after adjusting for covariates. These findings suggest that there are both specific and overlapping neural and behavioral correlates related to smoking exposure depending on the amount of exposure versus smoking exposure per se. With respect to the dosage of smoking, current assessments often do not allow for a detailed analysis of linear associations, instead using a cut-off approach as in the present study, with up to 5 and over 5 cigarettes smoked per day. Given the partially different findings when considering dosage information versus a “yes/no” smoking status, it might be beneficial to integrate more fine-grained dosage information in future studies. Future longitudinal studies with larger sample sizes could also integrate additional control variables for developmental changes to better understand the dynamic interplay between early exposures, such as maternal smoking, and various maternal factors over the course of a child’s development. By examining developmental trajectories over extended periods, researchers can identify how early life exposures interact with maternal and environmental factors to influence long-term outcomes.

In conclusion, this study extends the perspective to longer term neurophysiological effects of maternal smoking during pregnancy on brain activity and behavioral patterns in young adults. The findings suggest that prenatal smoking exposure may have stable effects on brain activity patterns in young adulthood. Conversely, the influence on externalizing behaviors appears to be more strongly influenced by familial factors (maternal psychopathology) and the lifestyle of the individual (substance use).

3 GENERAL DISCUSSION

This dissertation investigates the long-term effects of prenatal tobacco exposure on both neurophysiological and behavioral outcomes in school age and young adulthood. Drawing from the results of two studies, this work highlights the significant associations between prenatal smoking and alterations in brain activity, specifically in the delta and theta frequency bands of EEG, as well as increased externalizing behavioral problems. These findings suggest that prenatal tobacco exposure is linked not only to immediate neurodevelopmental disruptions but also to long-lasting changes in both brain function and behavior, with complex interactions between genetic, familial, and environmental factors.

Neurophysiological Effects of Prenatal Tobacco Exposure

The results of the EEG analyses demonstrated persistent changes in the delta and theta frequency bands in individuals prenatally exposed to tobacco, indicating a reduction in slower brain activity. These findings are consistent with existing literature that suggests prenatal tobacco exposure can have lasting effects on brain maturation, particularly in regions associated with cognitive functions, emotional regulation, and sleep. Specifically, the decrease in delta band activity observed in young adults aligns with prior research that associates delta waves with restorative processes, such as deep sleep, memory consolidation, and cognitive functioning. Disruptions in these processes could have lasting effects on attention, memory, and emotional regulation, which are crucial for development throughout life.

The decreased delta and theta power in adults with prenatal tobacco exposure suggests that the effects of prenatal smoking extend beyond early childhood and may reflect a persistent alteration in brain maturation. Interestingly, the second study found increased delta and theta activity in early adulthood, suggesting that prenatal tobacco exposure may initially speed up certain neural processes, which later result in a depletion or stunting of neurodevelopmental progress in adulthood. This observation emphasizes that the impacts of prenatal tobacco exposure are not necessarily linear and may differ across developmental stages, with initial compensatory mechanisms followed by long-term deficits.

Behavioral Effects and Moderation by Familial Factors

Beyond the neurophysiological changes, the present study also investigated the behavioral consequences of prenatal tobacco exposure, particularly focusing on internalizing and externalizing. The findings revealed that prenatal exposure to tobacco was associated with increased externalizing behaviors, including attention problems and delinquency. However, after adjusting for covariates such as maternal psychopathology, substance use, and other familial factors, the direct effect of prenatal tobacco exposure on behavioral outcomes became less pronounced. This suggests that while prenatal smoking may play a role in shaping behavioral vulnerability, the effect is likely mediated by a complex interplay of genetic predispositions and environmental influences, including maternal mental health and the child’s own substance use.

The moderation of prenatal smoking's impact on behavior by maternal psychopathology is an important finding of this research. It aligns with the broader literature suggesting that maternal mental health during pregnancy can significantly influence offspring development, particularly in terms of behavioral regulation (Gartstein & Skinner, 2018). The results underscore the importance of considering prenatal exposures within the context of broader familial risk factors. Maternal psychopathology, in particular, may increase the likelihood of behavioral problems in children, not only through direct genetic transmission but also by influencing the prenatal environment (e.g., stress, substance use), and may even interact with prenatal tobacco exposure to produce compounded effects.

Moreover, the role of the child's substance use in moderating these effects highlights the ongoing interaction between prenatal influences and postnatal behaviors. It is well-established that substance use in adolescence and young adulthood can exacerbate pre-existing vulnerabilities, suggesting that individuals exposed to prenatal smoking may be more susceptible to developing addictive behaviors or mood disorders later in life. These findings point to the importance of early intervention and prevention programs that address both prenatal and postnatal risk factors, particularly those targeting substance use and mental health in vulnerable populations.

Dose-Dependent Effects of Prenatal Smoking and Methodological Considerations

One of the key methodological strengths of this dissertation was the use of a dose-dependent approach to examine the effects of prenatal tobacco exposure. By comparing individuals exposed to different quantities of maternal smoking (1-5 cigarettes/day vs. >5 cigarettes/day), we observed that higher levels of exposure were associated with more pronounced alterations in brain activity, particularly in the delta frequency band. This finding suggests that there may be a dose-response relationship between prenatal smoking and neurophysiological outcomes, with heavier exposure leading to more significant brain activity alterations.

However, the categorical nature of the smoking assessment — grouping participants into only two categories based on daily cigarette consumption — limits our ability to fully capture the range of exposure levels and potential linear dose-response effects. Future studies should aim to include more refined measures of tobacco exposure, including precise self-reports or biomarkers that can assess the exact quantity of smoking and its impact more accurately. A continuous measure of smoking exposure could allow for a more nuanced understanding of the relationship between the degree of exposure and long-term outcomes.

3.1 SUMMARY OF FINDINGS AND RELEVANCE

The studies in the present work provide critical insights into the long-term neurodevelopmental and behavioral consequences of prenatal smoking exposure, particularly with regard to neurophysiological markers and ADHD-related outcomes across the lifespan. These findings underline the lasting impact of maternal smoking on brain activity and behavioral patterns in children and young adults.

The first study focused on school-aged children, exploring how maternal smoking during pregnancy affected EEG brain activity and ADHD-related symptoms. The results revealed that children exposed to prenatal tobacco use exhibited significantly higher brain activity in the delta and theta frequency bands compared to their non-exposed peers. These changes in brain activity were independent of key covariates, such as the child’s sex, age, and maternal psychopathology, suggesting that prenatal exposure to smoking has a direct impact on resting-state brain function. Furthermore, the study demonstrated that while prenatal smoking was associated with increased hyperactivity, the degree of this symptomatology was modulated by other maternal factors, including maternal age and alcohol consumption during pregnancy. This highlights the complex interaction between genetic, environmental, and prenatal factors in shaping neurodevelopment.

The second study expanded on the same cohort into young adulthood, further explored the enduring effects of prenatal smoking exposure on brain activity and behavioral outcomes. This research specifically examined the EEG power at rest and its association with internalizing and externalizing problem symptoms. The results indicated that young adults who had been prenatally exposed to smoking displayed altered brain activity, particularly in the delta and theta frequency bands, consistent with the findings observed in the school-aged sample. Notably, these brain activity changes were linked to higher levels of externalizing behaviors, such as aggression and impulsivity. However, these behavioral effects were strongly influenced by maternal psychopathology, the child’s gender, and their own substance use, pointing to a complex, multi-layered interaction between prenatal exposures and later-life behavioral outcomes.

Importantly, the study found that while prenatal smoking exposure had a measurable effect on brain activity, the behavioral outcomes were more variable and depended on familial factors, including the mental health status of the mother and lifestyle choices made by the individual during their development. This suggests that while prenatal smoking may set the stage for long-term neurophysiological changes, the full expression of these effects is likely influenced by a range of social and environmental factors.

Together, these studies underscore the importance of considering prenatal exposures in the context of neurodevelopmental outcomes across the lifespan. The alterations in brain activity observed in both school-aged children and young adults highlight how early environmental factors, such as maternal smoking, can lead to lasting changes in brain function. Furthermore, the variability in behavioral outcomes — particularly in relation to ADHD-related symptoms and externalizing behaviors — points to the significant role of socio-demographic and familial factors in mediating these effects. These findings align with the growing body of research suggesting that prenatal smoking is a critical risk factor for neurodevelopmental disorders, with implications for early intervention and public health strategies aimed at reducing maternal tobacco smoking rates during pregnancy.

3.2 LIMITATIONS

Despite the valuable contributions of this dissertation, several limitations should be considered. First, while this study examines the effects of prenatal smoking on brain activity and behavior, it does not capture the full complexity of prenatal environmental exposures, including factors like maternal nutrition, stress, and alcohol use. Future research should expand on these variables to provide a more comprehensive understanding of the multifaceted prenatal environment and its influence on neurodevelopment. One of the primary limitations in both studies is the difficulty in establishing causality. Although prenatal smoking is associated with altered EEG patterns and behavioral outcomes, the presence of confounding factors complicates the interpretation of these relationships. For example, maternal psychopathology, substance use, and other socio-demographic variables (such as maternal age and alcohol consumption) were found to influence the outcomes in both studies. This suggests that while prenatal smoking may be a significant factor, the behavioral and neurophysiological outcomes observed may also be shaped by these other variables, making it challenging to isolate the specific contribution of smoking alone. Moreover, the role of genetics in the observed outcomes remains unclear and warrants further investigation. Another limitation is the homogeneity of the study samples. Both studies focused on cohorts from longitudinal studies with specific inclusion criteria, which may limit the generalizability of the findings to broader populations. The sample size in both studies was relatively moderate (e.g., 176 participants in the second study), and the participants were predominantly from specific geographical regions (Germany), which may not represent the diversity of maternal smoking effects in different cultural or socio-economic contexts. Additionally, the studies primarily focused on participants with relatively similar backgrounds, which limits the ability to generalize the findings to populations with more diverse socio-economic, ethnic, or genetic characteristics.

The reliance on self-reported measures, both in terms of maternal smoking habits and participant behavior, poses another limitation. Self-reports are inherently susceptible to recall bias and social desirability bias, where participants may underreport smoking or other behaviors that they perceive as undesirable. This can lead to an underestimation of the true extent of prenatal smoking exposure and its potential effects on neurodevelopmental outcomes. While the studies controlled for some of these biases by including a range of covariates, such as maternal psychopathology and substance use, the potential for inaccuracies in reporting remains.

EEG is a powerful tool for assessing brain activity, but it also has limitations in its ability to capture the full complexity of brain function. While the studies reported significant differences in delta and theta band power in prenatally exposed individuals, EEG only provides a snapshot of brain activity and cannot directly measure cognitive function or higher-order brain processes such as executive function or attention. Thus, while EEG changes are a useful marker for altered brain activity, they do not necessarily provide a direct link to specific behavioral outcomes, such as ADHD symptoms or externalizing behaviors. Future research could benefit from incorporating additional neuroimaging techniques, such as fMRI or PET scans, to provide a more comprehensive understanding of the neural mechanisms underlying these behavioral outcomes. Finally, the studies did not extensively consider the potential influence of postnatal environmental factors on the observed outcomes. The participants were exposed to a wide range of environmental influences after birth, such as parenting practices, education, and peer relationships, all of which may have contributed to their behavioral and neurophysiological development. Although the studies controlled for several maternal and demographic variables, the cumulative effect of these postnatal factors remains underexplored and could influence the observed results. Future studies could benefit from a more holistic approach, considering not only prenatal exposures but also the full range of environmental influences throughout the life course.

3.3 OUTLOOK

To build on the existing findings, further longitudinal studies should track individuals over a more extended period, from early childhood into adulthood, to better understand the full scope of the long-term effects of prenatal smoking. This approach would help to pinpoint critical windows of vulnerability and provide a clearer picture of how early neurophysiological changes, such as those observed in EEG patterns, correlate with the emergence of behavioral problems like ADHD or anxiety in later stages of life. Given the role of genetic predisposition in shaping the neurodevelopmental outcomes of children exposed to prenatal smoking, future research should explore gene-environment interactions in more detail. Research into specific genetic markers that may influence how an individual responds to prenatal exposures could help identify those at highest risk for developing neurodevelopmental disorders. For example, gene-environment studies could investigate how maternal smoking interacts with genetic variants related to dopamine regulation, which has been implicated in ADHD. Understanding these interactions could lead to more personalized approaches to prevention and treatment. The influence of socio-demographic factors, such as maternal age, socioeconomic status, and postnatal environmental influences (e.g., parenting styles, education, and peer interactions), requires further exploration. While these studies accounted for several covariates, a deeper investigation into how these variables interact with prenatal exposures could reveal pathways for intervention. Longitudinal data that also tracks postnatal development, such as caregiving environments and school experiences, would be invaluable in understanding the complex cascade of effects that prenatal smoking can have over the lifespan.

3.4 CONCLUSIONS

The research conducted for the present work significantly contributes to the understanding of the long-term impact of maternal smoking during pregnancy on both neurophysiological and behavioral outcomes in offspring. The studies examined two distinct developmental stages — school-aged children and young adults — highlighting how prenatal smoking can shape brain activity and behavioral tendencies, such as ADHD symptoms and externalizing behaviors, across the lifespan.

Key findings from these studies show that children exposed to maternal smoking exhibit distinctive EEG patterns, with increased delta and theta brain activity in school age, and with decreased delta and theta brain activity in early adulthood. Furthermore, these neurophysiological alterations are not isolated; they interact with socio-demographic factors, maternal psychopathology, and postnatal environments, indicating that the outcomes are multifactorial and complex. These results align with existing research, which also suggests that maternal smoking during pregnancy can increase the risk for ADHD, cognitive deficits, and emotional dysregulation in offspring (Biederman et al., 2006; Langley et al., 2012).

In addition to providing important clinical insights, these studies underscore the need for preventive measures and early interventions targeting maternal smoking cessation and support for children affected by prenatal smoking exposure. Although both studies offer strong evidence of the long-term consequences of prenatal smoking, they also highlight the complexity of these effects, shaped by a range of genetic, environmental, and behavioral factors.

Ultimately, the findings presented here are a reminder of the importance of prenatal care and the far-reaching impact that maternal health behaviors can have on child development. While progress has been made in understanding these effects, ongoing research is needed to refine our knowledge and develop effective strategies to prevent and manage the neurodevelopmental consequences of maternal smoking. Addressing this public health issue requires not only individual-focused interventions but also systemic efforts aimed at reducing smoking during pregnancy, thus decreasing the burden of related neurodevelopmental disorders.

4 SUMMARY

4.1 SUMMARY

This dissertation investigates the profound impact of maternal prenatal smoking on offspring neurodevelopment and behavioral outcomes, focusing on neurophysiological markers and ADHD-related symptoms in children and young adults. The research draws upon two studies that explore the effects of prenatal tobacco exposure on EEG brain activity and behavior across different stages of development.

The dissertation begins by addressing the critical significance of prenatal development, emphasizing the biological mechanisms at play during neurodevelopmental stages. The vulnerability of the developing brain to environmental influences, particularly tobacco exposure, is highlighted as a key area of concern. Maternal smoking during pregnancy has been shown to interfere with typical brain development, leading to lasting changes in brain activity that manifest in various cognitive and behavioral symptoms, including attention deficits and emotional regulation problems. A key focus of the research is the prenatal environment and the early-life risk factors that shape development. Maternal tobacco smoking is identified as a significant prenatal risk factor with long-lasting effects on offspring neurodevelopment. These effects are not only biological but also behavioral, contributing to the development of neurodevelopmental disorders such as ADHD, and externalizing behaviors such as aggression and impulsivity. The dissertation further explores the complex causal role of maternal prenatal smoking, with an emphasis on its contribution to behavioral problems across the lifespan. The long-term impacts of prenatal smoking are examined, showing how these early-life exposures influence neurophysiological and behavioral outcomes well into adulthood. The studies reviewed here highlight the persistent alterations in brain activity, particularly in the delta and theta frequency bands, and how these changes are linked to ADHD-related symptoms and externalizing behaviors. These findings underline the importance of early intervention and the need for strategies that target maternal smoking cessation to mitigate these risks.

Through its comprehensive analysis, this dissertation emphasizes the importance of understanding the mechanisms through which prenatal tobacco exposure affects neurodevelopment. By considering both biological and environmental factors, the research contributes valuable insights into how prenatal smoking leads to long-term cognitive and behavioral consequences.

4.2 ZUSAMMENFASSUNG

Diese Dissertation untersucht die tiefgreifenden Auswirkungen des mütterlichen pränatalen Rauchens auf die neurodevelopmentale Entwicklung und die Verhaltensweisen des Nachwuchses, mit einem Schwerpunkt auf neurophysiologischen Markern und ADHS-bezogenen Symptomen bei Kindern und jungen Erwachsenen. Die Forschung basiert auf zwei Studien, die die Auswirkungen der pränatalen Tabakexposition auf die EEG-Hirnaktivität und das Verhalten in verschiedenen Entwicklungsstadien untersuchen.

Die Dissertation beginnt mit der Thematisierung der kritischen Bedeutung der pränatalen Entwicklung, wobei die biologischen Mechanismen, die während der neurodevelopmentalen Stadien wirken, hervorgehoben werden. Die Verletzlichkeit des sich entwickelnden Gehirns gegenüber Umwelteinflüssen, insbesondere der Tabakexposition, wird als zentrales Anliegen betont. Es wird gezeigt, dass das mütterliche Rauchen während der Schwangerschaft die typische Gehirnentwicklung beeinträchtigen kann, was zu langfristigen Veränderungen der Hirnaktivität führt. Diese Veränderungen äußern sich in verschiedenen kognitiven und Verhaltenssymptomen, darunter Aufmerksamkeitsdefizite und Probleme bei der emotionalen Regulation. Ein zentraler Fokus der Forschung liegt auf der pränatalen Umgebung und den frühen Risikofaktoren, die die Entwicklung prägen. Das mütterliche Tabakrauchen wird als signifikanter pränataler Risikofaktor identifiziert, der langfristige Auswirkungen auf die neurodevelopmentale Entwicklung des Nachwuchses hat. Diese Effekte sind nicht nur biologischer, sondern auch verhaltensbezogener Natur und tragen zur Entwicklung neurodevelopmentaler Störungen wie ADHS sowie externalisierenden Verhaltensweisen wie Aggression und Impulsivität bei.

Die Dissertation untersucht darüber hinaus die komplexe kausale Rolle des mütterlichen pränatalen Rauchens und legt den Schwerpunkt auf dessen Beitrag zu Verhaltensproblemen über die gesamte Lebensspanne hinweg. Die langfristigen Auswirkungen des pränatalen Rauchens werden analysiert und zeigen, wie diese frühkindlichen Expositionen neurophysiologische und verhaltensbezogene Ergebnisse bis ins Erwachsenenalter beeinflussen. Die hier betrachteten Studien verdeutlichen die

anhaltenden Veränderungen der Hirnaktivität, insbesondere in den Delta- und Theta-Frequenzbändern, und wie diese Veränderungen mit ADHS-bezogenen Symptomen und externalisierenden Verhaltensweisen verknüpft sind. Diese Ergebnisse unterstreichen die Bedeutung früher Interventionen und die Notwendigkeit von Strategien, die auf die Raucherentwöhnung von Müttern abzielen, um diese Risiken zu mindern.

Durch ihre umfassende Analyse betont diese Dissertation die Bedeutung des Verständnisses der Mechanismen, durch die pränatale Tabakexposition die neurodevelopmentale Entwicklung beeinflusst. Indem sowohl biologische als auch umweltbedingte Faktoren berücksichtigt werden, liefert die Forschung wertvolle Einblicke in die langfristigen kognitiven und verhaltensbezogenen Konsequenzen des pränatalen Rauchens.

5 LITERATURE

Abbott, R., & Burkitt, E. (2023). *Child Development and the Brain: From Embryo to Adolescence*. Policy Press.

Abraham, M., Alramadhan, S., Iniguez, C., Duijts, L., Jaddoe, V. W. V., Dekker, H. T. D., Crozier, S., Godfrey, K. M., Hindmarsh, P., Vik, T., Jacobsen, G. W., Hanke, W., Sobala, W., Devereux, G., & Turner, S. (2017). A systematic review of maternal smoking during pregnancy and fetal measurements with meta-analysis. *PLOS ONE*, *12*(2), e0170946. https://doi.org/10.1371/journal.pone.0170946

Achenbach, T.M. (1997) Manual for the young adult self-report and young adult behaviour checklist. Department of Psychiatry, University of Vermont, Burlington. - References—Scientific Research Publishing. (o. J.). Abgerufen 21. November 2023, von https://scirp.org/reference/referencespapers.aspx?referenceid=721748

Albers, L., Sobotzki, C., Kuß, O., Ajslev, T., Batista, R. F., Bettiol, H., Brabin, B., Buka, S. L., Cardoso, V. C., Clifton, V. L., Devereux, G., Gilman, S. E., Grzeskowiak, L. E., Heinrich, J., Hummel, S., Jacobsen, G. W., Jones, G., Koshy, G., Morgen, C. S., … von Kries, R. (2018). Maternal smoking during pregnancy and offspring overweight: Is there a dose-response relationship? An individual patient data meta-analysis. *International Journal of Obesity (2005)*, *42*(7), 1249–1264. https://doi.org/10.1038/s41366-018-0050-0

Aldemir, R., Demirci, E., Per, H., Canpolat, M., Özmen, S., & Tokmakçı, M. (2018). Investigation of attention deficit hyperactivity disorder (ADHD) sub-types in children via EEG frequency domain analysis. *International Journal of Neuroscience*, *128*(4), 349–360. https://doi.org/10.1080/00207454.2017.1382493

ANEF, C. K., PhD, RN, FAAN, FNAP, NE-BC, L. A., DNP, RNC, MSN, & RN, M. V. B., PhD. (2019). *Comprehensive Neonatal Nursing Care*. Springer Publishing Company.

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment*, *9*, 449–461. https://doi.org/10.2147/NDT.S39776

Armitage, R., Emslie, G. J., Hoffmann, R. F., Rintelmann, J., & Rush, A. J. (2001). Delta sleep EEG in depressed adolescent females and healthy controls.

Journal of Affective Disorders, *63*(1), 139–148. https://doi.org/10.1016/S0165-0327(00)00194-4

Atluri, P., Fleck, M. W., Shen, Q., Mah, S. J., Stadfelt, D., Barnes, W., Goderie, S. K., Temple, S., & Schneider, A. S. (2001). Functional Nicotinic Acetylcholine Receptor Expression in Stem and Progenitor Cells of the Early Embryonic Mouse Cerebral Cortex. *Developmental Biology*, *240*(1), 143–156. https://doi.org/10.1006/dbio.2001.0453

Baayen, H., Vasishth, S., Kliegl, R., & Bates, D. (2017). The cave of shadows: Addressing the human factor with generalized additive mixed models. *Journal of Memory and Language*, *94*, 206–234. https://doi.org/10.1016/j.jml.2016.11.006

Baillet, S., Mosher, J. C., & Leahy, R. M. (2001). Electromagnetic brain mapping. *IEEE Signal Processing Magazine*, *18*(6), 14–30. IEEE Signal Processing Magazine. https://doi.org/10.1109/79.962275

Banderali, G., Martelli, A., Landi, M., Moretti, F., Betti, F., Radaelli, G., Lassandro, C., & Verduci, E. (2015). Short and long term health effects of parental tobacco smoking during pregnancy and lactation: A descriptive review. *Journal of Translational Medicine*, *13*, 327. https://doi.org/10.1186/s12967-015-0690-y

Barch, D. M., Albaugh, M. D., Baskin-Sommers, A., Bryant, B. E., Clark, D. B., Dick, A. S., Feczko, E., Foxe, J. J., Gee, D. G., Giedd, J., Glantz, M. D., Hudziak, J. J., Karcher, N. R., LeBlanc, K., Maddox, M., McGlade, E. C., Mulford, C., Nagel, B. J., Neigh, G., … Xie, L. (2021). Demographic and mental health assessments in the adolescent brain and cognitive development study: Updates and age-related trajectories. *Developmental Cognitive Neuroscience*, *52*, 101031. https://doi.org/10.1016/j.dcn.2021.101031

Barry, R. J., Clarke, A. R., Johnstone, S. J., Brown, C. R., Bruggemann, J. M., & van Rijbroek, I. (2009). Caffeine effects on resting-state arousal in children. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *73*(3), 355–361. https://doi.org/10.1016/j.ijpsycho.2009.05.012

Biederman, J., Monuteaux, M. C., Mick, E., Spencer, T., Wilens, T. E., Silva, J. M., Snyder, L. E., & Faraone, S. V. (2006). Young adult outcome of attention deficit hyperactivity disorder: A controlled 10-year follow-up study.

Psychological Medicine, *36*(2), 167–179. https://doi.org/10.1017/S0033291705006410

Blackburn, S. T. (2007). *Maternal, Fetal, & Neonatal Physiology: A Clinical Perspective*. Elsevier Health Sciences.

Brannigan, R., Tanskanen, A., Huttunen, M. O., Cannon, M., Leacy, F. P., & Clarke, M. C. (2022). Maternal smoking during pregnancy and offspring psychiatric disorder: A longitudinal birth cohort study. *Social Psychiatry and Psychiatric Epidemiology*, *57*(3), 595–600. https://doi.org/10.1007/s00127-021-02094-w

Braun, M., Klingelhöfer, D., Oremek, G. M., Quarcoo, D., & Groneberg, D. A. (2020). Influence of Second-Hand Smoke and Prenatal Tobacco Smoke Exposure on Biomarkers, Genetics and Physiological Processes in Children-An Overview in Research Insights of the Last Few Years. *International Journal of Environmental Research and Public Health*, *17*(9), 3212. https://doi.org/10.3390/ijerph17093212

Breteler, R., Pesch, W., Nadorp, M., Best, N., & Tomasoa, X. (2012). Neurofeedback in Residential Children and Adolescents with Mild Mental Retardation and ADHD Behavior. *Journal of Neurotherapy*, *16*(3), 172–182. https://doi.org/10.1080/10874208.2012.705742

Breuer, D., & Döpfner, M. (2008). Entwicklung eines Fragebogens zur Erfassung von Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (ADHS) bei Vorschulkindern im Eltern- und im Erziehungsurteil. In *Zeitschrift für Entwicklungspsychologie und pädagogische Psychologie* (Bd. 40, Nummer 1, S. 40–48).

Bridwell, D. A., Cavanagh, J. F., Collins, A. G. E., Nunez, M. D., Srinivasan, R., Stober, S., & Calhoun, V. D. (2018). Moving Beyond ERP Components: A Selective Review of Approaches to Integrate EEG and Behavior. *Frontiers in Human Neuroscience*, *12*, 106. https://doi.org/10.3389/fnhum.2018.00106

Brown, T. T., & Jernigan, T. L. (2012). Brain development during the preschool years. *Neuropsychology review*, *22*(4), 313–333. https://doi.org/10.1007/s11065-012-9214-1

Bublitz, M. H., & Stroud, L. R. (2012). Maternal Smoking During Pregnancy and Offspring Brain Structure and Function: Review and Agenda for Future Research. *Nicotine & Tobacco Research*, *14*(4), 388–397. https://doi.org/10.1093/ntr/ntr191

Burke, H., Leonardi-Bee, J., Hashim, A., Pine-Abata, H., Chen, Y., Cook, D. G., Britton, J. R., & McKeever, T. M. (2012). Prenatal and passive smoke exposure and incidence of asthma and wheeze: Systematic review and meta-analysis. *Pediatrics*, *129*(4), 735–744. https://doi.org/10.1542/peds.2011-2196

Burt, S. A. (2022). The Genetic, Environmental, and Cultural Forces Influencing Youth Antisocial Behavior Are Tightly Intertwined. *Annual Review of Clinical Psychology*, *18*(Volume 18, 2022), 155–178. https://doi.org/10.1146/annurev-clinpsy-072220-015507

Button, T. M. M., Maughan, B., & McGuffin, P. (2007). The relationship of maternal smoking to psychological problems in the offspring. *Early Human Development*, *83*(11), 727–732. https://doi.org/10.1016/j.earlhumdev.2007.07.006

Chen, C. (2000). Generalized additive mixed models. *Communications in Statistics-theory and Methods - COMMUN STATIST-THEOR METHOD*, *29*, 1257–1271. https://doi.org/10.1080/03610920008832543

Cheraghi, M., & Salvi, S. (2009). Environmental tobacco smoke (ETS) and respiratory health in children. *European Journal of Pediatrics*, *168*(8), 897–905. https://doi.org/10.1007/s00431-009-0967-3

Cicchetti, D. (2016). Socioemotional, Personality, and Biological Development: Illustrations from a Multilevel Developmental Psychopathology Perspective on Child Maltreatment. *Annual Review of Psychology*, *67*(Volume 67, 2016), 187–211. https://doi.org/10.1146/annurev-psych-122414-033259

Clarke, A., Barry, R., McCarthy, R., & Solikowitz, M. (2011). Correlation between EEG activity and behavior in children with attention-deficit/hyperactivity disorder. *Faculty of Health and Behavioural Sciences - Papers (Archive)*, 193–199. https://doi.org/10.1080/10874208.2011.595295

Clifford, A., Lang, L., & Chen, R. (2012). Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: A literature review. *Neurotoxicology and Teratology*, *34*(6), 560–570. https://doi.org/10.1016/j.ntt.2012.09.004

Coben, R., Clarke, A. R., Hudspeth, W., & Barry, R. J. (2008). EEG power and coherence in autistic spectrum disorder. *Clinical Neurophysiology*, *119*(5), 1002–1009. https://doi.org/10.1016/j.clinph.2008.01.013

Connolly, K. J., & Valsiner, J. (2002). *Handbook of Developmental Psychology*. 1–682.

Cornelius, M. D., & Day, N. L. (2009). Developmental consequences of prenatal tobacco exposure. *Current Opinion in Neurology*, *22*(2), 121–125. https://doi.org/10.1097/WCO.0b013e328326f6dc

Cornelius, M. D., Goldschmidt, L., & Day, N. L. (2012). Prenatal cigarette smoking: Long-term effects on young adult behavior problems and smoking behavior. *Neurotoxicology and Teratology*, *34*(6), 554–559. https://doi.org/10.1016/j.ntt.2012.09.003

Cortese, S. (2012). The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): What every clinician should know. *European Journal of Paediatric Neurology*, *16*(5), 422–433. https://doi.org/10.1016/j.ejpn.2012.01.009

Crume, T. (2019). Tobacco Use During Pregnancy. *Clinical Obstetrics and Gynecology*, *62*(1), 128. https://doi.org/10.1097/GRF.0000000000000413

Dahl, R. E. (2004). Adolescent Brain Development: A Period of Vulnerabilities and Opportunities. Keynote Address. *Annals of the New York Academy of Sciences*, *1021*(1), 1–22. https://doi.org/10.1196/annals.1308.001

Dall'Aglio, L., Muka, T., Cecil, C. A. M., Bramer, W. M., Verbiest, M. M. P. J., Nano, J., Hidalgo, A. C., Franco, O. H., & Tiemeier, H. (2018). The role of epigenetic modifications in neurodevelopmental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, *94*, 17–30. https://doi.org/10.1016/j.neubiorev.2018.07.011

Derauf, C., Lester, B. M., Neyzi, N., Kekatpure, M., Gracia, L., Davis, J., Kallianpur, K., Efird, J. T., & Kosofsky, B. (2012). Subcortical and cortical structural central nervous system changes and attention processing deficits in preschool-aged children with prenatal methamphetamine and tobacco exposure. *Developmental Neuroscience*, *34*(4), 327–341. https://doi.org/10.1159/000341119

Dodge, K. A., & Pettit, G. S. (2003). A biopsychosocial model of the development of chronic conduct problems in adolescence. *Developmental Psychology*, *39*(2), 349–371. https://doi.org/10.1037/0012-1649.39.2.349

Dolan, C. V., Geels, L., Vink, J. M., van Beijsterveldt, C. E. M., Neale, M. C., Bartels, M., & Boomsma, D. I. (2016). Testing Causal Effects of Maternal Smoking

During Pregnancy on Offspring's Externalizing and Internalizing Behavior. *Behavior Genetics*, *46*(3), 378–388. https://doi.org/10.1007/s10519-015-9738-2

Dong, T., Hu, W., Zhou, X., Lin, H., Lan, L., Hang, B., Lv, W., Geng, Q., & Xia, Y. (2018). Prenatal exposure to maternal smoking during pregnancy and attention-deficit/hyperactivity disorder in offspring: A meta-analysis. *Reproductive Toxicology (Elmsford, N.Y.)*, *76*, 63–70. https://doi.org/10.1016/j.reprotox.2017.12.010

D'Onofrio, B. M., Turkheimer, E. N., Eaves, L. J., Corey, L. A., Berg, K., Solaas, M. H., & Emery, R. E. (2003). The role of the Children of Twins design in elucidating causal relations between parent characteristics and child outcomes. *Journal of Child Psychology and Psychiatry*, *44*(8), 1130–1144. https://doi.org/10.1111/1469-7610.00196

D'Onofrio, B. M., Van Hulle, C. A., Waldman, I. D., Rodgers, J. L., Harden, K. P., Rathouz, P. J., & Lahey, B. B. (2008). Smoking during pregnancy and offspring externalizing problems: An exploration of genetic and environmental confounds. *Development and Psychopathology*, *20*(1), 139–164. https://doi.org/10.1017/S0954579408000072

Dorn, L. D., Hostinar, C. E., Susman, E. J., & Pervanidou, P. (2019). Conceptualizing Puberty as a Window of Opportunity for Impacting Health and Well-Being Across the Life Span. *Journal of Research on Adolescence*, *29*(1), 155–176. https://doi.org/10.1111/jora.12431

Dow-Edwards, D., MacMaster, F. P., Peterson, B. S., Niesink, R., Andersen, S., & Braams, B. R. (2019). Experience during adolescence shapes brain development: From synapses and networks to normal and pathological behavior. *Neurotoxicology and Teratology*, *76*, 106834. https://doi.org/10.1016/j.ntt.2019.106834

Efron, D. (2019). Chapter 1 - Attention Deficit Hyperactivity Disorder: An Overview. In H. Hiscock & E. Sciberras (Hrsg.), *Sleep and ADHD* (S. 1–28). Academic Press. https://doi.org/10.1016/B978-0-12-814180-9.00001-6

Eichler, A., Walz, L., Grunitz, J., Grimm, J., Van Doren, J., Raabe, E., Goecke, T. W., Fasching, P. A., Beckmann, M. W., Kornhuber, J., Kratz, O., Heinrich, H., & Moll, G. H. (2017). Children of Prenatally Depressed Mothers: Externalizing and Internalizing Symptoms are Accompanied by Reductions in Specific

Social-Emotional Competencies. *Journal of Child and Family Studies*, *26*(11), 3135–3144. https://doi.org/10.1007/s10826-017-0819-0

Ekblad, M., Korkeila, J., & Lehtonen, L. (2015). Smoking during pregnancy affects foetal brain development. *Acta Paediatrica*, *104*(1), 12–18. https://doi.org/10.1111/apa.12791

Ekblad, M., Korkeila, J., Parkkola, R., Lapinleimu, H., Haataja, L., Lehtonen, L., & PIPARI Study Group. (2010). Maternal smoking during pregnancy and regional brain volumes in preterm infants. *The Journal of Pediatrics*, *156*(2), 185-190.e1. https://doi.org/10.1016/j.jpeds.2009.07.061

Ekblad, M., Lehtonen, L., Korkeila, J., & Gissler, M. (2017). Maternal Smoking During Pregnancy and the Risk of Psychiatric Morbidity in Singleton Sibling Pairs. *Nicotine & Tobacco Research*, *19*(5), 597–604.

Ekblad, M. O., Ngum, P., Merisaari, H., Saunavaara, V., Parkkola, R., & Setänen, S. (2023). Maternal smoking during pregnancy negatively affects brain volumes proportional to intracranial volume in adolescents born very preterm. *Frontiers in Human Neuroscience*, *16*. https://www.frontiersin.org/articles/10.3389/fnhum.2022.1085986

Ekblad, M. O., Rolan, E., Marceau, K., Palmer, R., Todorov, A., Heath, A. C., & Knopik, V. S. (2019). Disruptive Behavior in Siblings Discordant for Exposure to Maternal Smoking During Pregnancy: A Multi-rater Approach. *Nicotine & Tobacco Research*, *22*(8), 1330–1338. https://doi.org/10.1093/ntr/ntz214

El Marroun, H., Schmidt, M. N., Franken, I. H. A., Jaddoe, V. W. V., Hofman, A., van der Lugt, A., Verhulst, F. C., Tiemeier, H., & White, T. (2014). Prenatal tobacco exposure and brain morphology: A prospective study in young children. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *39*(4), 792–800. https://doi.org/10.1038/npp.2013.273

Esser, G., & Schmidt, M. H. (2017). Die Mannheimer Risikokinderstudie. *Kindheit und Entwicklung*, *26*(4), 198–202. https://doi.org/10.1026/0942-5403/a000232

Franke, B., Faraone, S. V., Asherson, P., Buitelaar, J., Bau, C. H. D., Ramos-Quiroga, J. A., Mick, E., Grevet, E. H., Johansson, S., Haavik, J., Lesch, K.-P., Cormand, B., & Reif, A. (2012). The genetics of attention deficit/hyperactivity disorder in adults, a review. *Molecular Psychiatry*, *17*(10), 960–987. https://doi.org/10.1038/mp.2011.138

Froggatt, S., Covey, J., & Reissland, N. (2020). Infant neurobehavioural consequences of prenatal cigarette exposure: A systematic review and meta-analysis. *Acta Paediatrica (Oslo, Norway : 1992)*, *109*(6), 1112–1124. https://doi.org/10.1111/apa.15132

Gartstein, M. A., & Skinner, M. K. (2018). Prenatal influences on temperament development: The role of environmental epigenetics. *Development and Psychopathology*, *30*(4), 1269–1303. https://doi.org/10.1017/S0954579417001730

Gibb, R., & Kovalchuk, A. (2018). Chapter 1—Brain Development. In R. Gibb & B. Kolb (Hrsg.), *The Neurobiology of Brain and Behavioral Development* (S. 3–27). Academic Press. https://doi.org/10.1016/B978-0-12-804036-2.00001-7

Gramfort, A., Luessi, M., Larson, E., Engemann, D. A., Strohmeier, D., Brodbeck, C., Parkkonen, L., & Hämäläinen, M. S. (2014). MNE software for processing MEG and EEG data. *NeuroImage*, *86*, 446–460. https://doi.org/10.1016/j.neuroimage.2013.10.027

Gustavson, K., Ystrom, E., Stoltenberg, C., Susser, E., Surén, P., Magnus, P., Knudsen, G. P., Smith, G. D., Langley, K., Rutter, M., Aase, H., & Reichborn-Kjennerud, T. (2017). Smoking in Pregnancy and Child ADHD. *Pediatrics*, *139*(2), e20162509. https://doi.org/10.1542/peds.2016-2509

Hack, K., & Glanc, P. (2023). Normal First Trimester of Pregnancy. In J. S. Abramowicz & R. E. Longman (Hrsg.), *First-Trimester Ultrasound: A Comprehensive Guide* (S. 107–138). Springer International Publishing. https://doi.org/10.1007/978-3-031-24133-8_8

Hackshaw, A., Rodeck, C., & Boniface, S. (2011). Maternal smoking in pregnancy and birth defects: A systematic review based on 173 687 malformed cases and 11.7 million controls. *Human Reproduction Update*, *17*(5), 589. https://doi.org/10.1093/humupd/dmr022

Han, J.-Y., Kwon, H.-J., Ha, M., Paik, K.-C., Lim, M.-H., Gyu Lee, S., Yoo, S.-J., & Kim, E.-J. (2015). The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: A large population-based study. *Psychiatry Research*, *225*(1), 164–168. https://doi.org/10.1016/j.psychres.2014.11.009

Harmony, T. (2013). The functional significance of delta oscillations in cognitive processing. *Frontiers in Integrative Neuroscience*, *7*, 83. https://doi.org/10.3389/fnint.2013.00083

Havlicek, V., Childiaeva, R., & Chernick, V. (1977). EEG frequency spectrum characteristics of sleep states in infants of alcoholic mothers. *Neuropadiatrie*, *8*(4), 360–373. https://doi.org/10.1055/s-0028-1091532

Hein, A., Rauh, C., Engel, A., Häberle, L., Dammer, U., Voigt, F., Fasching, P. A., Faschingbauer, F., Burger, P., Beckmann, M. W., Kornhuber, J., & Goecke, T. W. (2014). Socioeconomic status and depression during and after pregnancy in the Franconian Maternal Health Evaluation Studies (FRAMES). *Archives of Gynecology and Obstetrics*, *289*(4), 755–763. https://doi.org/10.1007/s00404-013-3046-y

Hellström-Lindahl, E., Gorbounova, O., Seiger, A., Mousavi, M., & Nordberg, A. (1998). Regional distribution of nicotinic receptors during prenatal development of human brain and spinal cord. *Brain Research. Developmental Brain Research*, *108*(1–2), 147–160. https://doi.org/10.1016/s0165-3806(98)00046-7

Holz, N. E., Boecker, R., Baumeister, S., Hohm, E., Zohsel, K., Buchmann, A. F., Blomeyer, D., Jennen-Steinmetz, C., Hohmann, S., Wolf, I., Plichta, M. M., Meyer-Lindenberg, A., Banaschewski, T., Brandeis, D., & Laucht, M. (2014). Effect of prenatal exposure to tobacco smoke on inhibitory control: Neuroimaging results from a 25-year prospective study. *JAMA Psychiatry*, *71*(7), 786–796. https://doi.org/10.1001/jamapsychiatry.2014.343

Holz, N. E., Tost, H., & Meyer-Lindenberg, A. (2020). Resilience and the brain: A key role for regulatory circuits linked to social stress and support. *Molecular Psychiatry*, *25*(2), 379–396. https://doi.org/10.1038/s41380-019-0551-9

Huijbregts, S. C. J., Séguin, J. R., Zoccolillo, M., Boivin, M., & Tremblay, R. E. (2007). Associations of Maternal Prenatal Smoking with Early Childhood Physical Aggression, Hyperactivity-Impulsivity, and Their Co-Occurrence. *Journal of Abnormal Child Psychology*, *35*(2), 203–215. https://doi.org/10.1007/s10802-006-9073-4

Ino, T. (2010). Maternal smoking during pregnancy and offspring obesity: Meta-analysis. *Pediatrics International: Official Journal of the Japan Pediatric Society*, *52*(1), 94–99. https://doi.org/10.1111/j.1442-200X.2009.02883.x

Jacobsen, L. K., Slotkin, T. A., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2007). Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *32*(12), 2453–2464. https://doi.org/10.1038/sj.npp.1301398

Jansone, K., Eichler, A., Fasching, P. A., Kornhuber, J., Kaiser, A., Millenet, S., Banaschewski, T., Nees, F., & On Behalf Of The Imac-Mind Consortium, null. (2023). Association of Maternal Smoking during Pregnancy with Neurophysiological and ADHD-Related Outcomes in School-Aged Children. *International Journal of Environmental Research and Public Health*, *20*(6), 4716. https://doi.org/10.3390/ijerph20064716

Julian, M. M., Lawler, J. M., & Rosenblum, K. L. (2017). Caregiver-Child Relationships in Early Childhood: Interventions to Promote Well-Being and Reduce Risk for Psychopathology. *Current Behavioral Neuroscience Reports*, *4*(2), 87–98. https://doi.org/10.1007/s40473-017-0110-0

Kaiser, A., Aggensteiner, P.-M., Holtmann, M., Fallgatter, A., Romanos, M., Abenova, K., Alm, B., Becker, K., Döpfner, M., Ethofer, T., Freitag, C. M., Geissler, J., Hebebrand, J., Huss, M., Jans, T., Jendreizik, L. T., Ketter, J., Legenbauer, T., Philipsen, A., … On Behalf Of The ESCAlife-Consortium, null. (2021). EEG Data Quality: Determinants and Impact in a Multicenter Study of Children, Adolescents, and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD). *Brain Sciences*, *11*(2), 214. https://doi.org/10.3390/brainsci11020214

Karaca, N. H. (2022). Prenatal Development. In *Research Anthology on Advancements in Women's Health and Reproductive Rights* (S. 712–731). IGI Global Scientific Publishing. https://doi.org/10.4018/978-1-6684-6299-7.ch037

Karakaş, S. (2022). A comparative review of the psychophysiology of attention in children with and without attention deficit hyperactivity disorder. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *177*, 43–60. https://doi.org/10.1016/j.ijpsycho.2022.02.007

Keen, R. (2011). The Development of Problem Solving in Young Children: A Critical Cognitive Skill. *Annual Review of Psychology*, *62*(Volume 62, 2011), 1–21. https://doi.org/10.1146/annurev.psych.031809.130730

Kimonis, E. R., Frick, P. J., & Fleming, G. E. (2019). Externalizing Disorders of Childhood and Adolescence. In *Psychopathology* (5. Aufl.). Routledge.

Kitsune, G. L., Cheung, C. H. M., Brandeis, D., Banaschewski, T., Asherson, P., McLoughlin, G., & Kuntsi, J. (2015). A Matter of Time: The Influence of Recording Context on EEG Spectral Power in Adolescents and Young Adults with ADHD. *Brain Topography*, *28*(4), 580–590. https://doi.org/10.1007/s10548-014-0395-1

Kleinman, M. T. (2020). Carbon Monoxide. In *Environmental Toxicants* (S. 455–486). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781119438922.ch12

Knyazev, G. G. (2012). EEG delta oscillations as a correlate of basic homeostatic and motivational processes. *Neuroscience & Biobehavioral Reviews*, *36*(1), 677–695. https://doi.org/10.1016/j.neubiorev.2011.10.002

Kostović, I., Radoš, M., Kostović-Srzentić, M., & Krsnik, Ž. (2021). Fundamentals of the Development of Connectivity in the Human Fetal Brain in Late Gestation: From 24 Weeks Gestational Age to Term. *Journal of Neuropathology & Experimental Neurology*, *80*(5), 393–414. https://doi.org/10.1093/jnen/nlab024

Lambe, M., Hultman, C., Torrång, A., Maccabe, J., & Cnattingius, S. (2006). Maternal smoking during pregnancy and school performance at age 15. *Epidemiology (Cambridge, Mass.)*, *17*(5), 524–530. https://doi.org/10.1097/01.ede.0000231561.49208.be

Lambers, D. S., & Clark, K. E. (1996). The maternal and fetal physiologic effects of nicotine. *Seminars in Perinatology*, *20*(2), 115–126. https://doi.org/10.1016/S0146-0005(96)80079-6

Langley, K., Heron, J., Smith, G. D., & Thapar, A. (2012). Maternal and Paternal Smoking During Pregnancy and Risk of ADHD Symptoms in Offspring: Testing for Intrauterine Effects. *American Journal of Epidemiology*, *176*(3), 261–268. https://doi.org/10.1093/aje/kwr510

Langley, K., Holmans, P. A., van den Bree, M. B. M., & Thapar, A. (2007). Effects of low birth weight, maternal smoking in pregnancy and social class on the phenotypic manifestation of Attention Deficit Hyperactivity Disorder and associated antisocial behaviour: Investigation in a clinical sample. *BMC Psychiatry*, *7*, 26. https://doi.org/10.1186/1471-244X-7-26

Langley, K., Turic, D., Rice, F., Holmans, P., van den Bree, M. B. M., Craddock, N., Kent, L., Owen, M. J., O’Donovan, M. C., & Thapar, A. (2008). Testing for gene x environment interaction effects in attention deficit hyperactivity disorder and associated antisocial behavior. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics*, *147B*(1), 49–53. https://doi.org/10.1002/ajmg.b.30571

Laucht, M., Esser, G., & Schmidt, M. H. (1997). Developmental outcome of infants born with biological and psychosocial risks. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *38*(7), 843–853. https://doi.org/10.1111/j.1469-7610.1997.tb01602.x

Laucht, M., & Schmidt, M. H. (2004). [Maternal smoking during pregnancy: Risk factor for ADHD in the offspring?]. *Zeitschrift Fur Kinder- Und Jugendpsychiatrie Und Psychotherapie*, *32*(3), 177–185. https://doi.org/10.1024/1422-4917.32.3.177

Leary, S. D., Smith, G. D., Rogers, I. S., Reilly, J. J., Wells, J. C. K., & Ness, A. R. (2006). Smoking during pregnancy and offspring fat and lean mass in childhood. *Obesity (Silver Spring, Md.)*, *14*(12), 2284–2293. https://doi.org/10.1038/oby.2006.268

Lees, B., Mewton, L., Jacobus, J., Valadez, E. A., Stapinski, L. A., Teesson, M., Tapert, S. F., & Squeglia, L. M. (2020). Association of Prenatal Alcohol Exposure With Psychological, Behavioral, and Neurodevelopmental Outcomes in Children From the Adolescent Brain Cognitive Development Study. *American Journal of Psychiatry*. https://doi.org/10.1176/appi.ajp.2020.20010086

Li, J., Yin, H., Bibus, D. M., & Byelashov, O. A. (2016). The role of Omega-3 docosapentaenoic acid in pregnancy and early development. *European Journal of Lipid Science and Technology*, *118*(11), 1692–1701. https://doi.org/10.1002/ejlt.201600076

Lin, L.-Z., Xu, S.-L., Wu, Q.-Z., Zhou, Y., Ma, H.-M., Chen, D.-H., Chen, G.-B., Yu, H.-Y., Yang, B.-Y., Zeng, X.-W., Hu, L.-W., & Dong, G.-H. (2021). Association of Prenatal, Early Postnatal, or Current Exposure to Secondhand Smoke With Attention-Deficit/Hyperactivity Disorder Symptoms in Children. *JAMA Network Open*, *4*(5), e2110931. https://doi.org/10.1001/jamanetworkopen.2021.10931

Little, M. (2017). *Child Development*. Routledge.

Liu, J., Bann, C., Lester, B., Tronick, E., Das, A., Lagasse, L., Bauer, C., Shankaran, S., & Bada, H. (2010). Neonatal neurobehavior predicts medical and behavioral outcome. *Pediatrics*, *125*(1), e90-98. https://doi.org/10.1542/peds.2009-0204

Loffe, S., Childiaeva, R., & Chernick, V. (1984). Prolonged effects of maternal alcohol ingestion on the neonatal electroencephalogram. *Pediatrics*, *74*(3), 330–335.

Machado, C., Estévez, M., Leisman, G., Melillo, R., Rodríguez, R., DeFina, P., Hernández, A., Pérez-Nellar, J., Naranjo, R., Chinchilla, M., Garófalo, N., Vargas, J., & Beltrán, C. (2015). QEEG Spectral and Coherence Assessment of Autistic Children in Three Different Experimental Conditions. *Journal of Autism and Developmental Disorders*, *45*(2), 406–424. https://doi.org/10.1007/s10803-013-1909-5

Maggi, S., Irwin, L. J., Siddiqi, A., & Hertzman, C. (2010). The social determinants of early child development: An overview. *Journal of Paediatrics and Child Health*, *46*(11), 627–635. https://doi.org/10.1111/j.1440-1754.2010.01817.x

Malave, L., van Dijk, M. T., & Anacker, C. (2022). Early life adversity shapes neural circuit function during sensitive postnatal developmental periods. *Translational Psychiatry*, *12*(1), 1–14. https://doi.org/10.1038/s41398-022-02092-9

Marsh, R., Gerber, A. J., & Peterson, B. S. (2008). Neuroimaging Studies of Normal Brain Development and Their Relevance for Understanding Childhood Neuropsychiatric Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*(11), 1233–1251. https://doi.org/10.1097/CHI.0b013e318185e703

Mason, L. M., Barry, R. J., & Clarke, A. R. (2022). Age-related changes in the EEG in an eyes-open condition: I. Normal development. *International Journal of Psychophysiology*, *172*, 40–45. https://doi.org/10.1016/j.ijpsycho.2021.11.005

Mastorci, F., Lazzeri, M. F. L., Vassalle, C., & Pingitore, A. (2024). The Transition from Childhood to Adolescence: Between Health and Vulnerability. *Children*, *11*(8), Article 8. https://doi.org/10.3390/children11080989

McKernan, C. J., & Lucas-Thompson, R. G. (2018). Autonomic nervous system coordination moderates links of negative interparental conflict with adolescent externalizing behaviors. *Developmental Psychology*, *54*(9), 1697–1708. https://doi.org/10.1037/dev0000498

Melchior, M., Hersi, R., van der Waerden, J., Larroque, B., Saurel-Cubizolles, M.-J., Chollet, A., Galéra, C., & EDEN Mother-Child Cohort Study Group. (2015). Maternal tobacco smoking in pregnancy and children's socio-emotional development at age 5: The EDEN mother-child birth cohort study. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *30*(5), 562–568. https://doi.org/10.1016/j.eurpsy.2015.03.005

Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*, *137*(6), 959–997. https://doi.org/10.1037/a0024768

Minatoya, M., Araki, A., Itoh, S., Yamazaki, K., Kobayashi, S., Miyashita, C., Sasaki, S., & Kishi, R. (2019). Prenatal tobacco exposure and ADHD symptoms at pre-school age: The Hokkaido Study on Environment and Children's Health. *Environmental Health and Preventive Medicine*, *24*(1), 74. https://doi.org/10.1186/s12199-019-0834-4

Modabbernia, A., Reichenberg, A., Ing, A., Moser, D. A., Doucet, G. E., Artiges, E., Banaschewski, T., Barker, G. J., Becker, A., Bokde, A. L. W., Quinlan, E. B., Desrivières, S., Flor, H., Fröhner, J. H., Garavan, H., Gowland, P., Grigis, A., Grimmer, Y., Heinz, A., … IMAGEN Consortium. (2021). Linked patterns of biological and environmental covariation with brain structure in adolescence: A population-based longitudinal study. *Molecular Psychiatry*, *26*(9), 4905–4918. https://doi.org/10.1038/s41380-020-0757-x

Moylan, S., Gustavson, K., Øverland, S., Karevold, E. B., Jacka, F. N., Pasco, J. A., & Berk, M. (2015). The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: The Norwegian Mother and Child Cohort Study. *BMC Medicine*, *13*, 24. https://doi.org/10.1186/s12916-014-0257-4

Muñoz-Silva, A., Lago-Urbano, R., & Sanchez-Garcia, M. (2017). Family Impact and Parenting Styles in Families of Children with ADHD. *Journal of Child and Family Studies*, *26*(10), 2810–2823. https://doi.org/10.1007/s10826-017-0798-1

Mustafa, G., & Rashid, H. (2023). Exploring Cognitive Development through the Lens ofNeuroscience. *Cosmic Journal of Linguistics*, *2*(1), Article 1.

Nave, K.-A. (2010). Myelination and the trophic support of long axons. *Nature Reviews Neuroscience*, *11*(4), 275–283. https://doi.org/10.1038/nrn2797

Neuman, R. J., Lobos, E., Reich, W., Henderson, C. A., Sun, L.-W., & Todd, R. D. (2007). Prenatal smoking exposure and dopaminergic genotypes interact to cause a severe ADHD subtype. *Biological Psychiatry*, *61*(12), 1320–1328. https://doi.org/10.1016/j.biopsych.2006.08.049

Nickel, M., & Gu, C. (2018). Regulation of Central Nervous System Myelination in Higher Brain Functions. *Neural Plasticity*, *2018*(1), 6436453. https://doi.org/10.1155/2018/6436453

Nigg, J. T. (2017). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. *Journal of Child Psychology and Psychiatry*, *58*(4), 361–383. https://doi.org/10.1111/jcpp.12675

O'Connor, A. (2017). *Understanding Transitions in the Early Years: Supporting Change through Attachment and Resilience* (2. Aufl.). Routledge. https://doi.org/10.4324/9781315559100

Ogunjobi, T. T., Gbayisomore, T. J., Nneji, P. O., Olofin, O. O., Olowe, E. N., Gigam-Ozuzu, C. D., Afolabi, J. I., Okwuokei, N. B., Boluwaji, V. A., Ojeniran, T. P., Ogini, I. O., Adesope, S. O., Yissa, T. D., & Eji, C. A. (2024). Environmental Epigenetics and Its Impacts on Disease Susceptibility: A Comprehensive Review. *Medinformatics*. https://doi.org/10.47852/bonviewMEDIN42022945

Orleans, C. T., Barker, D. C., Kaufman, N. J., & Marx, J. F. (2000). Helping pregnant smokers quit: Meeting the challenge in the next decade. *Tobacco Control*, *9 Suppl 3*(Suppl 3), III6-11. https://doi.org/10.1136/tc.9.suppl_3.iii6

Osher, D., Cantor, P., Berg, J., Steyer, L., & Rose, T. (2021). Drivers of Human Development: How Relationships and Context Shape Learning and Development 1. In *The Science of Learning and Development*. Routledge.

Paul, L. K. (2011). Developmental malformation of the corpus callosum: A review of typical callosal development and examples of developmental disorders with callosal involvement. *Journal of Neurodevelopmental Disorders*, *3*(1), 3–27. https://doi.org/10.1007/s11689-010-9059-y

Paus, T., Nawazkhan, I., Leonard, G., Perron, M., Pike, G. B., Pitiot, A., Richer, L., Veillette, S., & Pausova, Z. (2008). Corpus callosum in adolescent offspring exposed prenatally to maternal cigarette smoking. *NeuroImage*, *40*(2), 435–441. https://doi.org/10.1016/j.neuroimage.2007.10.066

Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L.-G., Ingvar, M., & Buckner, R. L. (2006). Structure–Function Correlates of Cognitive Decline in Aging. *Cerebral Cortex*, *16*(7), 907–915. https://doi.org/10.1093/cercor/bhj036

Pfeifer, J. H., & Allen, N. B. (2021). Puberty Initiates Cascading Relationships Between Neurodevelopmental, Social, and Internalizing Processes Across Adolescence. *Biological Psychiatry*, *89*(2), 99–108. https://doi.org/10.1016/j.biopsych.2020.09.002

Pini, N., Sania, A., Rao, S., Shuffrey, L. C., Nugent, J. D., Lucchini, M., McSweeney, M., Hockett, C., Morales, S., Yoder, L., Ziegler, K., Perzanowski, M. S., Fox, N. A., Elliott, A. J., Myers, M. M., & Fifer, W. P. (2024). In Utero Exposure to Alcohol and Tobacco and Electroencephalogram Power During Childhood. *JAMA Network Open*, *7*(1), e2350528. https://doi.org/10.1001/jamanetworkopen.2023.50528

Podobinska, M., Szablowska-Gadomska, I., Augustyniak, J., Sandvig, I., Sandvig, A., & Buzanska, L. (2017). Epigenetic Modulation of Stem Cells in Neurodevelopment: The Role of Methylation and Acetylation. *Frontiers in Cellular Neuroscience*, *11*. https://doi.org/10.3389/fncel.2017.00023

Popova, S., Lange, S., Probst, C., Gmel, G., & Rehm, J. (2017). Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: A systematic review and meta-analysis. *The Lancet Global Health*, *5*(3), e290–e299. https://doi.org/10.1016/S2214-109X(17)30021-9

Puiu, A. A., Wudarczyk, O., Goerlich, K. S., Votinov, M., Herpertz-Dahlmann, B., Turetsky, B., & Konrad, K. (2018). Impulsive aggression and response inhibition in attention-deficit/hyperactivity disorder and disruptive behavioral disorders: Findings from a systematic review. *Neuroscience & Biobehavioral Reviews*, *90*, 231–246. https://doi.org/10.1016/j.neubiorev.2018.04.016

Raymond, C., Marin, M.-F., Majeur, D., & Lupien, S. (2018). Early child adversity and psychopathology in adulthood: HPA axis and cognitive dysregulations as potential mechanisms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *85*, 152–160. https://doi.org/10.1016/j.pnpbp.2017.07.015

Reulbach, U., Bleich, S., Knörr, J., Burger, P., Fasching, P. A., Kornhuber, J., Beckmann, M. W., & Goecke, T. W. (2009). [Pre-, peri- and postpartal depression]. *Fortschritte Der Neurologie-Psychiatrie*, *77*(12), 708–713. https://doi.org/10.1055/s-0028-1109822

Rice, F., Langley, K., Woodford, C., Davey Smith, G., & Thapar, A. (2018). Identifying the contribution of prenatal risk factors to offspring development and psychopathology: What designs to use and a critique of literature on maternal smoking and stress in pregnancy. *Development and Psychopathology*, *30*(3), 1107–1128. https://doi.org/10.1017/S0954579418000421

Rivkin, M. J. (2000). Developmental neuroimaging of children using magnetic resonance techniques. *Mental Retardation and Developmental Disabilities Research Reviews*, *6*(1), 68–80. https://doi.org/10.1002/(SICI)1098-2779(2000)6:1<68::AID-MRDD9>3.0.CO;2-9

Rivkin, M. J., Davis, P. E., Lemaster, J. L., Cabral, H. J., Warfield, S. K., Mulkern, R. V., Robson, C. D., Rose-Jacobs, R., & Frank, D. A. (2008). Volumetric MRI study of brain in children with intrauterine exposure to cocaine, alcohol, tobacco, and marijuana. *Pediatrics*, *121*(4), 741–750. https://doi.org/10.1542/peds.2007-1399

Rodríguez-Martínez, E. I., Angulo-Ruiz, B. Y., Arjona-Valladares, A., Rufo, M., Gómez-González, J., & Gómez, C. M. (2020). Frequency coupling of low and high frequencies in the EEG of ADHD children and adolescents in closed and open eyes conditions. *Research in Developmental Disabilities*, *96*, 103520. https://doi.org/10.1016/j.ridd.2019.103520

Rogers, J. M. (2019). Smoking and pregnancy: Epigenetics and developmental origins of the metabolic syndrome. *Birth Defects Research*, *111*(17), 1259–1269. https://doi.org/10.1002/bdr2.1550

Role, L. W., & Berg, D. K. (1996). Nicotinic receptors in the development and modulation of CNS synapses. *Neuron*, *16*(6), 1077–1085. https://doi.org/10.1016/s0896-6273(00)80134-8

Romer, D., Reyna, V. F., & Satterthwaite, T. D. (2017). Beyond stereotypes of adolescent risk taking: Placing the adolescent brain in developmental context.

Developmental Cognitive Neuroscience, *27*, 19–34. https://doi.org/10.1016/j.dcn.2017.07.007

Saad, J. F., Kohn, M. R., Clarke, S., Lagopoulos, J., & Hermens, D. F. (2018). Is the Theta/Beta EEG Marker for ADHD Inherently Flawed? *Journal of Attention Disorders*, *22*(9), 815–826. https://doi.org/10.1177/1087054715578270

Sakurai, T., & Gamo, N. J. (2019). Cognitive functions associated with developing prefrontal cortex during adolescence and developmental neuropsychiatric disorders. *Neurobiology of Disease*, *131*, 104322. https://doi.org/10.1016/j.nbd.2018.11.007

Saylor, K. E., & Amann, B. H. (2016). Impulsive Aggression as a Comorbidity of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology*, *26*(1), 19–25. https://doi.org/10.1089/cap.2015.0126

Sciberras, E., Mulraney, M., Silva, D., & Coghill, D. (2017). Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence. *Current Psychiatry Reports*, *19*(1), 1. https://doi.org/10.1007/s11920-017-0753-2

Sharma, A. J., Cogswell, M. E., & Li, R. (2008). Dose-Response Associations Between Maternal Smoking During Pregnancy and Subsequent Childhood Obesity: Effect Modification by Maternal Race/Ethnicity in a Low-Income US Cohort. *American Journal of Epidemiology*, *168*(9), 995–1007. https://doi.org/10.1093/aje/kwn223

Shiner, R., & Caspi, A. (2003). Personality differences in childhood and adolescence: Measurement, development, and consequences. *Journal of Child Psychology and Psychiatry*, *44*(1), 2–32. https://doi.org/10.1111/1469-7610.00101

Shuffrey, L. C., Myers, M. M., Isler, J. R., Lucchini, M., Sania, A., Pini, N., Nugent, J. D., Condon, C., Ochoa, T., Brink, L., du Plessis, C., Odendaal, H. J., Nelson, M. E., Friedrich, C., Angal, J., Elliott, A. J., Groenewald, C., Burd, L., Fifer, W. P., & PASS Network. (2020). Association Between Prenatal Exposure to Alcohol and Tobacco and Neonatal Brain Activity: Results From the Safe Passage Study. *JAMA Network Open*, *3*(5), e204714. https://doi.org/10.1001/jamanetworkopen.2020.4714

Siregar, S., & Lubis, A. N. M. T. (2023). STAGES OF EARLY CHILDHOOD COGNITIVE DEVELOPMENT: THE FOUNDATION OF INTELLECTUAL

GROWTH. *Jurnal Scientia*, *12*(04), Article 04. https://doi.org/10.58471/scientia.v12i04.2167

Slotkin, T. A. (1998). Fetal nicotine or cocaine exposure: Which one is worse? *The Journal of Pharmacology and Experimental Therapeutics*, *285*(3), 931–945.

Smedberg, J., Lupattelli, A., Mårdby, A.-C., & Nordeng, H. (2014). Characteristics of women who continue smoking during pregnancy: A cross-sectional study of pregnant women and new mothers in 15 European countries. *BMC Pregnancy and Childbirth*, *14*(1), 213. https://doi.org/10.1186/1471-2393-14-213

Sonuga-Barke, E. J. S., Cortese, S., Fairchild, G., & Stringaris, A. (2016). Annual Research Review: Transdiagnostic neuroscience of child and adolescent mental disorders – differentiating decision making in attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety. *Journal of Child Psychology and Psychiatry*, *57*(3), 321–349. https://doi.org/10.1111/jcpp.12496

Sturman, D. A., & Moghaddam, B. (2011). The neurobiology of adolescence: Changes in brain architecture, functional dynamics, and behavioral tendencies. *Neuroscience & Biobehavioral Reviews*, *35*(8), 1704–1712. https://doi.org/10.1016/j.neubiorev.2011.04.003

Sun, J., Liu, X., Zhao, M., Magnussen, C. G., & Xi, B. (2023). Dose–response association between maternal smoking during pregnancy and the risk of infant death: A nationwide, population-based, retrospective cohort study. *eClinicalMedicine*, *57*. https://doi.org/10.1016/j.eclinm.2023.101858

Swanson, J. M., Kinsbourne, M., Nigg, J., Lanphear, B., Stefanatos, G. A., Volkow, N., Taylor, E., Casey, B. J., Castellanos, F. X., & Wadhwa, P. D. (2007). Etiologic Subtypes of Attention-Deficit/Hyperactivity Disorder: Brain Imaging, Molecular Genetic and Environmental Factors and the Dopamine Hypothesis. *Neuropsychology Review*, *17*(1), 39–59. https://doi.org/10.1007/s11065-007-9019-9

Tan, C. M. J., & Lewandowski, A. J. (2019). The Transitional Heart: From Early Embryonic and Fetal Development to Neonatal Life. *Fetal Diagnosis and Therapy*, *47*(5), 373–386. https://doi.org/10.1159/000501906

Tarver, J., Daley, D., & Sayal, K. (2014). Attention-deficit hyperactivity disorder (ADHD): An updated review of the essential facts. *Child: Care, Health and Development*, *40*(6), 762–774. https://doi.org/10.1111/cch.12139 ten Donkelaar, H. J., Takakuwa, T., Vasung, L., Yamada, S., Shiota, K., & van der Vliet, T. (2023). Overview of the Development of the Human Brain and Spinal Cord. In H. J. ten Donkelaar, M. Lammens, & A. Hori (Hrsg.), *Clinical Neuroembryology: Development and Developmental Disorders of the Human Central Nervous System* (S. 1–76). Springer International Publishing. https://doi.org/10.1007/978-3-031-26098-8_1

Testa, M., Quigley, B. M., & Eiden, R. D. (2003). THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON INFANT MENTAL DEVELOPMENT: A META-ANALYTICAL REVIEW. *Alcohol and Alcoholism*, *38*(4), 295–304. https://doi.org/10.1093/alcalc/agg087

Thapar, A., Cooper, M., Eyre, O., & Langley, K. (2013). Practitioner Review: What have we learnt about the causes of ADHD? *Journal of Child Psychology and Psychiatry*, *54*(1), 3–16. https://doi.org/10.1111/j.1469-7610.2012.02611.x

Thapar, A., Fowler, T., Rice, F., Scourfield, J., van den Bree, M., Thomas, H., Harold, G., & Hay, D. (2003). Maternal Smoking During Pregnancy and Attention Deficit Hyperactivity Disorder Symptoms in Offspring. *American Journal of Psychiatry*, *160*(11), 1985–1989. https://doi.org/10.1176/appi.ajp.160.11.1985

Thapar, A., Rice, F., Hay, D., Boivin, J., Langley, K., van den Bree, M., Rutter, M., & Harold, G. (2009). Prenatal Smoking Might Not Cause Attention-Deficit/Hyperactivity Disorder: Evidence from a Novel Design. *Biological Psychiatry*, *66*(8), 722–727. https://doi.org/10.1016/j.biopsych.2009.05.032

Thielen, A., Klus, H., & Müller, L. (2008). Tobacco smoke: Unraveling a controversial subject. *Experimental and Toxicologic Pathology*, *60*(2), 141–156. https://doi.org/10.1016/j.etp.2008.01.014

Thomas, J. C., Letourneau, N., Campbell, T. S., Tomfohr-Madsen, L., & Giesbrecht, G. F. (2017). Developmental origins of infant emotion regulation: Mediation by temperamental negativity and moderation by maternal sensitivity. *Developmental Psychology*, *53*(4), 611–628. https://doi.org/10.1037/dev0000279

Thompson, A., & Steinbeis, N. (2020). Sensitive periods in executive function development. *Current Opinion in Behavioral Sciences*, *36*, 98–105. https://doi.org/10.1016/j.cobeha.2020.08.001

Tiesler, C. M. T., & Heinrich, J. (2014). Prenatal nicotine exposure and child behavioural problems. *European Child & Adolescent Psychiatry*, *23*(10), 913–929. https://doi.org/10.1007/s00787-014-0615-y

Tistarelli, N., Fagnani, C., Troianiello, M., Stazi, M. A., & Adriani, W. (2020). The nature and nurture of ADHD and its comorbidities: A narrative review on twin studies. *Neuroscience & Biobehavioral Reviews*, *109*, 63–77. https://doi.org/10.1016/j.neubiorev.2019.12.017

Tooley, U. A., Bassett, D. S., & Mackey, A. P. (2021). Environmental influences on the pace of brain development. *Nature Reviews Neuroscience*, *22*(6), 372–384. https://doi.org/10.1038/s41583-021-00457-5

Trevarthen, C. (1993). The function of emotions in early infant communication and development. In *New Perspectives in Early Communicative Development*. Routledge.

Tye, C., Rijsdijk, F., & McLoughlin, G. (2014). Genetic overlap between ADHD symptoms and EEG theta power. *Brain and Cognition*, *87*, 168–172. https://doi.org/10.1016/j.bandc.2014.03.010

Vo Van, P., Alison, M., Morel, B., Beck, J., Bednarek, N., Hertz-Pannier, L., & Loron, G. (2022). Advanced Brain Imaging in Preterm Infants: A Narrative Review of Microstructural and Connectomic Disruption. *Children*, *9*(3), Article 3. https://doi.org/10.3390/children9030356

Voutilainen, T., Keski-Nisula, L., Rysä, J., & Kärkkäinen, O. (2024). Parental cigarette smoking before and during pregnancy in a cohort of 21 472 pregnancies. *Basic & Clinical Pharmacology & Toxicology*, *134*(4), 543–555. https://doi.org/10.1111/bcpt.13987

Wakschlag, L. S., Pickett, K. E., Cook, E., Benowitz, N. L., & Leventhal, B. L. (2002). Maternal Smoking During Pregnancy and Severe Antisocial Behavior in Offspring: A Review. *American Journal of Public Health*, *92*(6), 966–974. https://doi.org/10.2105/AJPH.92.6.966

Walsh, F. (2016). Family resilience: A developmental systems framework. *European Journal of Developmental Psychology*, *13*(3), 313–324. https://doi.org/10.1080/17405629.2016.1154035

Wang, Y. (2024). Environmental and Nutritional Diseases. In K. Chen, L. Liang, M. Li, & Y. Pan (Hrsg.), *Textbook of Pathologic Anatomy: For Medical Students* (S. 161–200). Springer Nature. https://doi.org/10.1007/978-981-99-8445-9_6

Weitzman, M., Byrd, R. S., Aligne, C. A., & Moss, M. (2002). The effects of tobacco exposure on children's behavioral and cognitive functioning: Implications for clinical and public health policy and future research. *Neurotoxicology and Teratology*, *24*(3), 397–406. https://doi.org/10.1016/s0892-0362(02)00201-5

Wolraich, M. L., Chan, E., Froehlich, T., Lynch, R. L., Bax, A., Redwine, S. T., Ihyembe, D., & Hagan, J. F., Jr. (2019). ADHD Diagnosis and Treatment Guidelines: A Historical Perspective. *Pediatrics*, *144*(4), e20191682. https://doi.org/10.1542/peds.2019-1682

Wood, S. N. (2004). Stable and Efficient Multiple Smoothing Parameter Estimation for Generalized Additive Models. *Journal of the American Statistical Association*, *99*(467), 673–686. https://doi.org/10.1198/016214504000000980

Wood, S. N. (2011). Fast Stable Restricted Maximum Likelihood and Marginal Likelihood Estimation of Semiparametric Generalized Linear Models. *Journal of the Royal Statistical Society Series B: Statistical Methodology*, *73*(1), 3–36. https://doi.org/10.1111/j.1467-9868.2010.00749.x

Y, H., J, C., Lh, Z., Ll, H., & Ff, K. (2020). Maternal Smoking During Pregnancy and ADHD: Results From a Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Journal of Attention Disorders*, *24*(12). https://doi.org/10.1177/1087054717696766

Yen, C., Lin, C.-L., & Chiang, M.-C. (2023). Exploring the Frontiers of Neuroimaging: A Review of Recent Advances in Understanding Brain Functioning and Disorders. *Life*, *13*(7), Article 7. https://doi.org/10.3390/life13071472

Zhong, X., & Chen, J. J. (2020). *Variations in the frequency and amplitude of resting-state EEG and fMRI signals in normal adults: The effects of age and sex* (S. 2020.10.02.323840). bioRxiv. https://doi.org/10.1101/2020.10.02.323840

Zonuzirad, M. (2024). Cellular and Molecular Biology of Neurodevelopment. In R. Kelishadi (Hrsg.), *Nature, Nurture, and Neurodevelopment: Comprehensive Overview* (S. 37–51). Springer Nature. https://doi.org/10.1007/978-981-97-7433-3_3

Zou, R., Boer, O. D., Felix, J. F., Muetzel, R. L., Franken, I. H. A., Cecil, C. A. M., & El Marroun, H. (2022). Association of Maternal Tobacco Use During Pregnancy With Preadolescent Brain Morphology Among Offspring. *JAMA Network Open*, *5*(8), e2224701. https://doi.org/10.1001/jamanetworkopen.2022.24701

6 SUPPLEMENTAL MATERIAL

6.1 SUPPLEMENT STUDY 1

Table S1: Sample characteristics in a study of prenatal tobacco exposure (N=142).

Characteristic	Total	Unexposed Children (N=116)		Children With Prenatal Tobacco Exposure (N=26)		
Youth Variables						
	N	N	%	N	%	*p*
Sex						.434
male	70	59	50.9	11	42.3	
female	72	57	49.1	15	57.7	
Prenatal alcohol exposure						.562
No	115	95	81.9	20	76.9	
Yes	27	21	18.1	6	23.1	
	Mean	Mean	SD	Mean	SD	*p*
Age (years)	7.73	7.72	0.65	7.76	0.74	.781
Gestational age	39.38	39.41	1.33	39.23	1.45	.533
Birth weight	3438.01	3453.91	494.28	3370.77	520.34	.446
Intelligence quotient	104.25	104.23	10.25	104.31	7.18	.972
Parent Variables						
Age at delivery	32.68	32.86	4.12	31.88	5.15	.299
	N	N	%	N	%	*p*
Marital status						.068
married	136	113	97.4	23	88.5	
single parent	6	3	2.6	3	11.5	
Maternal Psychopathology						.536
No	85	68	58.6	17	65.4	
Yes	34	29	25.0	5	19.2	
Unknown	23	19	16.4	4	15.3	
Paternal Psychopathology						.461
No	112	92	79.3	20	76.9	
Yes	14	12	10.3	2	7.7	
Unknown	16	12	8.3	4	15.3	

Note *(IDS, intelligence quotient)

Table S2: Brain activity descriptive characteristics for EEG resting-state conditions.

		Overall N=142		Exposed n=26		Not exposed n=116		
Eyes Closed		*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*
Delta	Frontal	6,52	2,23	6,47	2,12	6,53	2,27	.906
	Central	3,33	1,19	3,38	1,41	3,32	1,14	.804
	Posterior	3,27	1,31	3,45	1,54	3,23	1,26	.455
	Overall	4,47	1,41	4,53	1,55	4,46	1,39	.809
Theta	Frontal	1,53	0,72	1,36	0,74	1,57	0,71	.200
	Central	1,15	0,56	1,04	0,44	1,18	0,58	.272
	Posterior	1,31	0,68	1,27	0,72	1,32	0,67	.718
	Overall	1,35	0,61	1,24	0,62	1,37	0,60	.330
Alpha	Frontal	0,84	0,46	0,91	0,51	0,83	0,46	.434
	Central	0,73	0,41	0,84	0,46	0,71	0,40	.132
	Posterior	1,45	0,89	1,74	1,11	1,39	0,82	.066
	Overall	1,03	0,54	1,19	0,63	1,00	0,51	.153
Beta	Frontal	0,13	0,07	0,11	0,04	0,13	0,07	.014
	Central	0,08	0,04	0,07	0,03	0,09	0,05	.011
	Posterior	0,09	0,04	0,08	0,04	0,09	0,05	.399
	Overall	0,10	0,05	0,09	0,03	0,10	0,05	.024

		Overall N=142		Exposed n=26		Not exposed n=116		
Eyes open		*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*
Delta	Frontal	5,46	1,82	5,23	2,00	5,51	1,78	.473
	Central	3,46	0,92	3,58	1,20	3,44	0,85	.561
	Posterior	3,45	1,18	3,55	1,56	3,43	1,08	.634
	Overall	4,19	1,15	4,17	1,46	4,19	1,07	.950
Theta	Frontal	1,09	0,43	1,10	0,65	1,09	0,37	.952
	Central	0,91	0,38	0,91	0,47	0,91	0,36	.934
	Posterior	0,88	0,38	0,87	0,44	0,89	0,37	.841
	Overall	0,97	0,36	0,96	0,49	0,97	0,33	.950
Alpha	Frontal	0,46	0,21	0,49	0,23	0,46	0,21	.520
	Central	0,45	0,25	0,53	0,29	0,43	0,24	.099
	Posterior	0,52	0,41	0,63	0,53	0,50	0,38	.162
	Overall	0,48	0,27	0,55	0,32	0,47	0,25	.165
Beta	Frontal	0,16	0,08	0,14	0,05	0,17	0,09	.068
	Central	0,10	0,05	0,09	0,03	0,10	0,05	.019
	Posterior	0,09	0,04	0,08	0,03	0,09	0,04	.272
	Overall	0,12	0,05	0,10	0,03	0,12	0,05	.069

Table S3: Association of prenatal tobacco smoking of any severity with EEG brain activity and FBB-ADHD scales among school-aged children, ***unadjusted*** for covariates.

Eyes Closed		*B*	*SE B*	*β*	R^2	*F*	*t*	*p*
Delta	Frontal	.005	.004	.110	.012	1.69	1.30	.195
	Central	**.004**	**.002**	**.178**	**.032**	**4.55**	**2.13**	**.035**
	Posterior	**.005**	**.002**	**.184**	**.034**	**4.87**	**2.21**	**.029**
	Overall	**.004**	**.002**	**.166**	**.028**	**3.94**	**1.98**	**.049**
Theta	**Frontal**	**.002**	**.001**	**.175**	**.031**	**4.40**	**2.10**	**.038**
	Central	.001	.001	.111	.012	1.73	1.31	.191
	Posterior	**.002**	**.001**	**.192**	**.037**	**5.32**	**2.31**	**.023**
	Overall	**.002**	**.001**	**.181**	**.033**	**4.71**	**2.17**	**.032**
Alpha	**Frontal**	**.002**	**.001**	**.223**	**.050**	**7.25**	**2.69**	**.009**
	Central	**.001**	**.001**	**.172**	**.030**	**4.25**	**2.06**	**.041**
	Posterior	.002	.001	.118	.014	1.97	1.40	.163
	Overall	**.002**	**.001**	**.178**	**.032**	**4.53**	**2.13**	**.035**
Beta	Frontal	.001	.000	.027	.001	.101	.317	.751
	Central	.001	.000	-.006	.000	.005	-.072	.942
	Posterior	.001	.000	.077	.006	.821	.906	.366
	Overall	.001	.000	.039	.002	.211	.460	.647

Eyes Open		*B*	*SE B*	*β*	R^2	*F*	*t*	*p*
Delta	Frontal	-.001	.003	-.015	.000	0.03	-0.18	.856
	Central	.002	.001	.143	.020	2.88	1.70	.092
	Posterior	.003	.002	.142	.020	2.82	1.69	.094
	Overall	.002	.002	.073	.005	0.73	0.85	.394
Theta	**Frontal**	**.001**	**.001**	**.177**	**.031**	**4.48**	**2.12**	**.036**
	Central	**.002**	**.001**	**.215**	**.046**	**6.70**	**2.59**	**.011**
	Posterior	**.002**	**.001**	**.213**	**.045**	**6.57**	**2.56**	**.011**
	Overall	**.001**	**.001**	**.220**	**.048**	**7.00**	**2.65**	**.009**
Alpha	Frontal	.001	.000	.153	.023	3.03	1.82	.071
	Central	**.001**	**.000**	**.197**	**.039**	**5.57**	**2.36**	**.020**
	Posterior	.001	.001	.102	.010	1.45	1.20	.231
	Overall	.001	.000	.152	.023	3.25	1.80	.074
Beta	Frontal	.001	.000	-.054	.003	0.40	-0.63	.529
	Central	.001	.000	.025	.001	0.09	0.30	.766
	Posterior	.001	.000	.059	.004	0.49	0.70	.485
	Overall	.001	.000	-.008	.000	0.01	-0.10	.922

FBB-ADHD	*B*	*SE B*	*β*	R^2	*F*	*t*	*p*
Hyperactivity	**1.26**	**.472**	**.219**	**.048**	**7.06**	**2.66**	**.009**
Attention deficit	.131	.338	.033	.001	.150	.387	.699
Impulsivity	.016	.463	.003	.000	.001	.034	.973
Total	.387	.349	.093	.009	1.23	1.11	.269

Table S4: Association of prenatal tobacco smoking of any severity with FBB-ADHD scales among school-aged children, ***adjusted*** for covariates.

FBB-ADHD	*B*	*Lower CI*	*Upper CI*	*R^2(adjusted)*	*p*	*SE*	*R^2(%)*
Hyperactivity	-.003	-.007	.001	.059	.476	.004	.600
Attention deficit	.002	-.001	.004	-.024	.599	.003	.940
Impulsivity	-.024	-.027	-.020	-.024	.896	.004	.960
Total	.000	-.004	.003	-.045	.876	.003	.950

Table S5: Significant associations between covariates included in GAMMs and outcomes.

	Brain activity	Impulsivity	Inattention	Hyperactivity	ADHD-FBB (Total)
		Higher scores = Greater problems			
Maternal measures					
↑ Age at birth	+			+	+
↑ Gestational age (week of pregnancy at birth)	+/-				
Psychopathology	+				
Smoking before pregnancy	-				
Alcohol consumption during pregnancy	-	+			+

Note. “+” = positive association, “-“ = negative association, “+/-“ = both positive and negative associations were observed. If there is no + or -, no significant association was observed in the GAMMs.

6.2 SUPPLEMENT STUDY 2

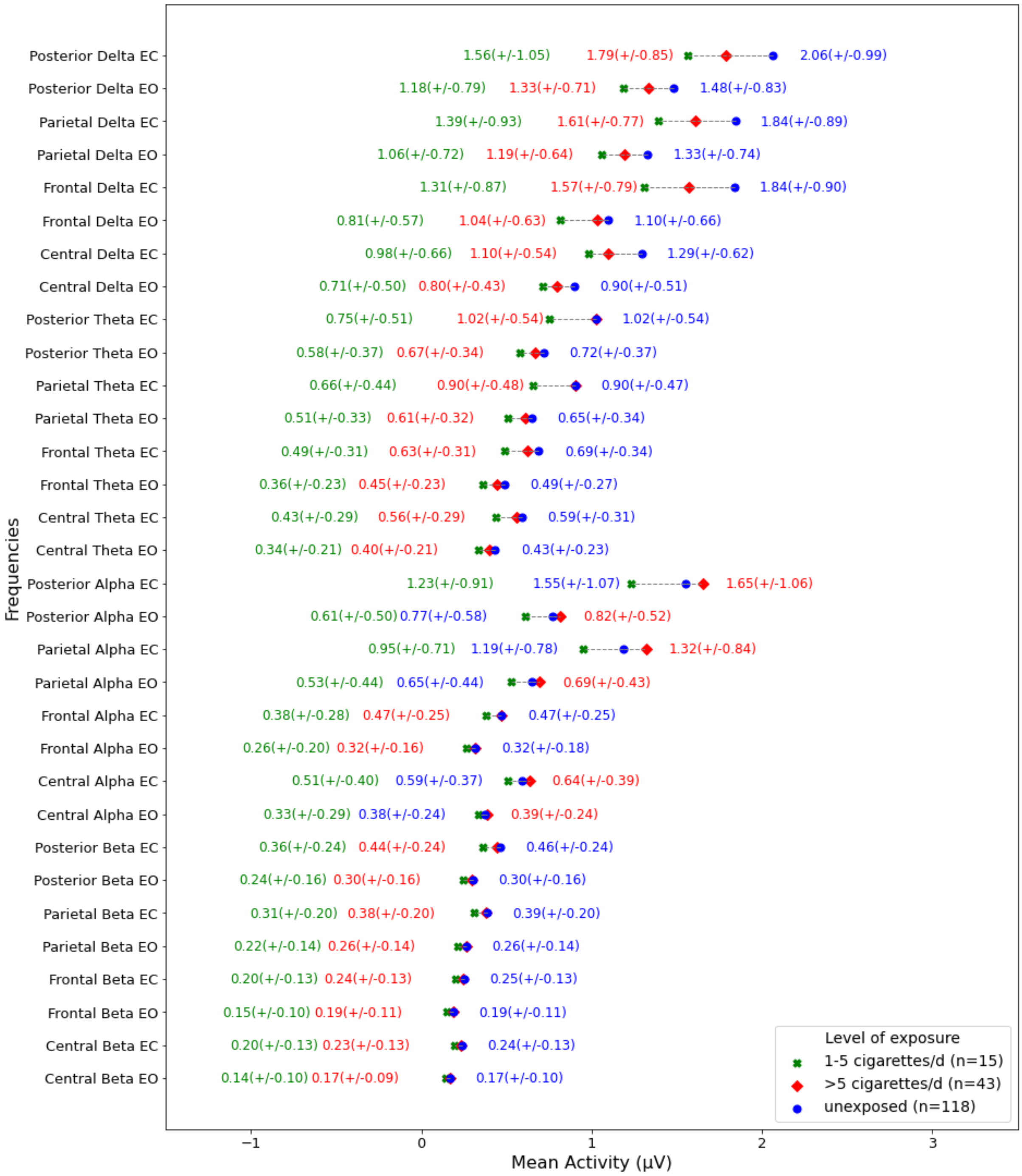

Figure S1. Brain activity descriptive characteristics for EEG resting-state conditions.

Table S1. Results of GAMMs for EEG Power Spectrum during eyes open (EO) condition in Relation to Prenatal Smoking Habits unadjusted for covariates

Frequency band		*1-5 cigarettes/day*			*>5 cigarettes/day*				
		B	**SE**	***p***	**B**	**SE**	***p***	**R2**	**R2 adj**
Delta	Central	-0.31	0.17	0.062	-0.19	0.11	0.075	3.21	0.02
	Frontal	-0.53	0.24	**0.028**	-0.265	0.15	0.089	3.73	0.03
	Parietal	-0.45	0.24	**0.059**	-0.23	0.15	0.131	2.84	0.02
	Posterior	-0.50	0.26	**0.058**	-0.28	0.17	0.106	3.00	0.02
Theta	Central	-0.16	0.08	**0.057**	-0.03	0.05	0.516	2.14	0.01
	Frontal	-0.21	0.09	**0.026**	-0.06	0.06	0.283	3.09	0.02
	Parietal	-0.24	0.13	**0.058**	0.00	0.08	0.990	2.12	0.01
	Posterior	-0.28	0.15	0.062	-0.00	0.10	0.984	2.05	0.01
Alpha	Central	-0.09	0.10	0.397	0.04	0.07	0.537	0.76	-0.00
	Frontal	-0.09	0.07	0.191	-0.01	0.04	0.938	1.00	-0.00
	Parietal	-0.24	0.22	0.271	0.13	0.14	0.352	1.44	0.00
	Posterior	-0.32	0.29	0.264	0.10	0.19	0.585	1.04	-0.00
Beta	Central	-0.04	0.03	0.235	-0.01	0.02	0.825	0.81	-0.00
	Frontal	-0.05	0.03	0.145	-0.01	0.03	0.802	1.22	0.01
	Parietal	-0.08	0.06	0.157	-0.01	0.04	0.831	1.16	0.00
	Posterior	-0.10	0.07	0.142	-0.02	0.04	0.686	1.26	0.00

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S2. Results of GAMMs for EEG Power Spectrum during eyes closed (EC) condition in Relation to Prenatal Smoking Habits unadjusted for covariates

Frequency band		*1-5 cigarettes/day*			*>5 cigarettes/day*				
		B	**SE**	***p***	**B**	**SE**	***p***	**R2**	**R2 adj**
Delta	Central	-0.18	0.13	0.177	-0.10	0.09	0.248	1.55	0.00
	Frontal	-0.28	0.18	0.114	-0.06	0.11	0.595	1.48	0.00
	Parietal	-0.27	0.20	0.169	-0.13	0.13	0.293	1.48	0.00
	Posterior	-0.30	0.22	0.172	-0.15	0.14	0.284	1.48	0.00
Theta	Central	-0.09	0.06	0.122	-0.04	0.04	0.367	1.61	0.00
	Frontal	-0.13	0.07	0.070	-0.04	0.04	0.356	2.10	0.01
	Parietal	-0.14	0.09	0.135	-0.04	0.06	0.522	1.37	0.00
	Posterior	-0.14	0.10	0.157	-0.05	0.06	0.457	1.30	0.00
Alpha	Central	-0.04	0.07	0.535	0.01	0.04	0.764	0.32	-0.01
	Frontal	-0.05	0.05	0.250	-0.00	0.03	0.910	0.77	-0.00
	Parietal	-0.12	0.12	0.323	0.05	0.08	0.542	0.92	-0.00
	Posterior	-0.16	0.15	0.298	0.05	0.10	0.645	0.87	-0.00
Beta	Central	-0.03	0.03	0.251	-0.00	0.02	0.902	0.76	-0.00
	Frontal	-0.04	0.03	0.216	0.00	0.02	0.900	0.95	-0.00
	Parietal	-0.05	0.04	0.227	0.00	0.02	0.981	0.87	-0.00
	Posterior	-0.06	0.04	0.205	-0.00	0.03	0.917	0.93	-0.00

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S3. Results of Generalized Additive Mixed Models (GAMMs) for YASR scales in Relation to Prenatal Smoking Habits unadjusted for covariates

	1-5 cigarettes/day			*>5 cigarettes/day*				
YASR Scales	**B**	**SE**	***p***	**B**	**SE**	***p***	**R2 (%)**	**R2 adj (%)**
Anxious	1.11	0.92	0.231	0.30	0.60	0.612	0.88	-0.00
Withdrawn	-0.74	1.39	0.597	-0.41	0.90	0.651	0.24	-0.01
Thought	-0.22	1.01	0.825	0.13	0.66	0.837	0.06	-0.01
Attention	1.20	0.96	0.212	0.54	0.55	0.325	0.71	0.00
Delinquent	0.27	0.85	0.749	0.41	0.55	0.458	0.34	-0.01
Aggressive	0.64	0.84	0.447	0.74	0.55	0.180	1.20	0.00
Internalizing	3.21	2.67	0.228	0.77	1.73	0.228	0.87	0.00
Externalizing	4.01	2.21	0.072	2.91	1.44	**0.045**	3.50	2.39

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

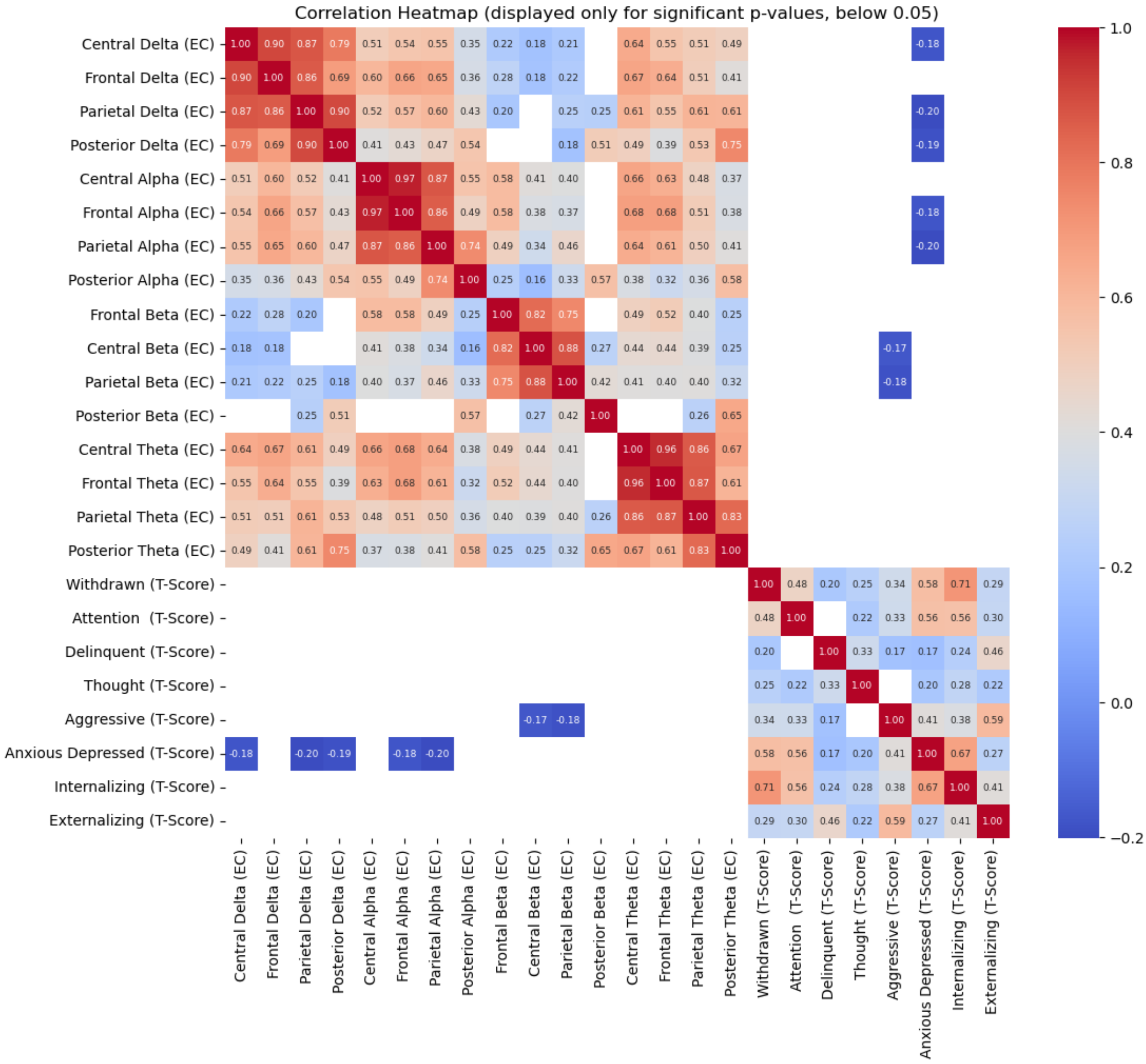

Figure S2. Correlation matrix for YASR scales and EEG Power Spectrum during eyes closed (EC) condition in the prenatally tobacco unexposed group.

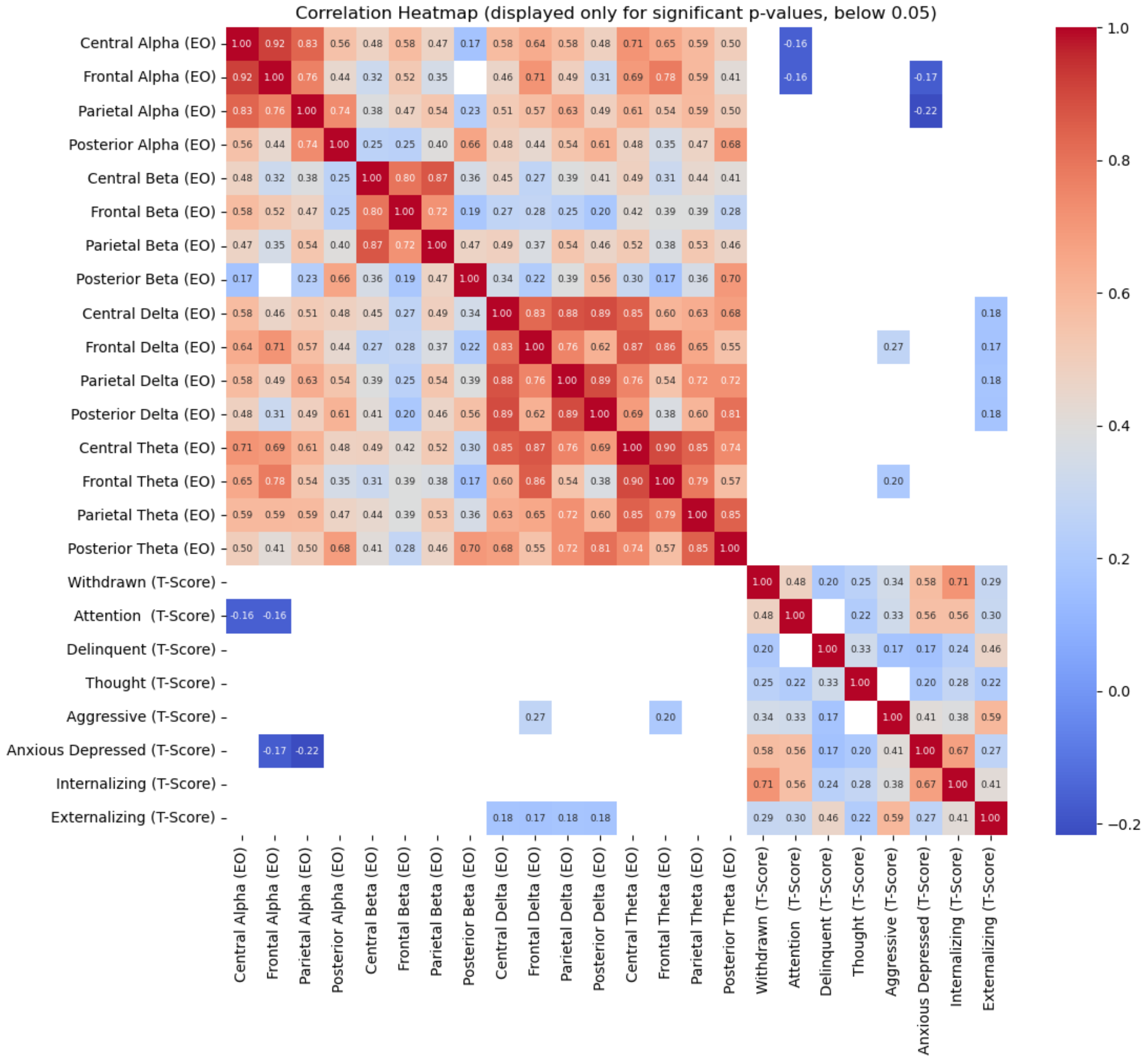

Figure S3. Correlation matrix for YASR scales and EEG Power Spectrum during eyes open (EO) condition in the prenatally tobacco unexposed group.

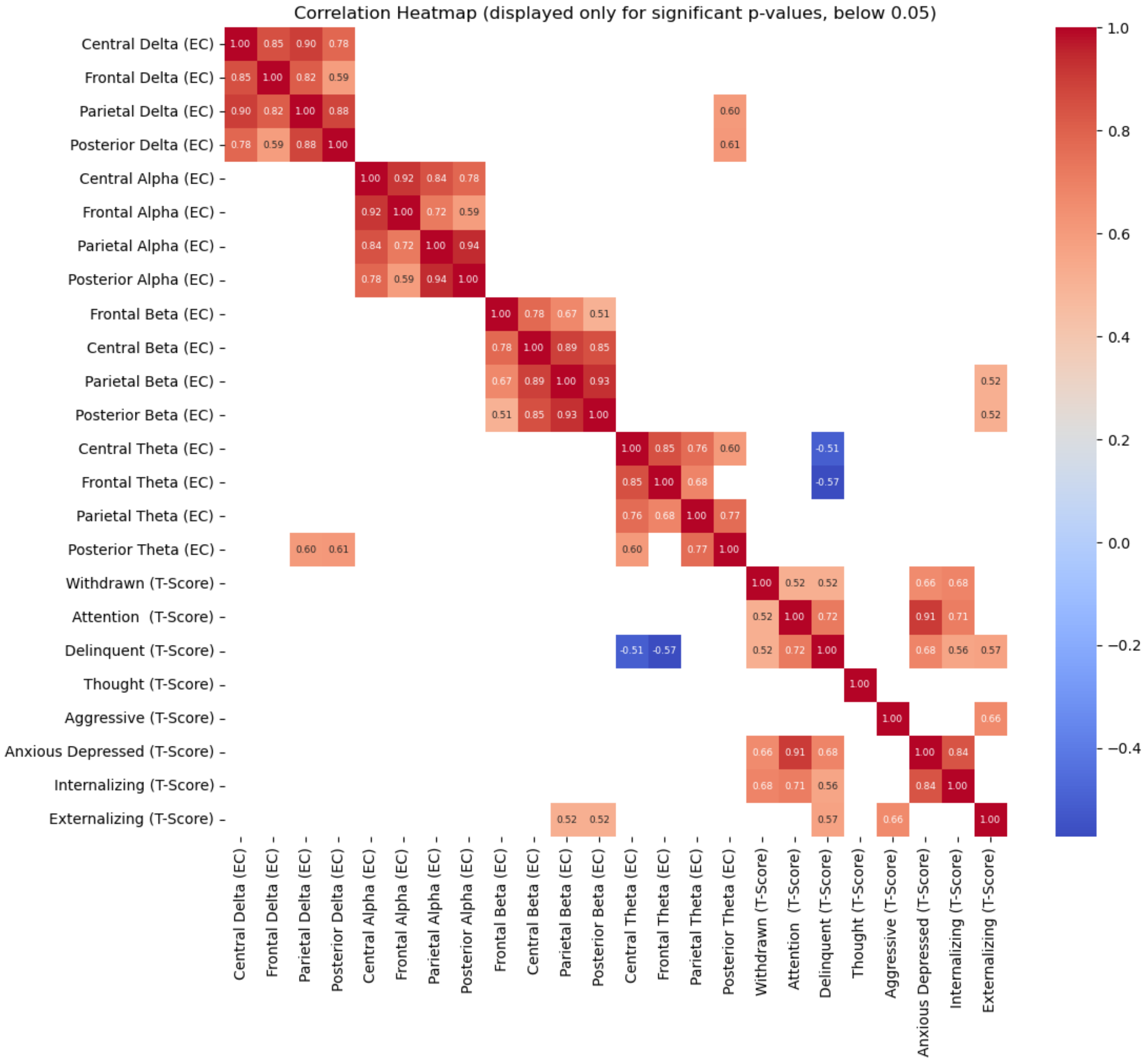

Figure S4. Correlation matrix for YASR scales and EEG Power Spectrum during eyes closed (EC) condition in the prenatally tobacco exposed (1-5 cigarettes/day) group.

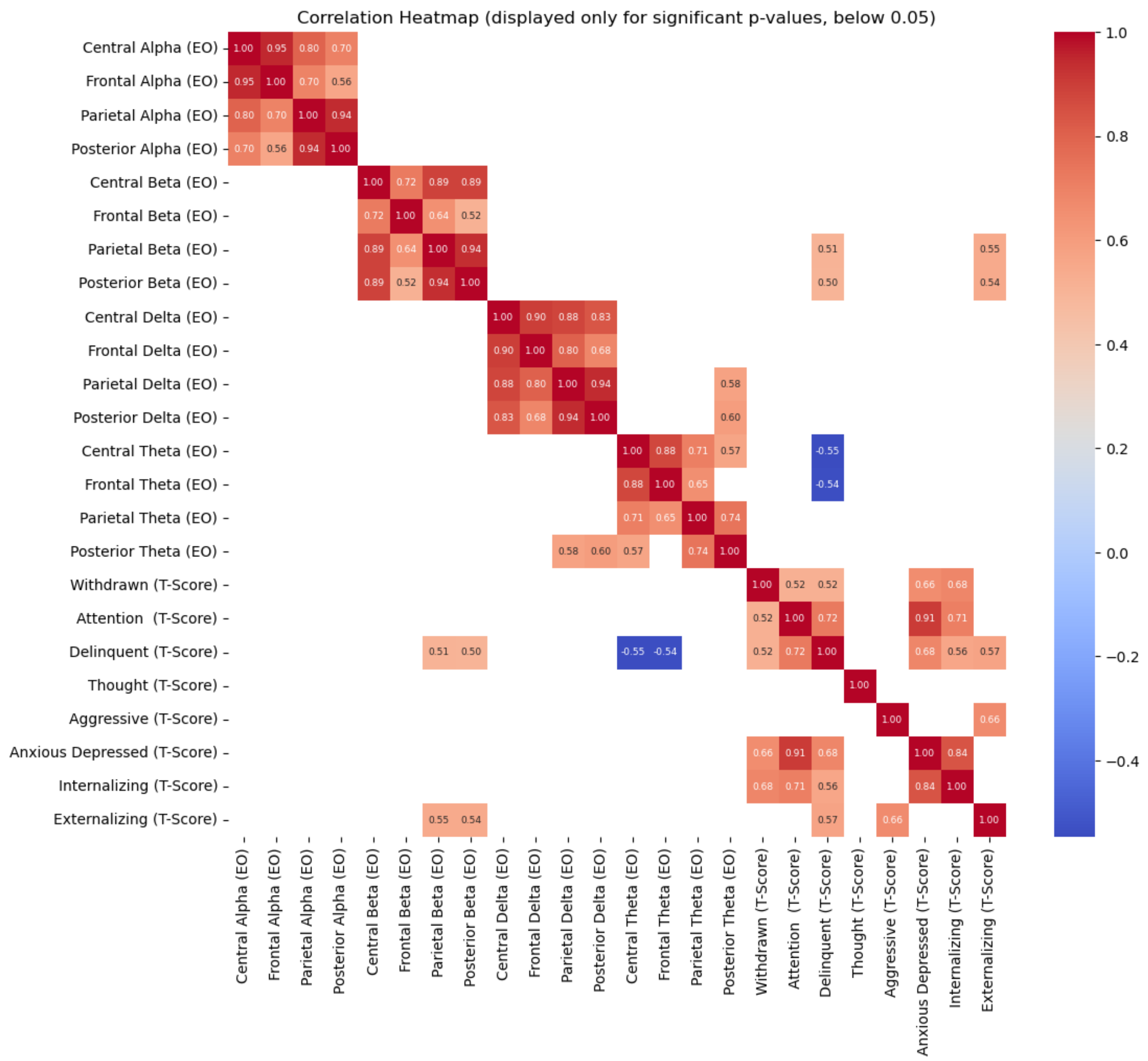

Figure S5. Correlation matrix for YASR scales and EEG Power Spectrum during eyes open (EO) condition in the prenatally tobacco exposed (1-5 cigarettes/day) group.

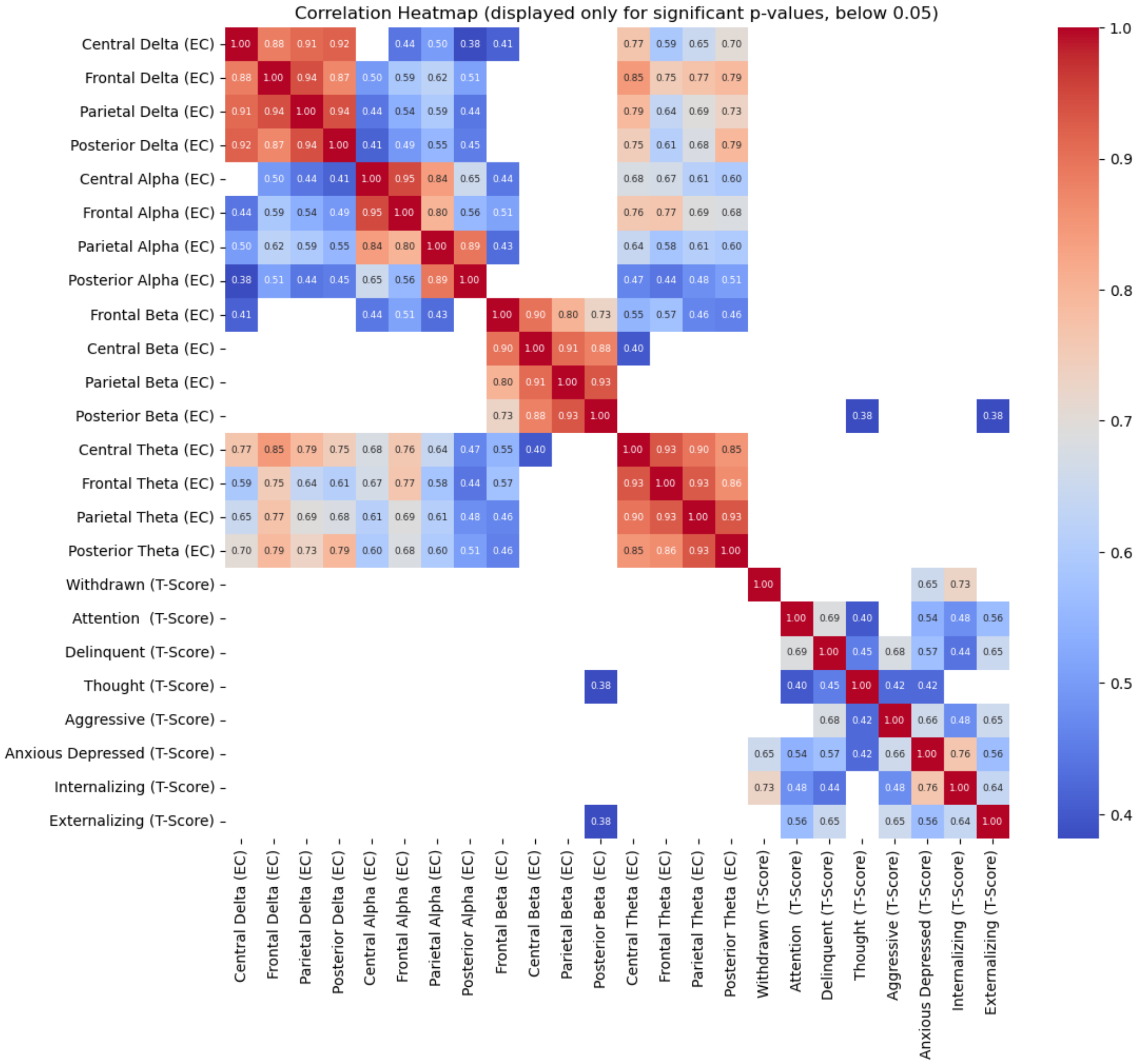

Figure S6. Correlation matrix for YASR scales and EEG Power Spectrum during eyes closed (EC) condition in the prenatally tobacco exposed (>5 cigarettes/day) group.

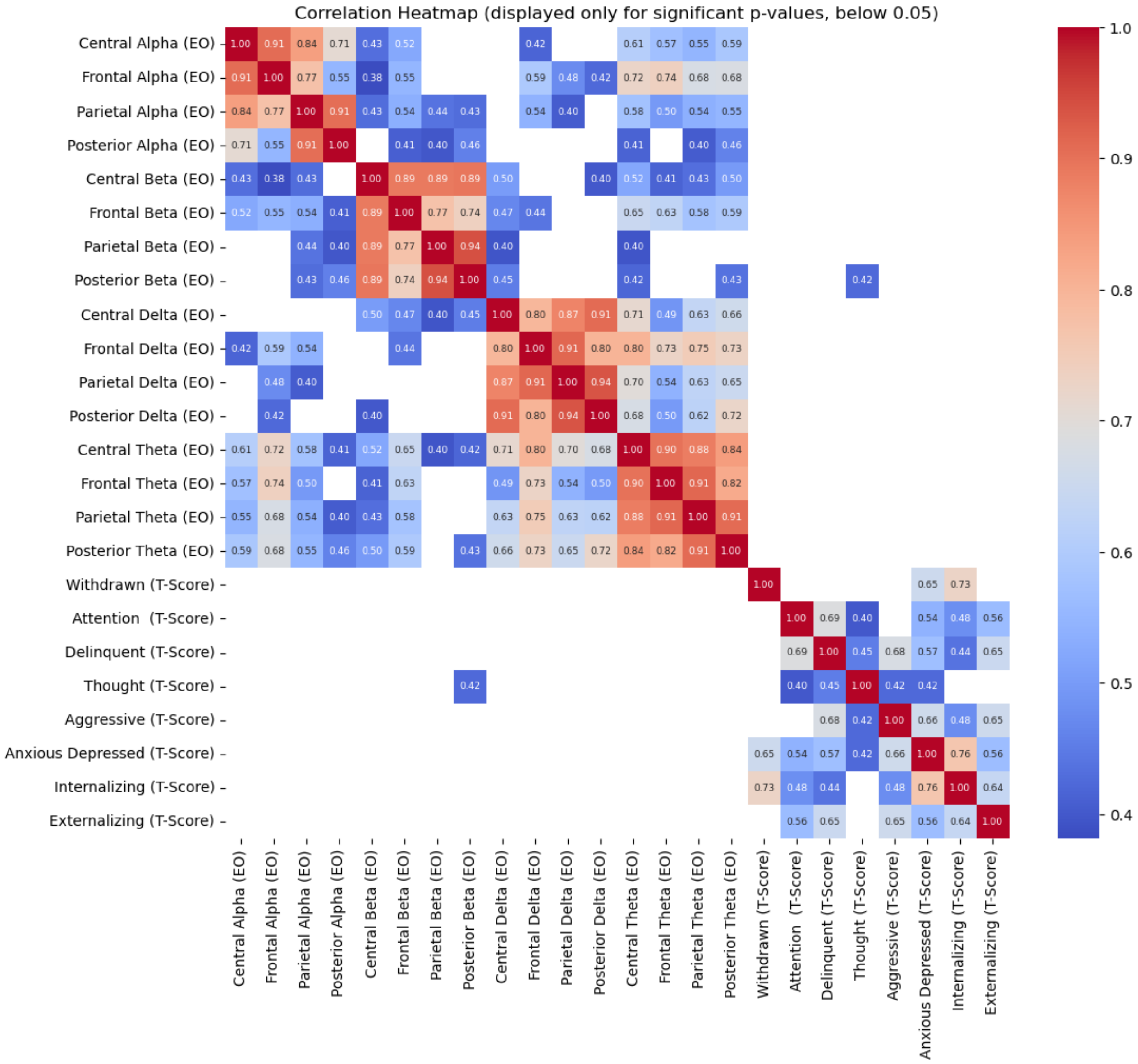

Figure S7. Correlation matrix for YASR scales and EEG Power Spectrum during eyes open (EO) condition in the prenatally tobacco exposed (>5 cigarettes/day) group.

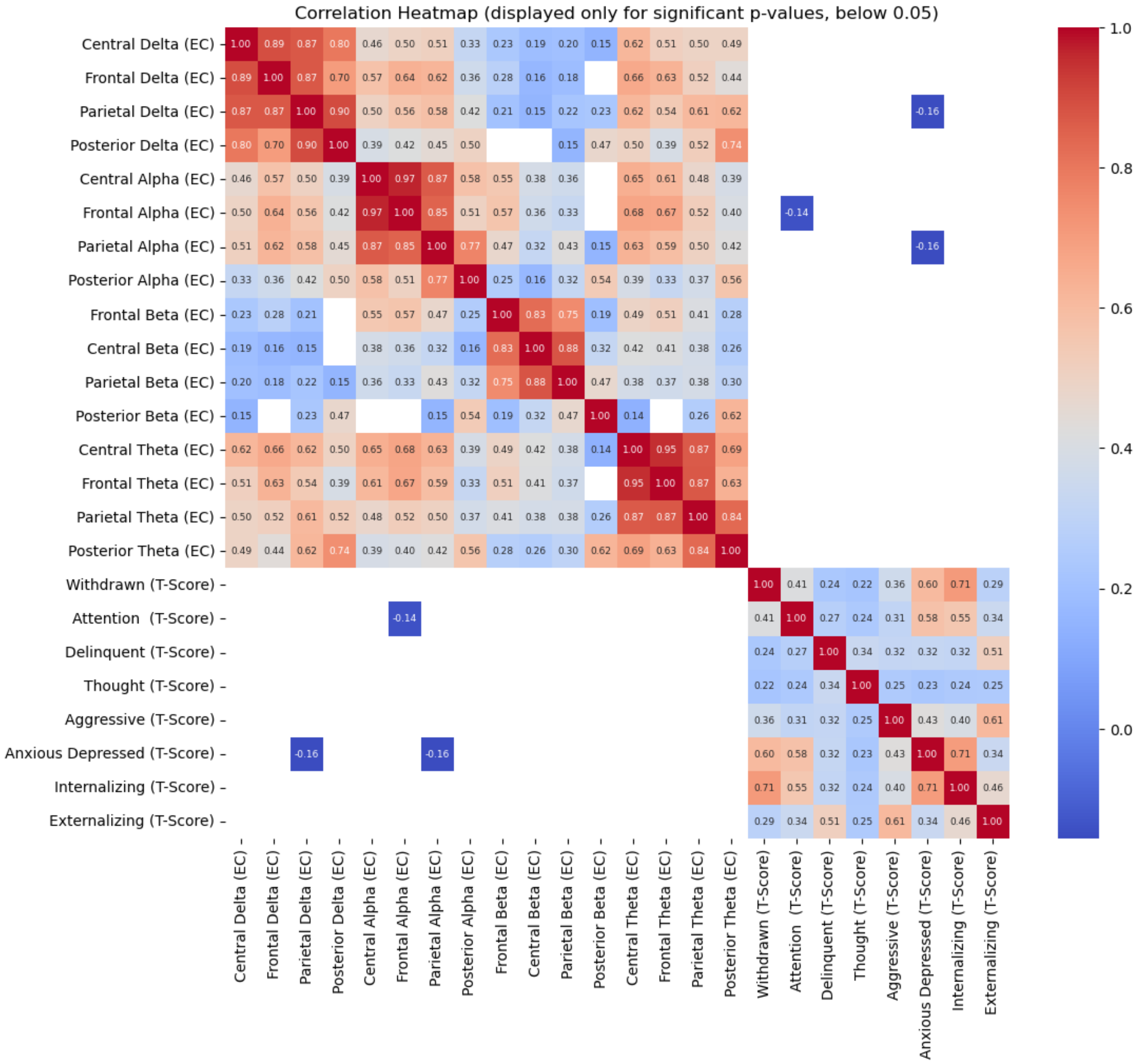

Figure S8. Correlation matrix for YASR scales and EEG Power Spectrum during eyes closed (EC) condition in the total sample.

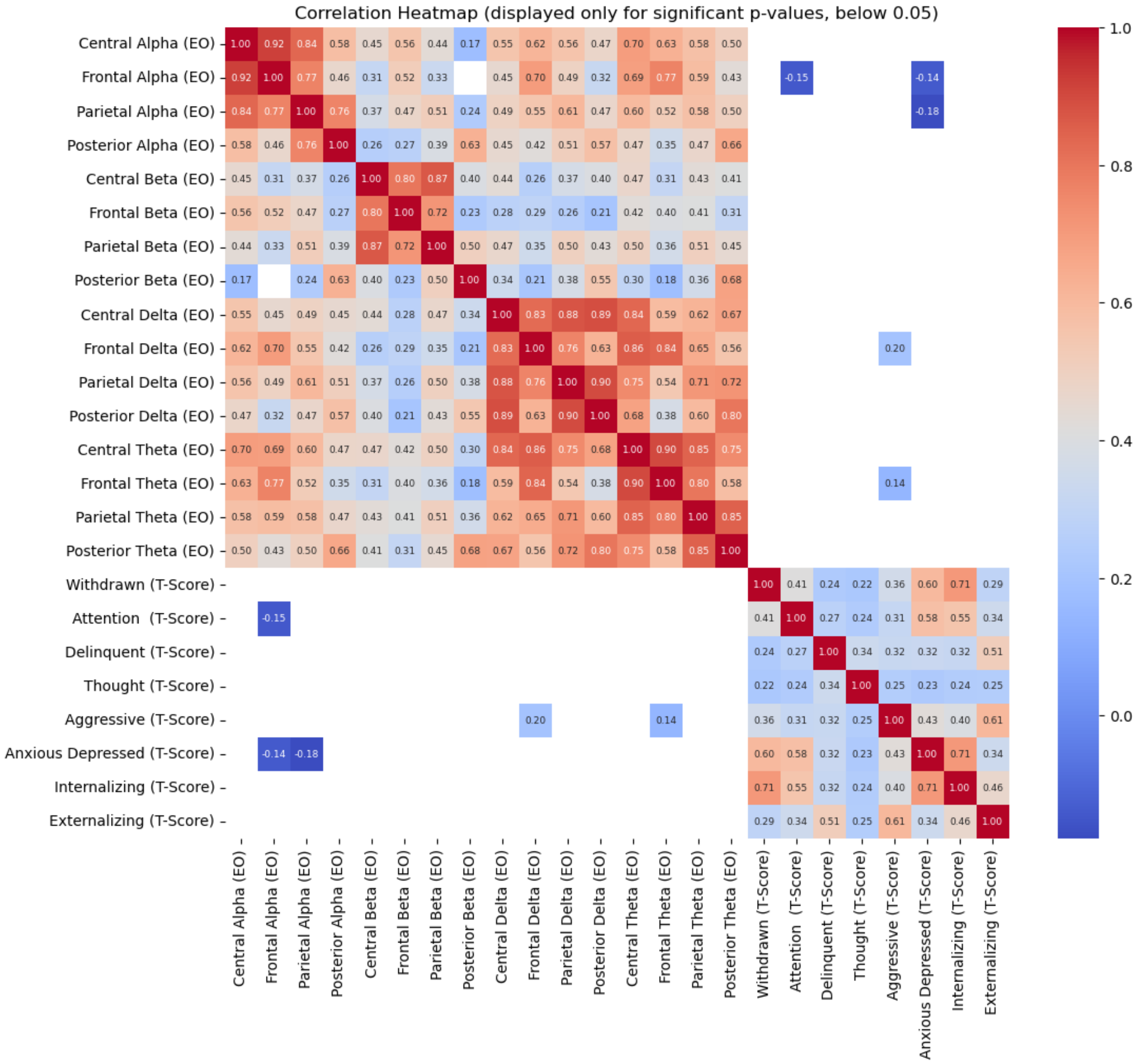

Figure S9. Correlation matrix for YASR scales and EEG Power Spectrum during eyes open (EO) condition in the total sample.

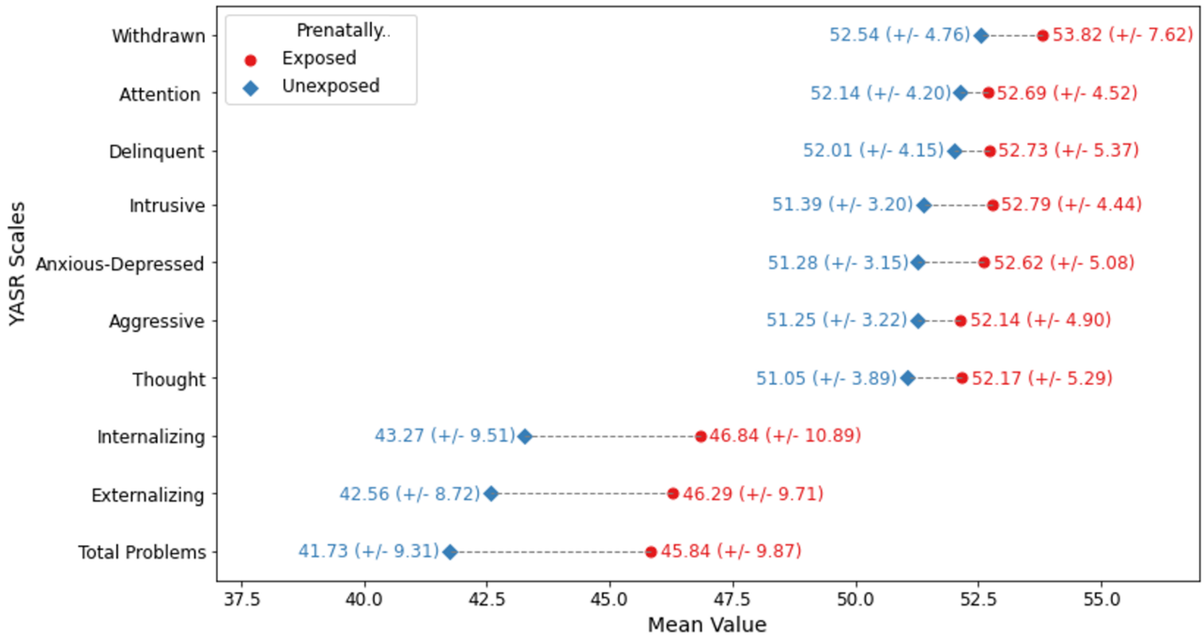

Figure S10. Descriptive statistics *M*(+/-*SD*) of the YASR subscales for prenatally tobacco exposed (*n*=55) and prenatally unexposed group (*n*=118).

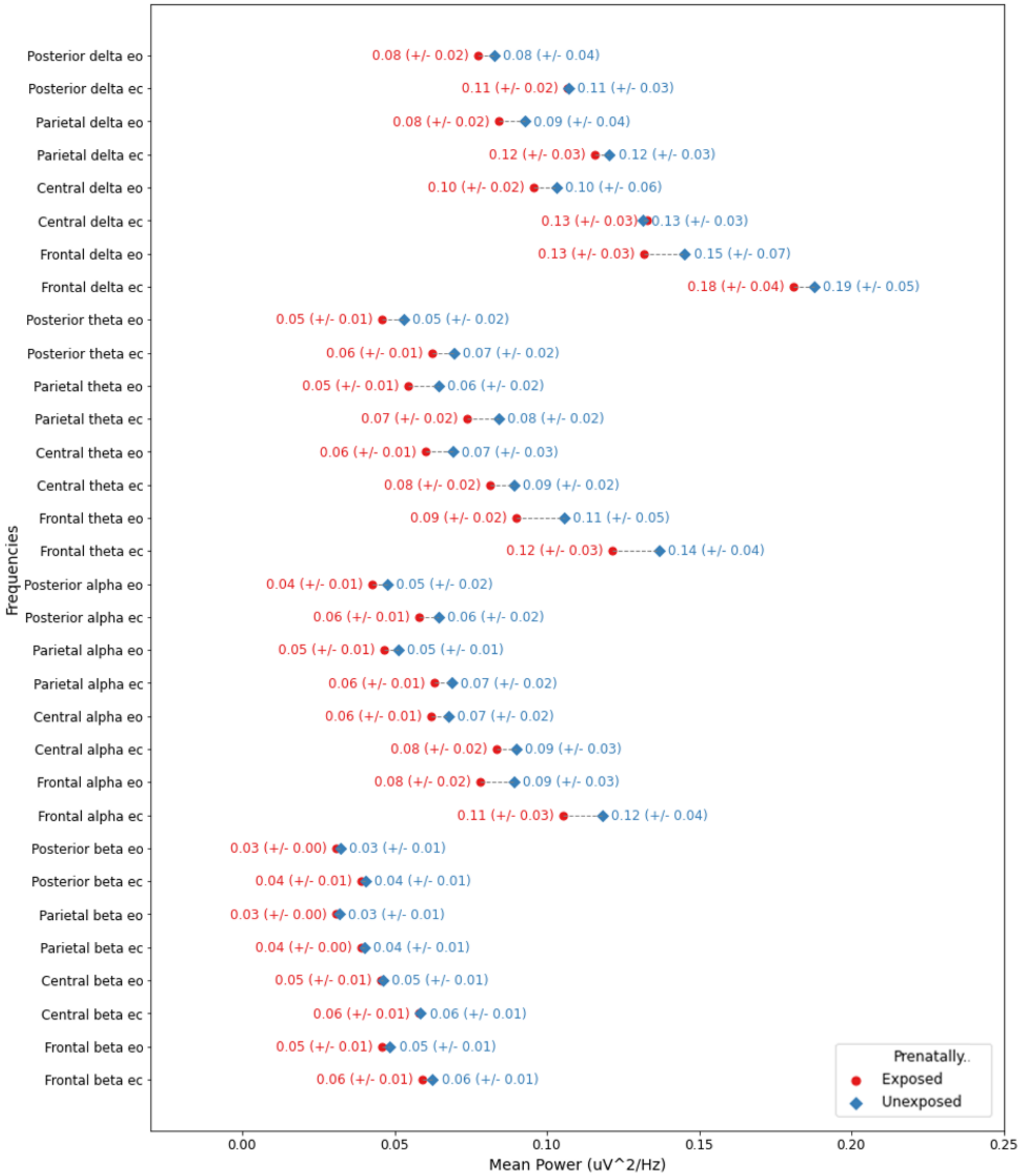

Figure S11. Brain activity descriptive characteristics *M*(+/-*SD*) of EEG resting-state conditions for prenatally tobacco exposed (*n*=55) and prenatally unexposed group (*n*=118).

Table S4. Results of GAMMs for EEG Power Spectrum during eyes open (EO) condition in Relation to Prenatal Smoking Habits (prenatally exposed vs. prenatally unexposed) **unadjusted for covariates**

		Exposed group				
Frequency band		**B**	**SE**	***p***	**R2**	**R2 adj**
Delta	Central	-0.01	0.01	0.410	0.35	0.00
	Frontal	-0.01	0.01	0.240	0.70	0.00
	Parietal	-0.01	0.01	0.181	0.91	0.00
	Posterior	-0.01	0.01	0.401	0.36	0.00
Theta	Central	-0.01	0.00	0.054	1.88	0.01
	Frontal	-0.02	0.01	**0.040**	2.13	0.02
	Parietal	-0.01	0.00	**0.006**	3.83	0.03
	Posterior	-0.01	0.00	**0.027**	2.48	0.02
Alpha	Central	-0.01	0.00	0.109	0.76	0.01
	Frontal	-0.01	0.01	**0.045**	1.31	0.02
	Parietal	-0.01	0.00	**0.036**	2.03	0.01
	Posterior	0.00	0.00	0.053	2.23	0.01
Beta	Central	0.00	0.00	0.057	1.83	0.01
	Frontal	0.00	0.00	0.520	0.21	0.00
	Parietal	0.00	0.00	0.206	0.82	0.00
	Posterior	0.00	0.00	0.398	0.37	0.00

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S5. Results of GAMMs for EEG Power Spectrum during eyes closed (EC) condition in Relation to Prenatal Smoking Habits (prenatally exposed vs. prenatally unexposed) **unadjusted for covariates**

		Exposed group				
Frequency band		**B**	**SE**	***p***	**R2**	**R2 adj**
Delta	Central	0.00	0.01	0.783	0.04	0.00
	Frontal	-0.01	0.01	0.418	0.34	0.00
	Parietal	0.00	0.01	0.396	0.37	0.00
	Posterior	0.00	0.01	0.925	0.00	-0.01
Theta	Central	-0.01	0.00	**0.038**	2.17	0.02
	Frontal	-0.02	0.01	**0.017**	2.87	0.02
	Parietal	-0.01	0.00	**0.009**	3.43	0.03
	Posterior	-0.01	0.00	0.053	1.90	0.01
Alpha	Central	-0.01	0.00	0.139	1.11	0.01
	Frontal	-0.01	0.01	0.051	1.93	0.01
	Parietal	-0.01	0.00	**0.046**	2.02	0.02
	Posterior	-0.01	0.00	0.056	1.85	0.01
Beta	Central	0.00	0.00	0.077	1.58	0.01
	Frontal	0.00	0.00	0.628	0.08	0.00
	Parietal	0.00	0.00	0.303	0.54	0.00
	Posterior	0.00	0.00	0.526	0.21	0.00

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S6. Results of GAMMs for YASR scales in Relation to Prenatal Smoking Habits (prenatally exposed vs. prenatally unexposed) **unadjusted for covariates**

	Exposed group				
YASR Scales	**B**	**SE**	***p***	**R2 (%)**	**R2 adj (%)**
Anxious	1.35	1.66	**0.005**	2.02	0.02
Withdrawn	1.28	0.49	**0.006**	2.41	0.02
Thought	1.12	0.56	**0.047**	1.28	0.01
Attention	0.55	0.56	0.329	0.31	0.00
Delinquent	0.72	0.59	0.224	0.48	0.00
Aggressive	0.89	0.49	0.069	1.07	0.01
Internalizing	1.40	0.47	**0.003**	2.86	0.03
Externalizing	3.58	1.30	**0.006**	2.41	0.02

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S7. Results of GAMMs for EEG Power Spectrum during eyes open (EO) condition in Relation to Prenatal Smoking Habits (prenatally exposed vs. prenatally unexposed) **adjusted for covariates**

		Exposed group				
Frequency band		**B**	**SE**	***p***	**R2**	**R2 adj**
Delta	Central	0.00	0.01	0.903	41.10	0.33
	Frontal	-0.01	0.01	0.334	8.37	0.00
	Parietal	0.00	0.01	0.576	38.10	0.30
	Posterior	0.00	0.01	0.820	46.40	0.40
Theta	Central	-0.01	0.01	0.276	7.55	0.00
	Frontal	-0.01	0.01	0.240	9.61	0.02
	Parietal	-0.01	0.00	0.094	15.30	0.08
	Posterior	0.00	0.00	0.265	28.90	0.20
Alpha	Central	-0.01	0.00	0.114	10.80	0.03
	Frontal	-0.01	0.01	0.068	17.30	0.10
	Parietal	-0.01	0.00	0.058	12.50	0.04
	Posterior	-0.01	0.00	0.059	10.30	0.01
Beta	Central	0.00	0.00	0.893	9.67	0.03
	Frontal	0.00	0.00	0.819	5.59	-0.02
	Parietal	0.00	0.00	0.841	16.60	0.08
	Posterior	0.00	0.00	0.970	13.30	0.05

Note: B represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S8. Results of GAMMs for EEG Power Spectrum during eyes closed (EC) condition in Relation to Prenatal Smoking Habits (prenatally exposed vs. prenatally unexposed) **adjusted for covariates***

Frequency band		Exposed group **B**	**SE**	***p***	**R2**	**R2 adj**
Delta	Central	0.00	0.01	0.428	15.60	0.09
	Frontal	0.00	0.01	0.906	15.70	0.09
	Parietal	0.00	0.01	0.700	25.50	0.19
	Posterior	0.00	0.01	0.361	21.40	0.15
Theta	Central	0.00	0.00	0.423	17.50	0.11
	Frontal	-0.01	0.01	0.289	18.60	0.12
	Parietal	-0.01	0.00	0.095	23.20	0.17
	Posterior	0.00	0.00	0.261	22.20	0.16
Alpha	Central	-0.01	0.01	0.228	11.80	0.05
	Frontal	-0.01	0.01	0.215	17.30	0.11
	Parietal	-0.01	0.00	0.126	10.60	0.03
	Posterior	-0.01	0.00	0.089	8.21	0.00
Beta	Central	0.00	0.00	0.967	10.30	0.03
	Frontal	0.00	0.00	0.565	5.42	-0.02
	Parietal	0.00	0.00	0.969	9.59	0.03
	Posterior	0.00	0.00	0.812	9.43	0.02

Note: *participant's sex, age, maternal psychopathology (assessed through an interview question with dichotomous self-rating), maternal alcohol consumption during first three month after giving birth, week of pregnancy at birth, smoking habits of participants and alcohol intake; *B* represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

Table S9. Results of GAMMs for YASR scales in Relation to Prenatal Smoking Habits (prenatally exposed vs. prenatally unexposed) **adjusted for covariates***

YASR Scales	Exposed group **B**	**SE**	***p***	**R2 (%)**	**R2 adj (%)**
Anxious	0.76	0.56	0.174	12.50	0.08
Withdrawn	0.58	0.69	0.488	9.26	0.04
Thought	0.44	0.63	0.481	11.30	0.07
Attention	-0.58	0.62	0.344	20.50	0.16
Delinquent	-0.97	0.58	0.096	23.80	0.20
Aggressive	-0.26	0.52	0.616	14.70	0.10
Internalizing	0.84	0.51	0.102	15.10	0.11
Externalizing	1.75	1.50	0.245	10.40	0.06

Note: *participant's sex, age, maternal psychopathology (assessed through an interview question with dichotomous self-rating), maternal alcohol consumption during first three month after giving birth, week of pregnancy at birth, smoking habits of participants and alcohol intake; *B* represents the regression coefficient, *SE* represents the standard error, and *p* represents the *p*-value. R^2 and R^2adj represent the variance explained and adjusted variance explained, respectively.

7 CURRICULUM VITAE AND PUBLICATIONS

Curriculum Vitae

Karina Janson

M. Sc. Psych.

*26th of March 1995 in Astana

Nationality: German

e-mail:karina.janson@zi-mannheim.de

phone:+49-157-3231-0907

Research foci

- Utilizing multimodal neuroimaging techniques, such as electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI), to explore the interaction between genetic predispositions and environmental factors in the development of childhood behavioral and mental health disorders.
- Neurodevelopmental processes underlying mental health disorders in children and adolescents, with a particular emphasis on Attention-Deficit/Hyperactivity Disorder (ADHD)
- Examining the role of parental and prenatal influences on brain development and behavior, focusing on how parental behavior, environment, and genetic factors interact to shape neurodevelopmental outcomes, including the risk for ADHD

Work experience

Since 02/2022	**Clinic for Child and Adolescent Psychiatry and Psychotherapy**, Central Institute of Mental Health, Mannheim Research/scientific assistant (PhD student); research groups: *Developmental Clinical Neurophysiology and Attention-*

	Deficit/Hyperactivity Disorder (ADHD) in childhood and adolescence
02/2018-02/2022	**Clinic for Child and Adolescent Psychiatry and Psychotherapy**, Central Institute of Mental Health, Mannheim Student (research) assistant; research groups: *Developmental Clinical Neurophysiology, Attention-Deficit/Hyperactivity Disorder (ADHD) in childhood and adolescence*
04/2016-02/2018	**Clinic for Child and Adolescent Psychiatry and Psychotherapy**, Central Institute of Mental Health, Mannheim Student trainee
06/2016-12/2016	**Psychological Outpatient Clinic**, Otto-Selz Institut, Mannheim Student trainee; focus: Clinical Psychological Diagnostics

(Academic) Education

10/2018-09/2020	University of Kaiserslautern Master of Science (M. Sc.) cognitive science (grade: 1.4; date: 7th of September 2020) Topic of the master´s thesis: *Evaluation of Short-term Stability in EEG Power Spectrum and Event-Related Potential (P3) During the Continuous Performance Task in Healthy School-Age Children*
09/2014-01/2018	University of Mannheim Bachelor of Science (B. Sc.) psychology
09/2013-07/2014	State Studienkolleg Nordhausen: W-Course (Economics) Focus: Economics, Mathematics
09/2002-06/2013	German Gymnasium Astana

Publication list

First author:

Jansone K, Eichler A, Fasching PA, Kornhuber J, Kaiser A, Millenet S, Banaschewski T, Nees F, On Behalf Of The Imac-Mind Consortium. Association of Maternal Smoking during Pregnancy with Neurophysiological and ADHD-Related Outcomes in School-Aged Children. Int J Environ Res Public Health. 2023 Mar 7;20(6):4716. doi: 10.3390/ijerph20064716. PMID: 36981624; PMCID: PMC10048892.

Janson K, Holz NE, Kaiser A, Aggensteiner P, Baumeister S, Brandeis D, Banaschewski T, Nees F; IMAC-Mind Consortium. Long-term impact of maternal prenatal smoking on EEG brain activity and internalizing/externalizing problem symptoms in young adults. Addict Behav. 2025 Jan;160:108175. doi: 10.1016/j.addbeh.2024.108175. Epub 2024 Sep 23. PMID: 39341184.

Gottfried, K., **Janson, K.,** Holz, N. E., Reis, O., Kornhuber, J., Eichler, A., … Nees, F. (2025). Semantic search helper: A tool based on the use of embeddings in multi-item questionnaires as a harmonization opportunity for merging large datasets – A feasibility study. European Psychiatry, 68(1), e8. doi:10.1192/j.eurpsy.2024.1808 (shared first authorship)

Janson, K., Bokde, A. L. W., Desrivières, S., Garavan, H., Gowland, P., Grigis, A., Heinz, A., Martinot, J.-L., Paillère Martinot, M.-L., Artiges, E., Papadopoulos Orfanos, D., Paus, T., Poustka, L., Smolka, M. N., Holz, N. E., Vaidya, N., Walter, H., Whelan, R., Schumann, G., Flor, H., Reis, O., Schwarz, E., Banaschewski, T., Nees, F., IMAGEN Consortium, & CoviDrug Consortium (under review). In its very early phases, COVID-19 shifts the associations between alcohol consumption and psychological symptoms in young adults.

Janson, K., Gottfried, K., Banaschewski, T., Nees, F., & IMAC-Mind Consortium (submitted). ItemComplex: A Python-based Framework for Ex-post Harmonization across Multi-item Instrument Data for Appropriate Handling of Large Cohort Data Sets.

Co-author:

Kaiser A, Aggensteiner PM, Holtmann M, Fallgatter A, Romanos M, **Abenova K,** Alm B, Becker K, Döpfner M, Ethofer T, Freitag CM, Geissler J, Hebebrand J, Huss M, Jans

T, Jendreizik LT, Ketter J, Legenbauer T, Philipsen A, Poustka L, Renner T, Retz W, Rösler M, Thome J, Uebel-von Sandersleben H, von Wirth E, Zinnow T, Hohmann S, Millenet S, Holz NE, Banaschewski T, Brandeis D, On Behalf Of The ESCAlife-Consortium. EEG Data Quality: Determinants and Impact in a Multicenter Study of Children, Adolescents, and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD). Brain Sci. 2021 Feb 10;11(2):214. doi: 10.3390/brainsci11020214. PMID: 33578741; PMCID: PMC7916500.

Ruchay Z, Pape J, Cordt JS, Kerres C, Siehl S, **Jansone K**, Ackermann J, Guenther V, Mettler L, Allahqoli L, Maass N, Nees F, Alkatout I. Does an aptitude for surgery exist and can we predict it? An experimental study. Int J Surg. 2024 Aug 1;110(8):4727-4735. doi: 10.1097/JS9.0000000000001577. PMID: 38729125; PMCID: PMC11325891.

Maja Neidhart, Rikka Kjelkenes, **Karina Jansone**, Barbora Rehák Bučková, Nathalie Holz, Frauke Nees, Henrik Walter, Gunter Schumann, Michael A. Rapp, Tobias Banaschewski, Emanuel Schwarz & Andre Marquand on behalf of the environMENTAL consortium. A protocol for data harmonization in large cohorts. Nat. Mental Health 2, 1134–1137 (2024). https://doi.org/10.1038/s44220-024-00315-0

Ziegler, M., Aggensteiner, P. M., Becker, K., Döpfner, M., Geissler, J., Hohmann, S., Holz, N., Huber, R., Igel, C., **Janson, K.,** Mechler, K., Millenet, S., Romanos, M., Brandeis, D., Banaschewski, T., & Kaiser, A. (submitted). 24h-actigraphy profiles of children with and without ADHD using functional linear modeling (FLM) – better insights or just more data?

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