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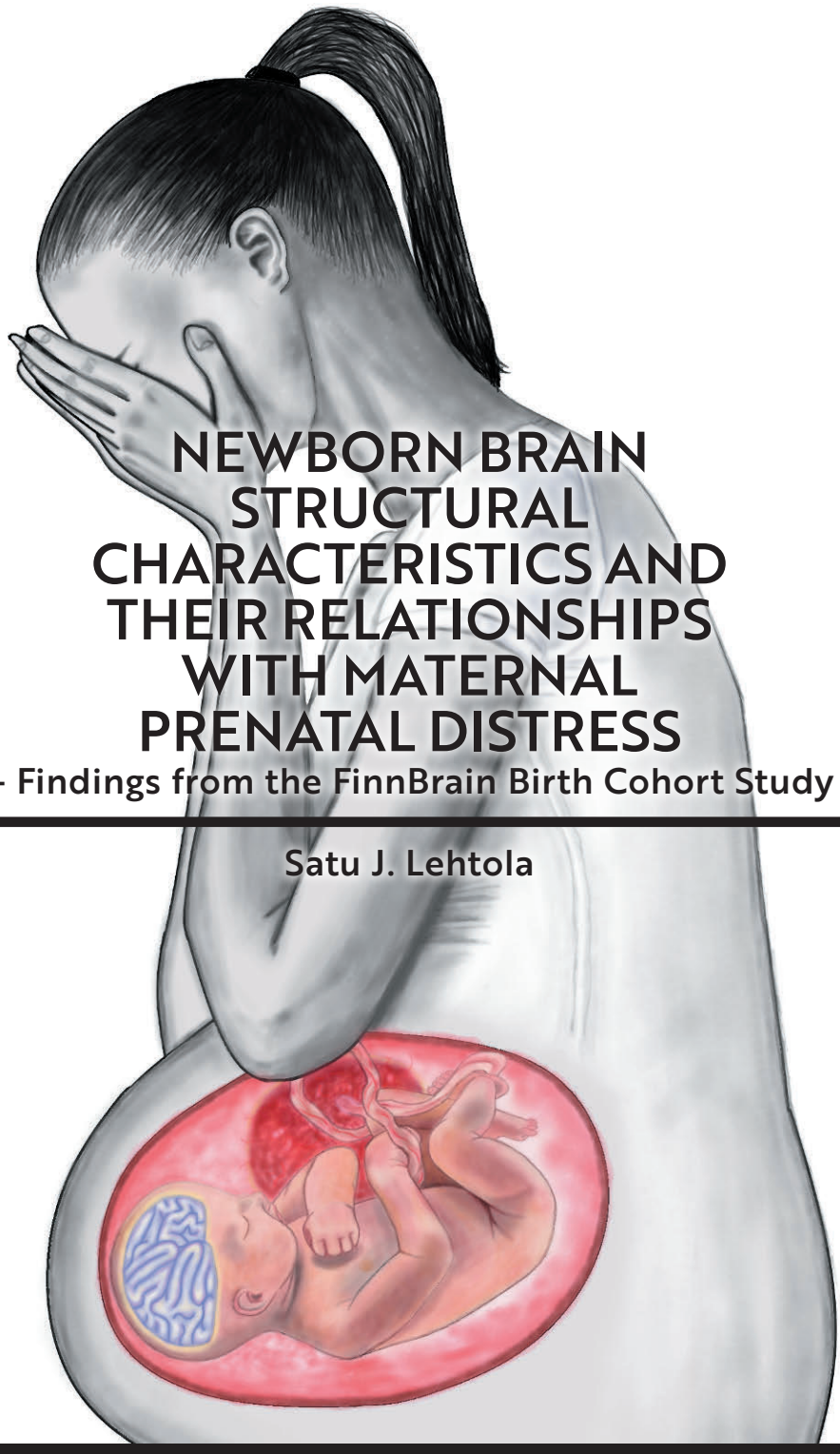

NEWBORN BRAIN STRUCTURAL CHARACTERISTICS AND THEIR RELATIONSHIPS WITH MATERNAL PRENATAL DISTRESS

– Findings from the FinnBrain Birth Cohort Study

Satu J. Lehtola

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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

Cover Image: Satu J. Lehtola

ISBN 978-951-29-8263-9 (PRINT)
ISBN 978-951-29-8264-6 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy, Turku, Finland 2020

To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Psychiatry
SATU J. LEHTOLA: Newborn brain structural characteristics and their relationships with maternal prenatal distress - Findings from the FinnBrain Birth Cohort MRI Study
Doctoral dissertation, 189 pp.
Doctoral Programme in Clinical Research (DPCR)
December 2020

ABSTRACT

Plasticity renders the brain sensitive to its intrauterine environment and susceptible to alterations during early brain development. The amygdala and hippocampus, structures key in socioemotional functions, are susceptible to these alterations. Understanding the normal variation in the newborn brain facilitates the recognition of such aberrant developmental trajectories, which may occur after exposure to maternal prenatal psychological distress (PPD) and result in a predisposition to psychopathology.

This study aimed to 1) describe the normal variation of newborn brain volumetric measures in relation to newborn characteristics; 2) assess the prevalence and risk factors of incidental findings in newborn brain magnetic resonance imaging (MRI); 3) investigate how different types and timings of maternal PPD associate with newborn amygdalar and hippocampal volumes, and whether this association is modified by newborn sex. Information on maternal depressive and anxiety symptoms was gathered at gestational weeks (GW) 14, 24 and 34, and pregnancy-specific anxiety (PSA) symptoms at GW24. Newborns were imaged with MRI at two to five weeks of postnatal age (n=175). The sub studies constituted variant samples sizes from the total population.

Newborn brain lobar volumes were similarly asymmetric in both sexes. Modest sex differences were observed in regional brain volumes. Newborn age predicted larger volumes of gray and white matter. The prevalence of incidental findings in brain MRI was 7.4 % and that of hemorrhages 6.9 %. Risk factors for hemorrhages were vaginal and vacuum-assisted deliveries. All the different types of PPD associated with the left newborn amygdalar volume at GW24 in a sex-specific manner. In males, PPD predicted smaller amygdalar volumes, while in females larger amygdalar volumes. Further analyses suggested a negative association between PSA and the right hippocampal volume in females. Newborn sex appears to be a significant factor moderating the relationship between PPD and newborn brain structures, suggesting sex-specific susceptibility to psychopathologies.

KEYWORDS: newborn brain, incidental finding, amygdala, hippocampus, maternal prenatal psychological distress

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Psykiatrian oppiaine
SATU J. LEHTOLA: Vastasyntyneen aivojen rakenteelliset ominaisuudet ja niiden yhteydet äidin raskaudenaikaiseen stressiin – tuloksia FinnBrain syntymäkohortin MRI-tutkimuksesta
Väitöskirja, 189 s.
Turun kliininen tohtoriohjelma (TKT)
joulukuu 2020

TIIVISTELMÄ

Aivojen muovautuvuus herkistää aivot kohdunsisäiselle ympäristölle ja lisää alttiutta muutoksille niiden kehityksessä. Muutoksille herkkiä rakenteita ovat mantelitumake ja aivoturso, jotka ovat tärkeitä sosioemotionaalisissa toiminnoissa. Aivorakenteiden normaalivaihtelun ymmärtäminen helpottaa poikkeavien kehityssuuntien havaitsemista, jollaisia voi kehittyä äidin raskaudenaikaiselle psykologiselle stressille (RPS) altistumisen jälkeen ja jotka voivat altistaa psykiatrisille häiriöille.

Tutkimuksen tavoitteena oli 1) kuvata vastasyntyneiden aivorakenteiden tilavuuksien normaalivaihtelua suhteessa vastasyntyneen ominaisuuksiin; 2) kartoittaa vastasyntyneiden aivojen magneettikuvantamisen sattumalöydösten esiintyvyys ja riskitekijät; 3) tutkia äidin RPS:n eri tyyppien ja ajoituksen yhteyttä vastasyntyneen mantelitumakkeen ja aivoturson tilavuuksiin, sekä vaikuttaako vastasyntyneen sukupuoli yhteyteen. Raskaana olevien äitien masennus- ja ahdistuneisuusoireita mitattiin raskausviikoilla (RV) 14, 24, 34 ja raskausspesifistä ahdistuneisuutta (RSA) RV:lla 24. Vastasyntyneet (n=175) kuvattiin magneettikameralla kahden-viiden viikon ikäisinä syntymän jälkeen. Osatutkimuksien otoskoot koostuivat vaihtelevista osista koko tutkimuspopulaatiota.

Vastasyntyneen aivolohkojen asymmetriassa ei ollut eroa sukupuolten välillä. Maltillisia sukupuolieroja havaittiin aivotilavuuksissa rajatuilla alueilla. Vastasyntyneen ikä ennusti suurempia harmaan ja valkean aineen tilavuuksia. Sattumalöydösten esiintyvyys aivokuvissa oli 7.4 % ja verenvuotojen 6.9 %. Verenvuotojen riskitekijät olivat alatie- ja imukuppisynnytykset. RPS:n eri tyypit olivat vahvimmin yhteydessä vastasyntyneiden vasemman mantelitumaketilavuuden kanssa RV:lla 24 sukupuoliriippuvaisella tavalla, mikä ilmeni pienempinä tilavuuksina poikavauvoilla ja suurempina tilavuuksina tyttövauvoilla. Lisäanalyysit viittasivat negatiiviseen yhteyteen RPS:n ja tyttöjen oikean aivotursotilavuuden välillä. Sukupuoli vaikuttaisi säätelevän RPS:n vaikutuksia vastasyntyneen aivoihin mahdollisesti lisäten alttiutta tietyllä sukupuolella toista useammin esiintyville psykiatrisille häiriöille.

AVAINSANAT: vastasyntyneen aivot, sattumalöydös, mantelitumake, aivoturso, äidin raskaudenaikainen psykologinen stressi

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Abbreviations

ACTH	Adrenocorticotropic hormone
ADHD	Attention deficit/hyperactivity disorder
AI	Asymmetry Index
AD	Axial Diffusivity
BMI	Body Mass Index
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
(p)CRH	(Placental) Corticotropin releasing hormone
DNA	Deoxyribonucleic acid
DSS	Deep subcortical structures
EPDS	Edinburgh Postnatal Depression Scale
FA	Fractional Anisotropy
FT	Foetal testosterone
$GABA_A$	Gamma-aminobutyric acid A
GCI	Generalized Conformity Index
GxE	Gene-environment interaction
GM	Gray matter
GR	Glucocorticoid receptor
GW	Gestational week
HPA	Hypothalamic-pituitary-adrenal
ICV	Intracranial volume
IL	Interleukin
IPH	Intraparenchymal hemorrhage
MDD	Major depressive disorder
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared Rapid Acquisition Gradient Echo
MR	Mineralocorticoid receptor
(s/f)MRI	(Structural/Functional) Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
PPD	Prenatal psychological distress
PRAQ(-R2)	Pregnancy-related Anxiety Questionnaire (Revised 2)

PSA	Pregnancy-specific anxiety
PTSD	Posttraumatic stress disorder
SCL-90	Symptom Checklist 90
SDH	Subdural hemorrhage
TBV	Total brain volume
TCV	Total cortical volume
TE	Echo time
TGM	Total gray matter volume
TI	Inversion time
TR	Repetition time
TWM	Total white matter volume
VP	Vasopressin
WM	White matter
11-β-HSD-2	11-beta-hydroxystreoid-dehydrogenase-type 2

List of Original Publications

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

I Lehtola SJ, Tuulari JJ, Karlsson L, Parkkola R, Merisaari H, Saunavaara J, Lähdesmäki T, Scheinin NM, Karlsson H. Associations of age and sex with brain volumes and asymmetry in 2–5-week-old infants. Brain Structure and Function, 224(1) 501–513, 2019.

II Kumpulainen V, Lehtola SJ, Tuulari JJ, Silver E, Copeland A, Korja R, Karlsson H, Karlsson L, Merisaari H, Parkkola R, Saunavaara J, Lähdesmäki T, Scheinin NM. Prevalence and risk-factors of incidental findings in Brain MRIs of healthy neonates – the FinnBrain Birth Cohort Study. Frontiers in Neurology, 10, 2020.

III Lehtola SJ, Tuulari JJ, Scheinin NM, Karlsson L, Parkkola R, Merisaari H, Lewis JD, Fonov VS, Collins DL, Evans A, Saunavaara J, Hashempour N, Acosta H, Karlsson H. Newborn amygdalar volumes are associated with maternal prenatal psychological distress in a sex-dependent way. NeuroImage: Clinical, 102380. 2020.

IV Lehtola SJ, Tuulari JJ, Karlsson L, Parkkola R, Lewis JD, Fonov VS, Collins DL, Evans A, Saunavaara J, Pelto J, Hashempour N, Lähdesmäki T, Scheinin NM, Karlsson H. Sex-specific changes in newborn limbic structures after exposure to maternal pregnancy-specific anxiety. (Manuscript)

1 Introduction

Delineating deviant brain developmental trajectories relies on knowledge of normal brain structure and development. Despite this crucial role of knowledge on early brain development in pathology recognition, rather few studies have concentrated on the structural characteristics of the newborn brain. Previous evidence indicates right-left hemispheric and/or lobar asymmetry to be present in the foetal and newborn brain (Gilmore et al., 2007; Rajagopalan et al., 2011; Tanaka et al., 2012). However, the results are in part inconsistent, and overall, the direction and location of these asymmetries in relation to newborn age and sex are poorly understood due to the relatively small number of studies performed. Sex seems to regulate brain growth as studies have reported larger total gray and white matter volumes in males compared to females, however, more subtle regional sex differences have also been described (Ruigrok et al., 2014). While previous studies have demonstrated the importance of a longer gestation in relation to larger brain volumes and newborn growth (Aanes et al., 2015; Bora et al., 2014; Munakata et al., 2013), information on whether the duration of pregnancy affects the brain volumes of term-born neonates is less certain. Additionally, some studies have observed a positive connection between birth weight and brain growth, but generally evidence is limited regarding the relationship between growth metrics and brain volumetric measures in full-term newborns. In conclusion, to date, much uncertainty still exists on the effects of sex, age and growth metrics on brain volumes and asymmetry in full-term newborns.

When conducting research on normal brain development, incidental findings, consisting mostly of hemorrhages and cysts, are a common occurrence in pediatric MR imaging. The prevalence of incidental findings varies greatly across studies; however, evidence has established birth-related hemorrhages to be the most prevalent finding. (Lind et al., 2010; Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004; Whitehead et al., 2013) Although common, the risk factors for these incidental hemorrhages remain somewhat elusive. Vaginal delivery is a known risk factor (Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004), but the findings are contradictory regarding assisted delivery, caesarian section, and other obstetric factors (Åberg et al., 2016; Ekéus et al., 2014; Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014). Additionally, the clinical significance of incidental

hemorrhages concerning later development and child outcome, especially in asymptomatic children, needs elaboration.

A variety of studies have established a link between maternal prenatal psychological distress (PPD) and impaired neurodevelopment, as well as an increased risk for psychopathology in the offspring (O'Donnell et al., 2014a; Van den Bergh et al., 2018). Furthermore, exposure to PPD has been associated with alterations in the offspring brain morphology of the amygdala and hippocampus (Van den Bergh et al., 2018), brain regions closely related to socioemotional behaviour and threat processing, and the pathophysiology of many psychiatric disorders (Passamonti et al., 2012; Schumann et al., 2011, 2004; Videbech, 2004; Woon and Hedges, 2008). Interestingly, some of these studies in children show the effects of PPD on the amygdalar volume to be sex specific (Acosta et al., 2019; Wen et al., 2017). Similar studies in newborns, designed to minimize the confounding effect of postnatal life circumstances, are limited, and the results partially inconsistent (Qiu et al., 2017, 2013; Rifkin-Graboi et al., 2013; Wu et al., 2020). Thus, more research on the influence of PPD on newborn brain is essential, including determining whether newborn sex acts as a moderating factor in this relationship creating a sex-specific susceptibility to PPD.

To these ends, the aims of this study were to first define newborn brain total and lobar volumetric measures and asymmetry, and explore their relationship to newborn sex, age, and growth metrics. Next, to assess the prevalence and types of incidental findings in newborn brain MRI and their risk factors, as well as clinical significance. Finally, to investigate how different types of prenatal maternal psychological distress affect the volumetric measures of the amygdala and hippocampus in newborns and to assess the relevance of newborn sex in these possible relationships.

2 Review of the Literature

2.1 Normal early brain development

The formation of the central nervous system (CNS) is a complex process, comprising of the proliferation, migration, and transition of the neural progenitor cells into the neural plate, which then folds to form the neural tube (Figure 1) and later develops into the brain and the spinal cord (Elshazzly et al., 2019). The beginning of this process can be first seen at approximately day 18 after fertilization, and by the end of the embryonic period (the first eight weeks of development), the elementary structures of the CNS are established (Nieuwenhuys et al., 2008). The gross anatomical changes in the brain structures are the result of extensive transformations on the cellular level. In most brain areas, neurons are produced from the embryonic period until mid-gestation (Stiles and Jernigan, 2010). Neurons migrate radially from the ventricular zone, developed from the neural tube, and tangentially from a secondary proliferative zone in ganglionic eminences towards the neocortex. The neocortex is the thin, gray, superficial layer of the brain containing nerve cells (Gibb and Kolb, 2018). Apart from the neocortex, neurons form gray matter (GM) structures in other parts of the CNS, such as the deep subcortical structures (DSS) and spinal column. Then the neurons start branching out to form connections with other neurons by extending their dendrites and axons, which form the brain white matter (WM) tracts (Stiles and Jernigan, 2010).

After gestational week (GW) 18 the brain has grown sufficiently large for it to be evaluated by magnetic resonance imaging (MRI) (Barkovich and Barkovich, 2019). During this time of proliferation and migration, the brain volumes grow exponentially. Between GW18 and GW39, the cortical GM volume increases 21-fold, WM 22-fold, and the DSS 10-fold. Growth of WM and DSS is greater in the second trimester compared with the third, whereas cortical GM grows twice as much in the third trimester compared to the second – just as the migrating neurons arrive to their destinations (Andescavage et al., 2016). However, WM grows generally at a slower pace compared to GM but the growth period extends until early adulthood as the WM tracts gradually form myelin sheaths, a process called myelinization (Girard et al., 1991).

At first, the human brain is a smooth structure, which gradually evolves into the folded adult pattern of gyri and sulci through gyrification by an orderly progression. The longitudinal fissure starts to form first rostro-caudally as early as GW8 until GW22 (Nishikuni and Ribas, 2013; Stiles and Jernigan, 2010). The next stage is the formation of other primary sulci: Sylvian, Cingulate, Parieto-Occipital and Calcarine between GW14 and GW16; Central and Superior Temporal between GW20 and GW24 and Superior Frontal, Precentral, Inferior Frontal, Postcentral, as well as Intraparietal between GW25 and GW26 (Nishikuni and Ribas, 2013; Stiles and Jernigan, 2010). Secondary sulci form during late pregnancy (GW30-35), and the development of tertiary sulci starts from GW36 and continues to the postnatal period (Nishikuni and Ribas, 2013; Stiles and Jernigan, 2010). As the foetal brain grows and develops, it also produces a great number of neurons, of which 50 % or more are eliminated prenatally by naturally occurring cell death called apoptosis (Chan et al., 2002). This vast number of neurons create an extensive connective network by synapses, a large proportion of which are drastically cut down by synaptic pruning taking place mostly during the postnatal period (Gibb and Kolb, 2018). This function of pruning is meant to eliminate all unnecessary connections allowing more reserves to be directed to the areas or synapses that are more frequently used. Overall, brain development is a continuously changing process of cell proliferation, synaptogenesis, and WM maturation, as well as cell death and synaptic pruning that is reflected in differential growth trajectories, which depend on the region and function assigned to that region (Nieuwenhuys et al., 2008; Stiles and Jernigan, 2010). Some studies have argued that these changes might be seen in the MRI studies done in newborns, children, and adolescents, as regional cortical thinning and thickening (Remer et al., 2017; Shaw et al., 2008; Sowell et al., 2007).

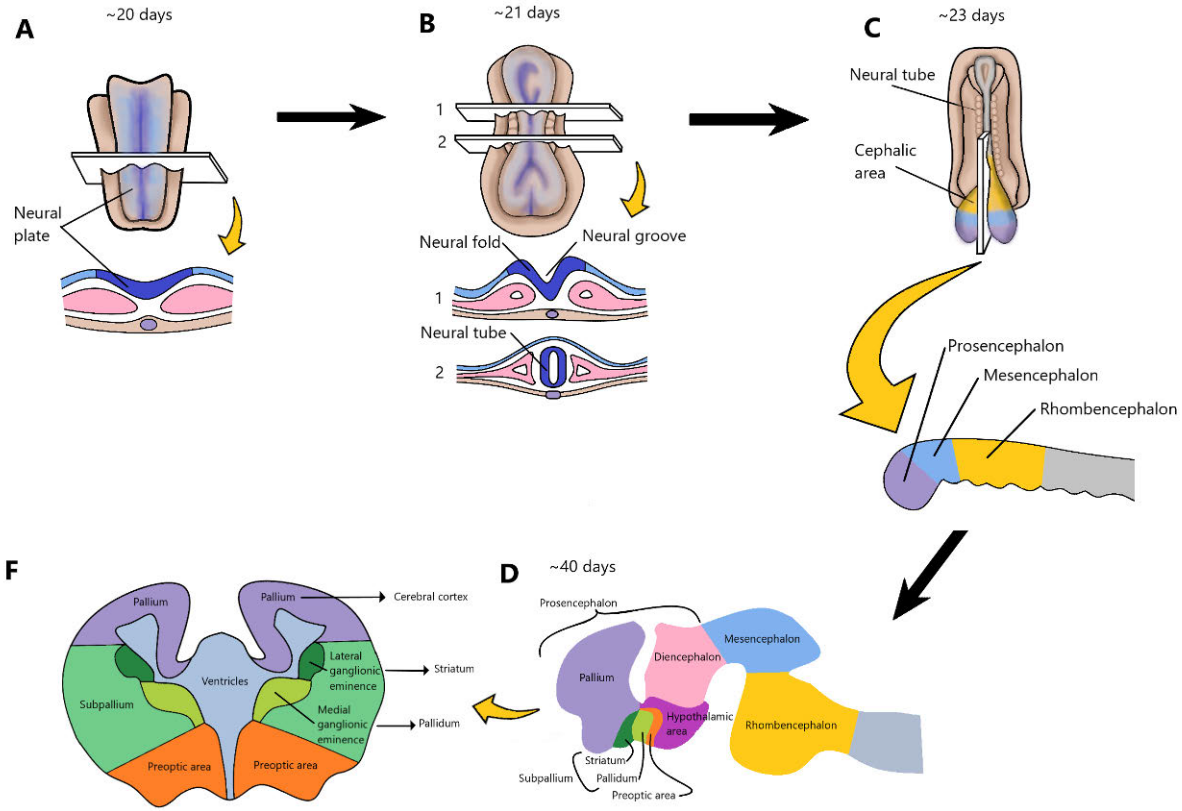

Figure 1. Schematic illustration of the early brain development. A) The neural plate at approximately 20 days; B) The folding of the neural plate to the neural tube at approximately 21 days; C) The cephalic portion enlarges and forms three distinct brain vesicles the Prosencephalon (Forebrain), Mesenphalon (Midbrain), and Rhobencephalon (Hindbrain); D) The Prosencephalon develops further to the Pallium, Subpallium, Hypothalamic area and Diencephalon at approximately 40 days; F) A coronal plane of the future cerebral cortex (Pallium) and basal ganglia (Subpallium), with the secondary proliferative zones, the ganglionic eminences, from wich the tangentially migrating neurons originate. First row images are the author's illustration. Second row images are adapted from Malt et al. (2016).

2.1.1 Hemispheric and lobar asymmetry

The brain hemispheres go through dynamic changes throughout life. In the foetus, the left hemisphere demonstrates a larger volume than the right from mid to late pregnancy; and this applies also to DSS, but the latter seems to equalize by term (Andescavage et al., 2016). In newborns, the left hemisphere has also been observed to be larger than the right (Gilmore et al., 2007), however, during childhood and adolescence, the hemispheric asymmetry seems to gain its adult-like form of rightward asymmetry (Giedd et al., 1996; Reiss et al., 1996), although one study observed this only in WM volume (Matsuzawa, 2001).

The lobes of the human brain (Figure 2) are also asymmetric by hemisphere: studies across a wide age range (from foetuses to adolescents) have shown the right temporal lobe to be larger than the left (Dean et al., 2018a; Mark et al., 1999; Matsuzawa, 2001; Rajagopalan et al., 2011), and in foetal and infant brain, the left occipital lobe was found to be larger than the right (Gilmore et al., 2007; Rajagopalan et al., 2011). However, especially later in postnatal life, brain developmental trajectories depend on brain region, hemisphere, and sex (Tanaka et al., 2012). Gray matter (GM) volume in the frontal lobe peaks approximately one year earlier in females than in males, between the ages 9 and 12 years (Giedd et al., 1999; Lenroot et al., 2007a; Tanaka et al., 2012). The temporal lobe has been observed to have similar growth patterns between sexes around the same age cohort (Lenroot et al., 2007a; Tanaka et al., 2012), although one study reported its peak age to be slightly earlier in males (16.5 years) than females (16.7 years) (Giedd et al., 1999). Although some evidence exists on early brain asymmetry, few studies have yet investigated brain asymmetry in newborns and whether it is affected by newborn age and sex.

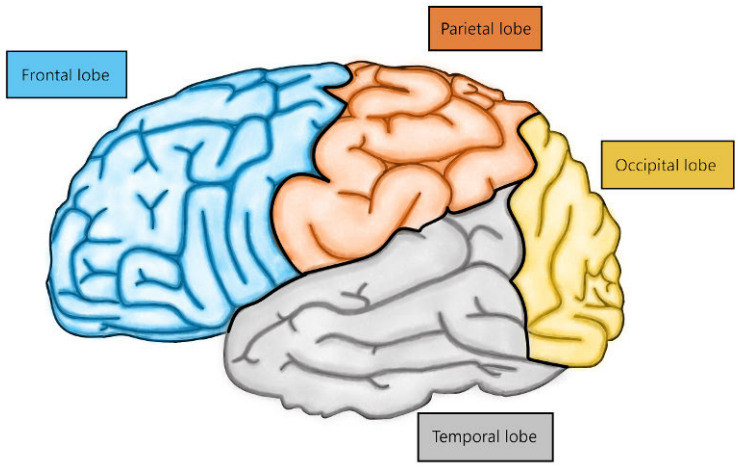

Figure 2. The lobes of the human brain. Author's illustration.

2.1.2 Limbic system

The limbic system is considered to be a functional concept (not empirically proven) consisting of certain brain areas and their connections, which form intricate neural circuits. The limbic system integrates internal and external sensory input to adapt the individual into the environment by regulating autonomic functions (including hormone production from the hypothalamus), memory, emotions, and motivation (McLachlan, 2009; Rajmohan and Mohandas, 2007). Although no universal definition of the structures which comprise the limbic system exists, the following components are usually mentioned: limbic cortex (cingulate gyrus, parahippocampal gyrus), hippocampal formation (dentate gyrus, hippocampus, subicular complex), amygdala, septal area and hypothalamus. Some of these structures also have close connections to some of the other cortical areas and DSS: the hippocampus with the entorhinal cortex; the amygdala with the prefrontal/temporal association cortices, orbitofrontal and anterior temporal cortices, as well as the thalamus. The limbic structures, in particular the amygdala and hippocampus, have been associated with psychopathology (see paragraph 2.1.3), however, the links between the findings and the symptomatology are unclear. Previous studies have shown stress to induce morphological changes in both the amygdala and hippocampus, as well as greater depressive or anxiety-like behaviour (Leuner and Gould, 2010; Roozenaal et al., 2009) (see paragraph 2.5). Thus, it is important to better understand their characteristics in infancy, and the possible susceptibility to exposures such as maternal prenatal psychological distress. The following paragraphs will concentrate more closely on these two structures: the amygdala and the hippocampus.

2.1.2.1 Amygdala

The amygdala is a formation of clustered nuclei located in the anterior part of the temporal lobe (Schumann et al., 2011; Swanson, 2006) (Figure 3). It is involved in the functions of emotional memory, social cognition, fear conditioning, aggression, and anxiety (Rajmohan and Mohandas, 2007). The amygdala has three regions differentiated by their cytoarchitectonic organization and network connections. The structure most pertinent to fear conditioning is the basolateral nuclear group of the amygdala, which consists of the lateral, basolateral, paralaminar, basomedial and endopiriform nuclei, and connections amongst them (Mai and Paxinos, 2011). The activity of the basolateral amygdala influences memory integration and plastic features of other brain regions, such as the hippocampus (Roozenaal et al., 2009). In addition, the amygdala appears to display structural plasticity when subjected to stress (see paragraphs 2.4 and 2.5).

The development of the amygdaloid complex starts by the thickening of the ventrocaudal wall of the interventricular foramen approximately 6 weeks after

conception, and occurs simultaneously with the evagination of the cerebral hemisphere (Humphrey, 1968). Cell migration originates from two ganglionic eminences that form the primordial amygdala, in which three major parts are recognizable: the anterior amygdaloid area, the basolateral complex, and the corticomedial complex (Humphrey, 1968; Muller and O'Rahilly, 2006). The differentiation pace of the complexes vary as the corticomedial complex develops faster than the basolateral complex (Muller and O'Rahilly, 2006). This is possibly due to the early connection of the corticomedial complex with the brainstem, whereas the basolateral parts have strong connections with association areas in the neocortex, which also develop later (Ulfig et al., 2003).

After GW8, a relocation of structures occurs: the lateral parts rotate medially and posterior parts shift anteriorly. The medial nucleus changes its position the least (Humphrey, 1968). In addition, at this stage, the developing amygdaloid nuclei are closely connected to the pathways connecting a part of the forebrain to the hindbrain (medial forebrain bundle), as well as to the surrounding formations of hippocampus, hypothalamus and thalamus composing the primordial limbic system (Muller and O'Rahilly, 2006). Between GW22 and GW25 transient columnar cell clusters appear in the inferior parts of the amygdaloid nuclei and within them the radial glial fibres (Nikolić and Kostović, 1986), which are hypothesized to represent cell and axon migration (Rakic, 1995; Ulfig et al., 2003). GW26 to GW34 the clustered column formations start to lose contact from the ganglionic eminences and the fibres have shifted from within the columns to surround them in a basket-like position (Setzer and Ulfig, 1999). Then between GW35 and GW42, columnar cell aggregations are no longer visible and fewer fibres can be detected in the basket-like formation (Setzer and Ulfig, 1999; Ulfig et al., 2003). After GW39, various neuronal types can be distinguished (Ulfig et al., 2003, 1999). Thus, by eight to nine gestational months neural cell migration has mainly ended and the amygdalar cellular structure is highly similar to that of the mature amygdala (Ulfig et al., 2003, 1999).

In MRI studies, rightward amygdalar asymmetry has been observed in one month olds (Dean et al., 2018a) that resembles the asymmetry in an adult amygdala (Pedraza et al., 2004). However, in another study, rightward asymmetry was present only in the male amygdala of 109 healthy individuals aged one month to 25 years (Uematsu et al., 2012). Moreover, evidence from dissections of adult human amygdalae suggests that asymmetry differs between the amygdalar nuclei, with the LA nucleus showing greater asymmetry than others (Murphy Jr et al., 1987).

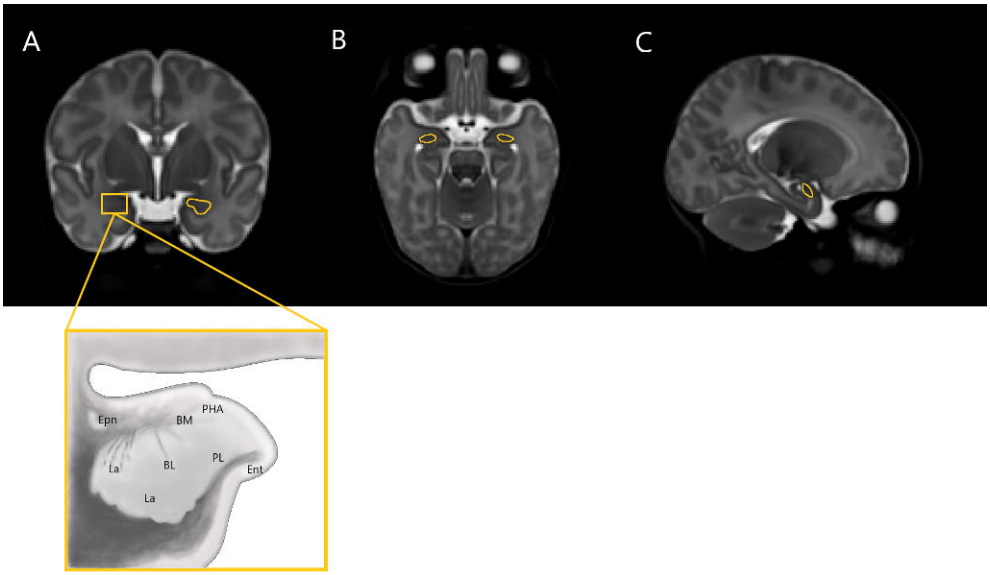

Figure 3. Author's illustration of the location and shape of the newborn amygdala in coronal, axial and sagittal planes. The lower image illustrates the different amygdalar fields in a coronal plane. Endopiriform nucleus (Epn), Parahippocampal-amygdaloid transition area (PHA), Basomedial (BM), Basolateral (BL), Lateral (La), Paralaminar nucleus (PL), Entorhinal cortex (Ent).

2.1.2.2 Hippocampus

The hippocampus is located in the medial and dorsal aspects of the temporal lobe, close to the amygdala (Insausti and Amaral, 2012) (Figure 4). The hippocampus is essential for long-term, declarative memory, but is also responsible for storing new memories with the adjacent cortex, parahippocampal and entorhinal regions, as well as the processing of fearful memories in conjunction with the amygdala and prefrontal cortex (Rajmohan and Mohandas, 2007). The hippocampus is a highly plastic structure, which maintains neurogenesis and dynamic modifications of dendrites and synapses into adulthood (Leuner and Gould, 2010). This structural plasticity is subject to several modifying environmental factors (Leuner and Gould, 2010), which are discussed more in detail in paragraphs 2.4 and 2.5.

The structures of the primordial hippocampal formation can be identified histologically as early as at GW9 (Humphrey, 1967). At GW10 a broad shallow hippocampal sulcus appears when the telencephalic wall of the primordial dentate gyrus becomes thicker than that of the cornu ammonis (Humphrey, 1967; Kier et al., 1997). Between GW15 and GW19, the hippocampus has begun to flex over the parahippocampal gyrus, thus forming the hippocampal fissure. Subicular, ammonic, and dentate subfields are readily identifiable (Arnold and Trojanowski, 1996). At this foetal stage, neuroblasts migrate between the different cell layers and many of

them turn to mature pyramidal cells, but mostly immature cells are predominant, especially in the superficial parts (Arnold and Trojanowski, 1996).

By GW18 to 21, the hippocampal formation begins to resemble the adult hippocampal region (Kier et al., 1997), and rightward volumetric asymmetry can be detected (Ge et al., 2015). Between GW20 and GW25 the volume of the hippocampus has expanded, and it has continued to fold over the parahippocampal gyrus (Arnold and Trojanowski, 1996). The migrational cell streams become fewer, pyramidal cells grow, and are more sparsely located, and the number of immature cells decrease, especially in the deep cell layers (Arnold and Trojanowski, 1996). At GW32 to GW34 the cell migration has mostly ended, the organization of the cell layers is more evident, but there are still some clusters of immature cells scattered along the superficial parts (Arnold and Trojanowski, 1996). At GW39 to GW40 the predominantly adultlike cytoarchitectural features of the various hippocampal subfields are present (Arnold and Trojanowski, 1996). The right-larger-than-left hippocampal asymmetry seems to persist in infancy, childhood, into early adulthood (age 25), presumably because of the earlier need of visuospatial abilities, functions considered to reside in the right hemisphere (Mark et al., 1999; Thompson et al., 2009; Uematsu et al., 2012).

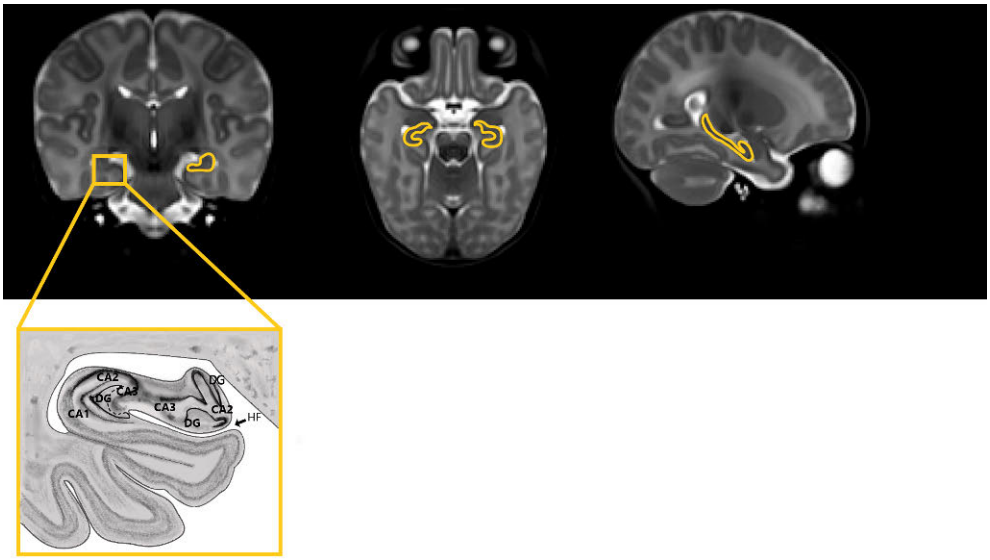

Figure 4. Author's illustration of the location and shape of the newborn hippocampus in coronal, axial and sagittal planes. The lower image illustrates the different hippocampal fields in a coronal plane. Cornu ammonis (CA) and its subfields 1-3, Dentate gyrus (DG), Hippocampal fissure (HF), Entorhinal cortex E), Perirhinal cortex (PRC). A dashed line indicates the border between the dentate gyrus from the CA3 subfield of the hippocampus.

2.1.3 Why are the amygdala and hippocampus important to investigate?

Many psychiatric disorders have been associated with changes in amygdalar and hippocampal volumes (Passamonti et al., 2012; Schumann et al., 2011, 2004; Videbech, 2004; Woon and Hedges, 2008). Larger amygdalar volume as well as an abnormal amygdalar growth trajectory were observed in children with autism (Groen et al., 2010; Mosconi et al., 2009; Schumann et al., 2011, 2009, 2004). Larger total and right amygdalar volumes (especially basolateral amygdala) were linked to children with generalized anxiety disorder (De Bellis et al., 2000), and high childhood anxiety (Qin et al., 2014). Furthermore, patients with first-episode depression presented larger amygdalar volumes than patients with recurrent depression, however, no difference between patients with recurrent depression and healthy controls was detected (Frodl et al., 2003). In line with this, in another study, there was no difference in amygdalar volume between patients with a depression history, and controls but the volumes of the core amygdalar nuclei were smaller in patients who had been depressed (Sheline et al., 1998). Moreover, stronger amygdalar connectivity in networks controlling attention, emotion, and perception regulation were associated with high childhood anxiety (Qin et al., 2014), depression (Jalbrzikowski et al., 2017), and conduct disorder (Passamonti et al., 2012).

Hippocampal volume reduction is a recognized feature in major depressive disorder (Videbech, 2004). Adults with childhood maltreatment induced post-traumatic stress disorder (PTSD) have also shown reduced hippocampal volumes; however, the finding was not yet present in the children with the same disorder, suggesting that the abnormal volumetric change occurs later in development (Woon and Hedges, 2008). Conversely, larger left hippocampal volumes have been observed in autistic individuals from childhood to adolescence (Groen et al., 2010; Schumann et al., 2004). Thus, the amygdala and hippocampus present as important brain regions to study from an early age to help better understand not only associations within these regions, but to discover any possible causal links regarding neurodevelopment and susceptibility to later psychopathology.

2.1.4 Newborn sex and the brain

In the later stages of development, sexual dimorphism of the brain has been detected (Guo et al., 2016). From early childhood to adulthood, males have larger intracranial, total brain, total GM and WM volumes than females (Koolschijn and Crone, 2013; Uematsu et al., 2012). However, the literature is scarce on the sex differences of the newborn brain. Dean et al. (2018a) observed greater absolute volumes of total brain volume, total GM and WM volume as well as subcortical GM and WM in one month old males compared to females at the same age, but after correction for intracranial

volume (ICV), the sex differences disappeared (Dean et al., 2018b). In the first three months of life, compared to females, males have a faster growth rate of the whole brain volume and several subcortical volumes (Holland et al., 2014). Lobar volume asymmetry seems to be similar in both sexes in healthy infants under two years of age (Tanaka et al., 2012), but each lobe follows its own growth trajectory regarding sex, brain region, and hemisphere (see 2.1.1 Hemispheric and lobar asymmetry). The amygdala and hippocampus grow at the same rate the first few years, after which the female amygdala reaches its peak age about one and a half years earlier than the male amygdala (between ages 9.6 to 12.6 years). The same applies for the hippocampus but the age difference between peak ages is only four to six months. (Uematsu et al., 2012). In the same study, both sexes had rightward asymmetry of the hippocampus, but only males had rightward asymmetry of the amygdala as well (Uematsu et al., 2012). However, in another study, no sex difference was found in the rightward amygdalar asymmetry (Dean et al., 2018a). To conclude, even though a general framework has been established concerning the sex differences in brain volumetric measures, much remains to be explored, even in normal development.

2.1.5 Newborn growth metrics, age, and the brain

Newborn body measures have been studied extensively in preterm populations, in which lower birth weight and height, as well as head circumference, have been associated with smaller brain volumes, especially in newborns with growth restrictions and extreme prematurity (Aanes et al., 2015; Cheong et al., 2008; Østgård et al., 2014; Padilla et al., 2015; Xydis et al., 2013). However, fewer studies have investigated the relationship between newborn body size, and age, and brain volumetric measures in full term-born individuals. Dean et al. (2018a) reported that larger head size and greater newborn age related to larger total brain volume, and additionally, greater birth weight to larger relative volumes of some DSS. In another study, birth weight associated positively with ICV and GM volumes in the lateral, temporal, inferior frontal and insular cortices, but negatively with GM volumes in the medial frontal cortex (Knickmeyer et al., 2016). Surprisingly, in the same study, newborns born earlier in gestation exhibited larger brain volumes than those who were born later (range GW at birth 27 to 42), possibly as a result of accelerated brain growth due to earlier exposure to the extrauterine environment. Together, few studies have investigated newborn age and growth metrics in relation to brain volumes in full-term infants. In addition, the results of these studies concerning age are inconsistent. Thus, further defining of these relationships is needed.

2.1.6 Incidental findings

Incidental findings are unexpectedly observed abnormalities in imaging that are unrelated to the research purpose. In the case of pediatric brain imaging, they most commonly comprise of hemorrhages and cysts (A. Lind et al., 2010; Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004; Whitehead et al., 2013). Several different types of hemorrhages classified by their anatomical location exist. For instance, paradural, subarachnoid, and intraparenchymal. Paradural hemorrhages are further divided into epidural and subdural hemorrhages (SDH), which can be supra- or infratentorial (Figure 5) (Gilles and Nelson, 2012). Cysts are fluid-filled sacs that are identified by their wall histology, location, and associated structures (Gilles and Nelson, 2012). The most common benign cysts observed in the newborn brain are pineal and caudothalamic cysts (A Lind et al., 2010; Whitehead et al., 2013). The prevalence of the incidental findings in newborns varies between different previous MR studies (cysts 1.9 to 57 %, hemorrhages 8.1 to 46 %) but they are generally regarded as common, in particular hemorrhages, considering the intensive pressure of the birth canal on the newborn head during childbirth (A. Lind et al., 2010; Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004; Whitehead et al., 2013). In addition, as incidental intracranial hemorrhages are usually asymptomatic, they are seldom detected and may be more frequent than estimated (Gupta et al., 2009).

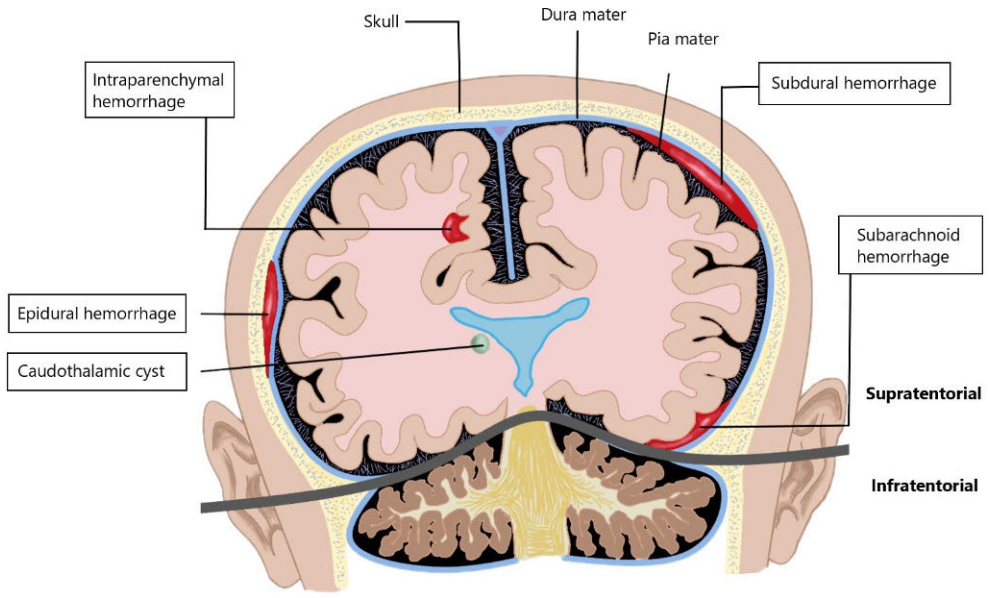

Figure 5. An illustration of the different types of incidental findings. Image adapted from https://www.myupchar.com/en/disease/brain-hemorrhage under the terms of the Creative Commons Attribution-Share Alike 4.0 International license (CC BY-SA 4.0).

Subdural hemorrhages (SDHs) are the most common and most reported findings of incidental hemorrhages (Hong and Lee, 2018; Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Whitby et al., 2004). They are caused by the tearing of blood vessels of the tentorium when the skull molds vertically (Gupta et al., 2009). When SDHs are observed right after birth, they usually present posteriorly (Gabaeff, 2013; Rooks et al., 2008; Tavani et al., 2003; Whitby et al., 2004), while SDHs caused by non-accidental head injuries (such as physical maltreatment) are generally localized in the interhemispheric fissure and over the hemispheres (Ewing-Cobbs et al., 2000; Poussaint and Moeller, 2002). In addition to SDH, subarachnoid (Hong and Lee, 2018; Looney et al., 2007), intraparenchymal (Hong and Lee, 2018; Looney et al., 2007; Sirgiovanni et al., 2014), and germinal matrix hemorrhages (Hong and Lee, 2018) are rarely discovered. Subarachnoid hemorrhage results when bridging blood vessels or dural sinuses tear during labour (Gupta et al., 2009). Spontaneous intraparenchymal hemorrhages can be caused by different reasons, but most commonly no cause is identified (Sandberg et al., 2001). Germinal matrix hemorrhages occur in the periventricular germinal region of the premature brain and can, at times, evolve to intraventricular hemorrhages (Luo et al., 2019). Birth-related hemorrhages often distribute widely forming a thin film and resolve without any complications or interventions (Gabaeff, 2013; Squier and Mack, 2009).

Several factors have been indicated as risk factors for intracranial hemorrhages (Gupta et al., 2009). The risk by mode of delivery varies between different studies. Symptomatic intracranial hemorrhages are in general rare, but their risk is higher in assisted deliveries (0.12%-0.87%), when compared with spontaneous labour (0,028%) (Ekéus et al., 2014; Simonson et al., 2007; Towner et al., 1999). C-section has also presented as a higher risk factor for symptomatic intracranial hemorrhages (0.11%) than spontaneous birth, the risk increasing after a failed assisted delivery attempt (0,30%) (Towner et al., 1999). Concerning asymptomatic intracranial hemorrhages, vaginal delivery is a clear risk factor (Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Whitby et al., 2004). However, the role of assisted delivery, caesarean section (c-section), or obstetric factors concerning the mother and the newborn remain unclear, as previous results are inconsistent. For instance, Looney et al. (2007) found no connection between asymptomatic intracranial hemorrhages and assisted delivery (executed either with vacuum or forceps). However, in other studies, the incidence of SDHs was higher in all of the vaginal delivery groups (assisted or not) compared to c-section (Rooks et al., 2008; Whitby et al., 2004). In addition, one study observed that detachment of the vacuum cup increased the risk of subarachnoid hematomas compared with when no detachment occurred (2.7% vs. 0.1%), however, the increase for subdural hematomas was not significant (Krispin et al., 2017). Overall, the risks by mode of delivery for asymptomatic intracranial hemorrhages are not clear, although the risks seem to

increase after attempted spontaneous vaginal delivery fails regardless of which method of delivery is subsequently chosen (Benedetti, 1999; Towner et al., 1999). Maternal prenatal pathologies (hypertension, abruption of placenta) as well as a newborn's low Apgar scores, thrombocytopenia, and low birth weight have all been shown to increase the risk of intracranial hemorrhages (Gupta et al., 2009; Jhawar et al., 2003; Rooks et al., 2008).

The majority of newborns with incidental findings are asymptomatic, and if this state prevails, it appears that no further complications will develop either. Common neurologic symptoms, such as decreasing level of consciousness, hypotonia, or seizure, can be signs of elevated intracranial pressure or other compression of brain structures caused by a growing cyst or hematoma, but are not specific to these findings. (Gupta et al., 2009) However, most incidental findings do not cause any complications and additionally, the majority of the hematomas are naturally resolved (Rooks et al., 2008; Whitby et al., 2004). Thus, considering the high and variant occurrence of incidental findings in studies and the increasing quantity of MR imaging in pediatric populations, it would be beneficial to refine the information on the prevalence and types of incidental findings, as well as their risk factors and possible clinical implications.

2.2 Maternal psychological distress

2.2.1 Epidemiology and definitions of maternal prenatal psychological distress

Maternal prenatal psychological distress (PPD) is a commonly used term in research to refer to pregnant women with symptoms or emotional responses to stress, however, the used stressors across studies vary greatly, from different symptom dimensions to external stressful life events (Da Costa et al., 1999; Huizink et al., 2003; Ingstrup et al., 2012; Jones et al., 2019). Most frequently PPD is thought to consist of symptoms of depression, anxiety, worries about the health of the baby or oneself, and a sense of isolation or depletion (Emmanuel and St John, 2010). In addition, daily hassles are sometimes used as an estimate of the stimulus aspect of stress (Da Costa et al., 1999). PPD is an increasingly important area of research as it has been associated with aberrant brain development and a higher risk for psychiatric disorders in the offspring (O'Donnell et al., 2014a; Van den Bergh et al., 2018).

The level of maternal distress varies as a function of time during pregnancy. Previous studies have observed depressive and anxiety symptoms to follow, on average, a U-shaped curve, with the highest levels of distress occurring in the first and the third trimesters (Figueiredo and Conde, 2011; Lee et al., 2007; Teixeira et al., 2009). However, recent evidence suggests that there is considerable variance in

symptoms between individuals depending on the symptom type and intensity (Baron et al., 2017; Korja et al., 2018; Sutter-Dallay et al., 2012; Vänskä et al., 2011). Higher educational level, older age, primiparity, living with a partner, and less frequent smoking are associated with low levels of PPD, while mothers with high levels of PPD had a lower education levels, more children, and more SSRI medication use (Korja et al., 2018; Rubertsson et al., 2014). However, a multitude of other background (personal mental and family history, history of miscarriage(s), life events one year prior to or during pregnancy, daily stressors, coping styles etc.) (Fontein-Kuipers et al., 2015) and current factors contribute to PPD as well, and many of these are still likely unidentified.

2.2.2 Prevalence and comorbidity

PPD is common amongst pregnant women, although its prevalence varies between studies. In low and middle income countries approximately 16 % of women suffer from common mental disorders prenatally (Fisher et al., 2012). This prevalence is similar to developed countries where 6.6 to 30.9 % experience symptoms of anxiety and 6.9 to 22 % symptoms of depression depending on the study (Andersson et al., 2006, 2003; Gavin et al., 2005; Koelewijn et al., 2017; Matthey et al., 2004; Rubertsson et al., 2014; Teixeira et al., 2009). Few studies have investigated the prevalence of pregnancy-specific-anxiety (PSA, see definition below) symptoms solely. One study found 11 % of 6443 women at GW24 or more to have PSA symptoms (Koelewijn et al., 2017), while in another study, the prevalence varied from 8.4 % in the first trimester to 22 % in the third trimester, being only 0.04 % in the second trimester (Madhavanprabhakaran et al., 2013). Comorbidity of anxiety and depressive symptoms is also common as 7.7 to 20.5 % of pregnant women report having both anxiety and depressive symptoms corresponding with the comorbid prevalence in non-pregnant populations (Andersson et al., 2006; Kendler et al., 2007; Mathew et al., 2011; Middeldorp CM, Cath DC, Van Dyck R, 2005; Teixeira et al., 2009).

2.2.3 Depressive symptoms

Depressive symptoms in pregnant women comprise similar symptoms as in non-pregnant individuals: depressed mood, loss of interest or pleasure in usual activities, weight change, insomnia, hypersomnia, fatigue, feelings of worthlessness or guilt, difficulties of concentrating, psychomotor agitation or retardation, and thoughts of death and suicide (Bennett et al., 2004). Symptoms can be mild, moderate, or severe and can vary during pregnancy (Bennett et al., 2004). Korja et al. (2018) identified five different trajectories of prenatal depressive symptoms in a population of 3,200

pregnant women: consistently low, consistently high, moderate, moderate and decreasing, and moderate and increasing levels of symptoms.

Several tools have been developed to screen prenatal depressive symptoms, as they increase the risk for postnatal depression (Leigh and Milgrom, 2008; Robertson et al., 2004), prematurity (Grigoriadis et al., 2013), problems in mother-infant interaction (Binda et al., 2019), and child wellbeing (Dunkel Schetter and Tanner, 2012; O'Donnell et al., 2014a). The questionnaires validated for use in obstetric populations (Holcomb et al., 1996; Murray and Cox, 1990; Rubertsson et al., 2011; Spitzer et al., 2000) include the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987), the Beck Depression Inventory (BDI) (Beck et al., 1961), and the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD-PHQ) (Spitzer et al., 1999). Of these, EPDS and BDI are most used in observational studies (Bennett et al., 2004).

2.2.4 General anxiety symptoms

General anxiety symptoms are part of a broader spectrum of anxiety symptoms. They are characterized by excessive, uncontrollable worry, and physical symptoms such as fatigue, irritability, tension, concentration difficulties, and insomnia (Misri et al., 2015). The level of anxiety varies during pregnancy. In fact, four prenatal anxiety symptom trajectories have been identified in a population of 3,200 pregnant women: consistently low, consistently high, high and decreasing, and moderate and increasing levels of symptoms (Korja et al., 2018).

Prenatal anxiety has been linked to many unfavorable impacts on not only pregnancy and neonate health, but also on long-term child health (Field, 2017). The concern over these outcomes is reflected in the wide variety of questionnaires that have been employed to measure prenatal general anxiety: The Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A) (Zigmond and Snaith, 1983), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970), GAD-7 (Spitzer et al., 2006), Symptom Checklist-90 Revised - Anxiety subscale (SCL-90-R) (Deogratis et al., 1973), Brief Measure of Worry Severity (BMWS) (Gladstone et al., 2005), and Cambridge Worry Scale (CWS) (Green et al., 2003).

2.2.5 Pregnancy-specific anxiety symptoms

Pregnancy-specific anxiety (PSA) is excessive worry and fear about childbirth, baby's health, as well as mother's health and appearance, and can be accompanied by physical symptoms (Bayrampour et al., 2016). In the light of recent literature, PSA is considered to be a distinctive syndrome in comparison to prenatal general anxiety and depressive symptoms. In a study examining the associations between

different symptoms of PPD, general anxiety and depressive symptoms explained only a small part of fears related to maternal appearance, child health, and childbirth (Huizink et al., 2004). Although PSA overlaps modestly with general anxiety and depressive symptoms, it has shown a differential longitudinal course (decrease from GW20 onwards) from conventional symptom measures (Blackmore et al., 2016). Interestingly, in other studies, PSA has been found to be highest during the first and third trimester (Da Costa et al., 1999; Madhavanprabhakaran et al., 2013). Compared to other symptoms of PPD, PSA also predicts gestational age at birth, newborn birth weight, and maternal postnatal mood disturbances (Blackmore et al., 2016), as well as child development and temperament (Huizink et al., 2003, 2002) differently, implying PSA is a more sensitive predictor of obstetric outcome (Blackmore et al., 2016).

The distinction of PSA from other symptoms of PPD has yielded specific tools to measure it. The Pregnancy-related Anxiety Questionnaire Revised (PRAQ-R) (Huizink et al., 2004) has been identified as an accurate indicator of PSA (Sinesi et al., 2019). The items assessing pregnancy specific worries in Wijma Delivery Expectancy/Experience Questionnaire (W-DEQ) and CWS show also good psychometric value (Sinesi et al., 2019). In addition, the Pregnancy-related anxiety Scale (PrAS) (Levin, 1991) has demonstrated excellent reliability and targeting for PSA (Brunton et al., 2018). However, unlike depressive and general anxiety symptom measures, PSA symptoms are not limited to a specific diagnosis and no threshold has been established that would oblige intervention.

2.2.6 Composite distress measurements

As mentioned previously, PPD symptoms are common and often comorbid during pregnancy (Holcomb et al., 1996; Murray and Cox, 1990; Rubertsson et al., 2011; Spitzer et al., 2000), thus, using a composite score might help to create a more robust tool to measure PPD. However, few studies have utilized this in their methods. Riis et al. (2016) explored the moderating effect of maternal psychological well-being on neuroendocrine-immune relations in children using a composite score formed of maternal depressive symptoms (measured by Center for Epidemiologic Studies Depression Scale, CESD-20), trait-anxiety (measured by STAI), and maternal parenting and life stress (measured by Parenting Stress Index – Short Form, PSI). Another study investigated the associations between maternal distress and child obesity (Ingstrup et al., 2012). The distress score was measured by nine questions, of which six questions were about anxiety and depression from the SCL-92 and three questions about general stress from the General Health Questionnaire (GHQ60) (Ingstrup et al., 2012). However, no consensus has been obtained of how to best grasp the general overlap of the different distress measures.

2.3 Maternal prenatal psychological distress, offspring neurodevelopment, and risk for psychopathology

Maternal prenatal psychological distress has been associated with many adverse outcomes in child neurodevelopment (Van den Bergh et al., 2018). PPD predicts the socioemotional and cognitive development of children and adolescents, exhibiting as difficult temperament, behavioural dysregulation (Acosta et al., 2019; Davis et al., 2007; Madigan et al., 2018; Nolvi et al., 2016; O'Donnell et al., 2014a; Pickles et al., 2017), and impaired memory performance (Buss et al., 2011; Sandman et al., 2012). With regard to socioemotional development, maternal PPD, especially anxiety, has been related to offspring internalizing symptoms (O'Donnell et al., 2014b), and externalizing symptoms (Korhonen et al., 2014; Van den Bergh and Marcoen, 2004), as well as child attention problems (Van Batenburg-Eddes et al., 2013; Van den Bergh and Marcoen, 2004). Internalizing symptoms correspond to symptoms similar to those in depression or anxiety, such as sadness, withdrawal, and somatic complaints, while externalizing symptoms are characterized by negligent, impulsive, and aggressive behaviour (Levesque, 2011).

PPD has also shown to increase the risk for (later) psychopathology in the offspring (O'Donnell et al., 2014a). For instance, children exposed to higher prenatal anxiety or depression had a two-fold increase for risk of developing a probable mental disorder (12.31 % vs. 6.83 %) (O'Donnell et al., 2014a). Similarly, a retrospective study of 3,626 individuals found that the children with mothers who reported stress during pregnancy were in a greater risk of developing a psychiatric disorder, especially a mood disorder (Brannigan et al., 2019). In line with this, elevated maternal prenatal anxiety was related to depressive symptoms, but only in female offspring adolescents (Van Den Bergh et al., 2008). Furthermore, children exposed to prenatal maternal depression were more likely to develop anxiety disorders by 18 years of age, whereas exposure to prenatal maternal anxiety increased the risk of comorbid anxiety and depression (Capron et al., 2015). In addition, elevated prenatal maternal anxiety has been related to attention deficit hyperactivity disorder (ADHD) symptoms, and self-reported anxiety in eight and nine-year-olds (Van den Bergh and Marcoen, 2004). These psychopathologies in the offspring exposed to PPD are considered to have a connection with the psychiatric conditions with a likely dysfunction of the limbic system described earlier (see paragraph 2.1.3). Therefore, it is vital to investigate whether PPD predisposes offspring to psychopathology and how, to create and imply preventative protocols at the right time for minimizing the harm to the developing brain.

2.4 Possible distress mediating and modifying mechanisms between mother and foetus

2.4.1 Timing of exposure to prenatal distress

The development of the central nervous system follows a certain timeframe, in which all of the steps happen in an orderly manner (Elshazzly et al., 2019; Stiles and Jernigan, 2010). During development, these fine-tuned processes are sensitive to all influences. It is hypothesized that during this time of sensitivity, maternal distress imposes programming effects on the foetus to prepare it for the early postnatal environment (Buss et al., 2012b). The response to these programming effects depends on the time and intensity of the exposure (Bock et al., 2015). The brain is an incredibly plastic organ, especially during early development (Hensch, 2004). However, evidence from previous studies suggests that some plastic functions of the brain are limited to a specific time period during development and cannot be maintained beyond this time (Hensch, 2004). For instance, it has been shown in animal studies that certain sensory input and sensorimotor experiences have different time windows of increased plasticity (Hensch, 2004).

Anxiety-like behaviour in rats has been studied regarding plasticity. Anxiogenic behaviour is controlled by the appropriate activation of a serotonin receptor during a particular period in early life. Knock-out mice without this receptor present increased anxiety-like behavior in adulthood. Conditional restoration of the receptor between postnatal days 5 and 21 in the hippocampus and cortex (but not in brainstem raphe nucleus) rescues the phenotype (Gross et al., 2002). Furthermore, offspring of prenatally stressed rat dams have more cognitive deficits and anxiety-like behaviour (Weinstock, 2011), however, the timing and the intensity of the exposure, as well as offspring age at testing influence the outcome.

Evidence from a longitudinal study suggests that while recurrent or chronic maternal depressive symptomatology predicts the socioemotional behaviour of adolescents better than the timing of the exposure to maternal distress, the timing might explain the deficiencies in neurological abilities depending on the developmental stage at the time of exposure (Korhonen et al., 2014). Thus, the differences in the timing of exposure to prenatal distress is an important factor to investigate regarding brain development. Overall, the exposure to maternal distress, accompanied with biological factors, during a sensitive time period of a developmental process might alter the course of development and predispose offspring to unfavorable outcomes that are affected by postnatal experiences as well.

2.4.2 Stress regulation and HPA axis function

The hypothalamus-pituitary-adrenal-axis (HPA axis) is a hormonal regulator of many processes in the body, including the stress response. Hypothalamic neurons secrete corticotropin-releasing-hormone (CRH) and vasopressin (VP), which both stimulate the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) (Katsu and Iguchi, 2016). ACTH stimulates the synthesis and release of glucocorticoids from the adrenal glands (Stephens and Wand, 2012). Cortisol is the main glucocorticoid in humans and has many functions, including inducing gluconeogenesis and metabolism, as well as decreasing immune response (Katsu and Iguchi, 2016). Most importantly, cortisol regulates neuronal growth by inhibiting neuronal proliferation and differentiation and by inducing glial cell proliferation (Aden et al., 2011; Moors et al., 2012). Another group of glucocorticoids is mineralocorticoids, which regulate the electrolyte and liquid balance in the body. The functions of glucocorticoids are exerted through glucocorticoid (GR) and mineralocorticoid (MR) receptors, which are also widely expressed in the brain (Sapolsky et al., 2000).

The activation of the HPA axis is moderated by a multiplicity of neurotransmitters with excitatory or inhibitory effects. HPA activity increases in stress exposure, and consequently, the concentration of corticosteroids in plasma increases (Jacobson and Sapolsky, 1991; Stephens and Wand, 2012). The hippocampus (amongst other brain regions) inhibits HPA activity at the hypothalamic level largely via corticosteroid feedback (Figure 6). The high number of hippocampal corticosteroid receptors enables the inhibition of HPA activity specific to different levels of glucocorticoids (Jacobson and Sapolsky, 1991). On the contrary, the amygdala may enhance HPA-activity (Figure 6), and like the hippocampus, is rich in GR and MR (Herman et al., 2005). The influence of the hippocampus and amygdala on the HPA axis is not direct but transmitted through subcortical intermediaries through which the signal can be combined as both pathways of excitatory and inhibitory signals overlap (Herman et al., 2005).

HPA activity is different in offspring exposed to prenatal distress. Rat studies have shown that stressing rats prenatally (space restriction, forced swimming, reversed light cycle, or administration of glucocorticoids, as well as other stressors) results in several long-term dysregulations of the offspring HPA axis: elevated response as seen as increased levels of corticosteroids and/or ACTH in the blood, to acute stress and prolonged recovery time, as well as impaired adaptation if exposed repeatedly to the same stressor (Weinstock, 2005). Importantly, it is difficult to draw causal conclusions by combining the results of different studies given that there are multiple interacting sources of variance, such as differences in stress nature and timing, as well as differences in when the foetal HPA turned active, and when it was tested (Weinstock, 2005).

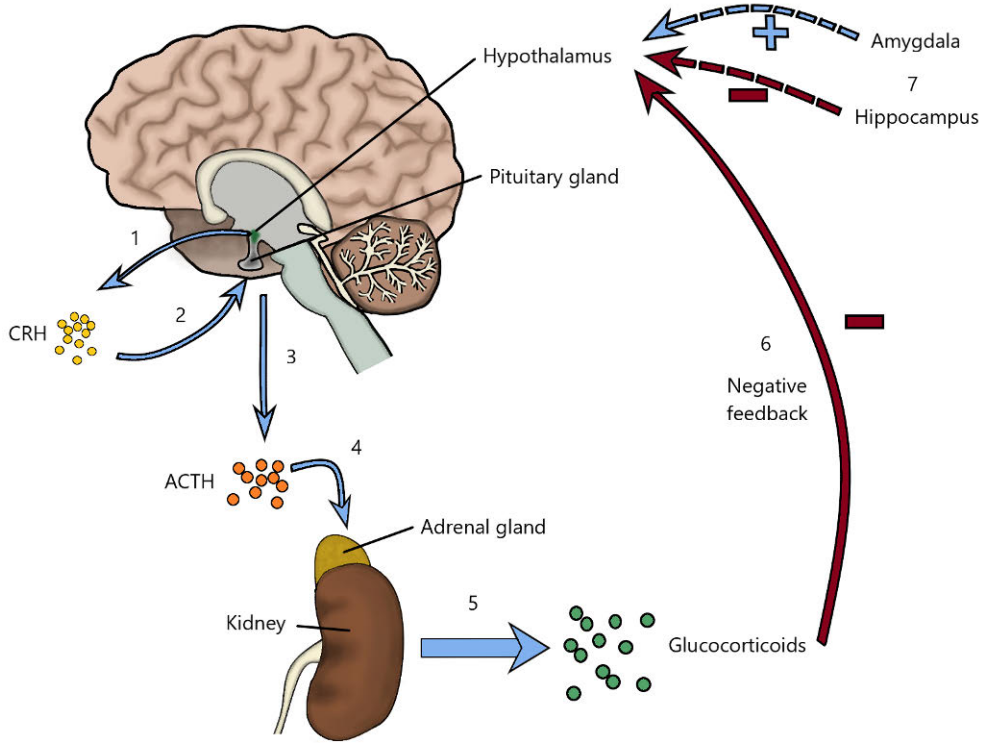

Figure 6. The HPA axis and its indirect regulation by amygdala and hippocampus. 1) Hypothalamus secretes corticotropin-releasing hormone (CRH); 2) CRH induces hormone production in the pituitary gland, which then 3) secretes adrenocorticotropic hormone (ACTH); 4) ACTH stimulates the adrenal glands on the kidneys; 5) Glucocorticoids are secreted from the adrenal glands; 6) The increased levels of plasma glucocorticoids act as a negative feedback loop inhibiting the secretion of CRH from the hypothalamus; 7) The hippocampus inhibits the HPA axis activity indirectly (dashed arrow), while the amygdala stimulates the HPA axis activity indirectly. Author's illustration.

The variance between studies is key also when evaluating PPD's effects on the offspring stress reactivity in humans, as the results are variable. For instance, maternal prenatal trait anxiety between GW12 and GW22 associated with high, flattened cortisol day-time profile in 14 and 15-year-old offspring adolescents, and with depressive symptoms, but the latter was observed only in female adolescents (Van Den Bergh et al., 2008). Then again, greater maternal prenatal anxiety at GW32 predicted higher awakening cortisol levels in 10-year-olds (O'Connor et al., 2005). In addition, greater pregnancy-related anxiety associated with higher salivary cortisol levels after a bathing session at five weeks of age, but lower cortisol levels after vaccination at eight weeks of age and maternal separation at five months of age (Tollenaar et al., 2011). Moreover, a variant of GR was found to moderate the association between maternal PPD and child emotional and

behavioural problems at three years of age. The interaction of the GR variant and maternal PPD also related to a decreased response to acute stress at 14 months of age (Velders et al., 2012).

To summarize, a connection seems to exist between PPD and altered offspring HPA activity, though the precise direction and effects of the altered cortisol levels are still unclear, and are most likely further influenced by genetic factors as well. The results of one study suggest that the influence of cortisol on the CNS might be dependent on its concentration, as lower cortisol concentrations increased progenitor cell proliferation and had differential effects on neurogenesis and cell differentiation, compared to high levels of cortisol (Anacker et al., 2013).

Maternal cortisol levels normally increase gradually over pregnancy towards the last trimester, reaching two- to three-fold levels compared to non-pregnant individuals (Mastorakos and Ilias, 2003). The foetus receives most of its cortisol from the mother. The absorption of cortisol is moderated by an enzyme expressed in the placenta, 11-beta-hydroxystreoid-dehydrogenase-type 2 (11-β-HSD-2), which turns cortisol into its inactive form cortisone (Mastorakos and Ilias, 2003). This placental barrier protects the foetus from higher cortisol levels of the mother. However, it seems PPD disrupts the barrier by a downregulation of 11-β-HSD-2 exposing the foetus to higher cortisol concentrations during pregnancy, even in mothers with normal cortisol concentrations (O'Donnell et al., 2012). Furthermore, in rat studies, the downregulation of 11-β-HSD-2 has been observed to increase amygdalar GR expression (Welberg et al., 2000) and, in reverse, to decrease hippocampal GR expression (Levitt et al., 1996). Amygdalar GR up-regulation has been associated with an anxiogenic phenotype in rat offspring (Welberg et al., 2000), while the down-regulation of hippocampal GR could be anticipated to reduce negative feedback and to result in an overactive HPA axis, as well as a differential cortisol concentration profile in the offspring (Cottrell, 2009; Uno et al., 1994).

In addition to 11-β-HSD-2, the placenta produces placental corticotropin-releasing hormone (pCRH), which partakes in the mother's HPA activity regulation (Thomson, 2013). Interestingly, exposure to elevated levels of pCRH has been linked to the thinning of several cortical regions, and cognitive and emotional deficit in six to nine-year-old children (Sandman et al., 2018). Animal studies have also shown that maternal prenatal synthetic corticosteroid treatment associates with cognitive impairment and neurocellular changes in the hippocampus (Brown et al., 1999).

2.4.3 Cytokines

Changes in maternal immunological activity during pregnancy are thought to be possible programming factors to influence foetal brain development (Buss et al.,

2012b). Cytokines are small cell-signaling proteins, part of which can reach the foetus through the placenta (Zaretsky et al., 2004). Interleukins (IL) are cytokines produced by one leukocyte that act on other leukocytes (Zhang and An, 2007). Mild symptoms of PPD (below clinical cut off points) have been associated with elevated levels of both proinflammatory cytokines (IL-5, IL-9, IL-13) and anti-allergenic and anti-inflammatory cytokines (IL-12, IL-10) during pregnancy; furthermore, maternal anxiety and depressive symptoms have been related to distinct cytokine profiles, to some extent (Karlsson et al., 2017). The results suggest that PPD alters maternal prenatal immunological balance, but the change might be partially dependent on symptom type (Karlsson et al., 2017). Moreover, another study found that exposure to increased maternal PPD associated with weaker inhibition of inflammatory cytokines by cortisol in children, this effect being significant only in females (Riis et al., 2016). Thus, PPD also seems to affect not only maternal immunological activity but that of the offspring as well. Furthermore, children of mothers with higher prenatal levels of a proinflammatory cytokine (IL-6) had retarded growth of frontolimbic WM during gestation, accelerated growth of the same area during the first year of life, and poorer cognitive development at 12 months of age (Rasmussen et al., 2019). Similarly, elevated levels of maternal IL-6 related to larger right amygdalar volume and stronger amygdalar connectivity in newborns, and lower impulse control at one year of age, the amygdalar findings mediating the effect between PPD and altered child behaviour (Graham et al., 2019).

2.4.4 Genetic variation and gene-environment interaction

Allele variation in certain genes related to serotonin or glucocorticoid activity (serotonin transporter gene, GR gene), combined with greater exposure to PPD, has displayed as more internalizing problems (Tiemeier et al., 2012), and anxiety and depressive symptoms in the offspring (Tiemeier et al., 2012). In a 2019 study, investigating to what degree the variation of amygdalar and hippocampal volumetry and connectivity are predicted by maternal PPD, socioeconomic status and newborn genotype, gene-environment interaction (GxE) models best explained the amygdalar volumetric measures, as well as the majority of hippocampal volumetric and connectivity measures; whereas the amygdalar connectivity measures were best explained by genotype alone (Ong et al., 2019). However, when the association of DNA methylation was considered, these models better explained amygdalar variation than others (genotype or GxE), but less so regarding the hippocampus (Ong et al., 2019). Another study from 2015 explored how offspring genotype (specifically Brain-derived neurotrophic factor [BDNF] gene polymorphism) affects the associations of DNA methylation with maternal

prenatal anxiety and with newborn amygdalar and hippocampal volumes (Chen et al., 2015). Depending on genotype, DNA methylation in these structures covaried with volume suggesting a differential activity of this brain region after exposure to PPD and possibly susceptibility of certain BDNF genotypes to the effects of PPD (Chen et al., 2015). Thus, the offspring genotype, gene-environment interaction and epigenetic variation (e.g. DNA methylation) influence the variation in the volumes and microstructures of the amygdala and hippocampus, and regulate their susceptibility to early environment and possibly in a region specific way (Chen et al., 2015; Ong et al., 2019).

2.4.5 Foetal sex

The response to prenatal stress of the human foetus is sexually dimorphic. Based on studies of foetal growth in the presence of a maternal illness, male and female foetuses have different adaptation strategies when exposed to stress: males continue growing regardless of the suboptimal intrauterine environment, whereas females' growth decreases, enabling them to survive possible future complications involving nutrition or oxygen supply (Clifton, 2010). Regarding neurodevelopment, evidence is accruing that offspring sex also moderates the effect of PPD on brain development through a variety of mechanisms, all of which have not yet been discovered.

The function of the placenta seems to be sexually dimorphic. Sex specific differences in placental steroid profile, responsiveness to cortisol (possibly via differences in GR expression or function), growth hormone concentrations, and gene expression related to immune function have been detected (Clifton, 2010). For instance, high maternal stress (traumatic experiences) in mid-pregnancy associated with sex-dependent changes in the expression of certain placental genes: nutrient sensor, glucose transporter, and hypoxia sensor genes; these associations were found to be significant only in males (Cowell et al., 2020).

Sex differences in the influence of maternal cortisol on offspring brain morphology and later developmental problems have also been observed. Exposure to elevated maternal cortisol concentrations in earlier pregnancy are associated with larger right amygdalar volumes and more affective problems in female offspring, but no associations regarding the hippocampus were observed in either sex (Buss et al., 2012a). Furthermore, amygdalar size partially mediated the association between maternal cortisol levels and offspring affective problems (Buss et al., 2012a). Similarly, female children of mothers with higher maternal cortisol concentrations during pregnancy had stronger amygdalar connectivity to brain regions engaged with sensory processing, which, in turn, associated with more internalizing problems; whereas in males, weaker amygdalar connectivity was observed and no association with internalizing symptoms was present (Graham et al., 2019).

Although little is yet known about the GR activity in the human foetal amygdala and hippocampus, a guinea pig study reported sex differences in regional GR and MR mRNA levels in the hippocampus during different stages of pregnancy, with females having significant increases in GR mRNA levels and decreases in MR mRNA levels, while no changes in GR and MR mRNA levels were detected in males or these changes occurred only postnatally (Owen and Matthews, 2003). Similar changes in humans may explain the volumetric alterations observed after exposure to higher levels of cortisol. In addition, foetal testosterone (FT) may also have organizing effects on the sexual dimorphism of the brain. A study investigated FT in 28 males aged 8 to 11 years, as well as sexual dimorphism of the brain in 217 children (N=101 males) and found that while some brain areas were larger in males and positively predicted by FT, some areas were larger in females and were negatively predicted by FT (Lombardo et al., 2012).

2.5 Maternal prenatal psychological distress and offspring amygdala

2.5.1 Animal studies

Studies in animals show that the amygdala is a critical structure concerning fear learning, which seems to be an important factor in anxiety-related behaviour (LeDoux, 2000). Evidence on prenatally stressed (PS) animals suggests that maternal stress during a sensitive time period in brain development may increase proneness to anxiety and depressive-like behaviour (Weinstock, 2008) (Table 1). For instance, offspring of mildly prenatally stressed (removal from cage, subcutaneous injection of saline in late pregnancy) rat dams showed increasing defensive-withdrawal and fearful behaviour after acute stress at postnatal days 45 to 60 compared to controls (Dickerson et al., 2005). The effects of prenatal stress on the amygdala display as developmental alterations in the different nuclei of the amygdala. Primarily maternal PS temporarily hindered the development of several amygdalar nuclei (lateral, basolateral and central) in the offspring (Kraszpulski et al., 2006), but later the same exposure induced growth of the lateral amygdalar nucleus in the offspring that continued into adulthood (Salm et al., 2004). This increase in volume was explained by a larger number of neurons and glia (Salm et al., 2004).

Amygdalar basolateral nucleus volume seems to predict differences in fear- and stress responses to stressors. In inbred mouse strains with variation in basolateral amygdala volumes, the smaller size of the basolateral nucleus was related to greater conditioned fear and corticosterone responses to stress (Yang et al., 2008). The authors speculated that the observed greater HPA activity might be a manifestation of abnormal amygdala function. Interestingly, anxiogenic

behaviour in PS rats related to sexually dimorphic changes in CRH receptor and binding protein mRNA expression as a sign of greater activity of the HPA axis in females (Zohar and Weinstock, 2011). PS exposure in female rats has also been associated with a change in the expression of transporters regulating inhibitory stimuli ($GABA_A$) in the amygdala, which may result in a more anxiogenic phenotype (Ehrlich et al., 2015).

2.5.2 Human studies

Despite the accumulating evidence from animal research and behavioural studies in humans on the link between PPD and the amygdala, relatively few studies have investigated human amygdalar volume in relation to PPD (Table 1). Qiu et al. (2017) investigated whether newborn's genomic profile risk score for major depressive disorder (MDD) moderated the effect of maternal prenatal depressive symptoms on newborn amygdalar and hippocampal volumes in two cohorts of different ethnicity: Asian and American. In the Asian cohort, maternal depressive symptomatology associated with larger right amygdalar volume in newborns with a high genetic risk for MDD, whereas in the American cohort this positive association was observed in newborns with a low risk for MDD (Qiu et al., 2017). The gene pathways that best mediated the effects of maternal symptoms and newborn genotype on amygdalar volumes were closely tied with glutamate receptor activity.

Although no sex differences in amygdalar volumes were found in the study by Qiu et al. (2017), other studies have shown that sex moderates the effect of PPD on amygdalar volume and developmental problems. One study detected greater right amygdalar volumes in female children (aged 4.5 years) after exposure to maternal prenatal depressive symptoms (Wen et al., 2017). Additionally, postnatal maternal depressive symptoms predicted right amygdalar microstructure, observed as higher fractional anisotropy (FA), in females but not in males (Wen et al., 2017). Acosta et al. (2019) observed that higher PSA in mid-pregnancy associated with greater left amygdalar volume in 4-year-old females compared to males and that the greater amygdalar volume was also related to less emotional symptoms, peer relationship problems and overall childhood difficulties. Another study found a connection between higher maternal prenatal depressive symptoms and lower FA and axial diffusivity (AD) in the right amygdala in both newborn sexes. However, no associations with amygdalar volumes were detected. (Rifkin-Graboi et al., 2013)

Effects of PPD have been detected also in the amygdalar connectivity of the offspring. Newborns exposed to maternal depressive symptoms during pregnancy exhibited bilateral negative functional connectivity between the amygdala and dorsal prefrontal cortex, and weaker structural connectivity between the amygdala and

ventral prefrontal cortex (Posner et al., 2016). However, in individuals aged 6 months, more maternal depressive symptoms prenatally presented as greater functional connectivity of the amygdala inside the limbic system, more specifically within connections with the insula, as well as the left temporal, bilateral anterior cingulate, medial orbitofrontal, and ventromedial prefrontal cortices; regions forming networks that regulate emotions, sensation, perception, and memory (Qiu et al., 2015).

Overall, the effects of PPD on newborn amygdalar volumes seem to be moderated by genotype (Qiu et al., 2017), while evidence from child studies suggests PPD to affect amygdalar volume in a sex-dependent way (Acosta et al., 2019; Wen et al., 2017), suggesting that the prenatally provoked changes in neurodevelopment might occur only later on. Evidence from connectivity studies suggests reduced amygdalar connectivity in newborns exposed to PPD (Posner et al., 2016), which turns to stronger connectivity in older individuals (Qiu et al., 2015), possibly as a sign of accelerated maturation and a predisposition to psychopathology.

Table 1. Studies in animals and humans on the associations between maternal distress and offspring amygdalar morphology. Region of interest (ROI), Prenatally stressed (PS), Control (C), Postnatal days (P), Basolateral (BL), Lateral (La), Central (Ce), Recombinant inbred strain C57BL/6 x DBA/2 (BXD RI); Glucocorticoid (GC); Corticotropin-releasing hormone (CRH); Corticotropin-releasing hormone receptor (CRHR); Corticotropin-releasing hormone binding-protein (CRH-BP); Escitalopram exposure (Escit); Chloride transporter (CIT); Serotonin receptor (SR); Growing up in Singapore Towards Health Outcomes (GUSTO); Gestational week (GW); Maternal prenatal depressive symptoms (MPDS); Structural magnetic resonance imaging (sMRI); Resting-state functional MRI (rs-fMRI); Diffusion tensor imaging (DTI); Center for Epidemiological Studies Depression Scale (CES-D); Edinburgh Postnatal Depression Scale (EPDS); Genomic profile risk score for major depressive disorder (GPRSMDD), Pregnancy-specific anxiety (PSA); Pregnancy-related Anxiety Questionnaire Revised 2 (PRAQ-R2).

	Author and year	Cohort if applicable	Species	Number (Male/Female)	Age at testing	Prenatal exposure	ROI	Method	Result	Sex difference
1	Salm et al. 2004		Rat, Sprague-Dawley	PS 9, C 8, only males	P80-P120	Novel environment, handling, saline injection	BL, La, Ce amygdala	Microscopy, stereological measures	La mean volume larger in PS, more neurons & glia	-
2	Dickerson et al. 2005		Rat, Sprague-Dawley	N not disclosed, only males	P21, P45, P60	Novel environment, handling, saline injection	Fearful behavior	Defensive-withdrawal, test, restraint stress	Increasing fearful behavior in PS with age and after acute stressor	-
3	Kraszpulski et al. 2006		Rat, Sprague-Dawley	N not disclosed, only males	P7, P25, P45, P60	Novel environment, handling, saline injection	BL, La, Ce amygdala	Microscopy, stereological measures	Reduced growth of BL, La & Ce at P7-P25, resolved at P45; elongation of La longer in PS	-
4	Yang et al. 2008		Mouse, 5-7 lines of BXD RI	190 males, 47 in small, 82 in medium, 61 in large BL group	P56	None	BL amygdala volume relation to anxiogenic & depressive-related behaviour, fear & memory learning, GC responses to stress	Novel open-field, elevated plus maze, light-dark exploration tests, Pavlovian fear conditioning, forced swim test, hot plate and GC blood samples	Relatively smaller BL associated with greater fear & stress reactivity (GC response greater in small BL mice after stress)	-
5	Zohar & Weinstock 2011		Rat, Wistar	Pups/litter mean: PS 11.8, C10.5; equal amounts of M & F in different test groups	P56-P63	Restraint stress, forced swim, elevated platform	Anxiogenic behaviour in relation to gene-expression of CRH markers in amygdala	Elevated plus maze, CRHR1&2 mRNA, CRH-BP mRNA	PS showed heightened anxiety which associated with downregulation of CRHR2 & CRH-BP mRNA in males, but upregulation of CRH & downregulation of CRHR2 in females	Yes
6	Ehrlich et al. 2015		Rat, Spraque-Dawley	Escit 11, C 12, PS 15, Escit + PS 10; only females	P90	Saline/escitalopram oxalate in saline, restraint, cage tilt, damp	Behavior, CIT & SR expression in BL amygdala	Open field, social interaction, novel object recognition,	PS increased anxiogenic behaviour, without Escit mitigating the effect. PS	-

	Author and year	Cohort if applicable	Species	Number (Male/Female)	Age at testing	Prenatal exposure	ROI	Method	Result	Sex difference
						bedding, cage changes, noise, overnight illumination		elevated plus maze, GC & estradiol concentrations	decreased cognitive performance. No association to GC concentrations. PS downregulated CIT. Escit upregulated SR.	
7	Rifkin-Graboi et al. 2013	GUSTO	Humans	157 (82/75)	Mean 38.8 weeks	MPDS, EPDS score at GW26	Amygdalar volume	sMRI (1.5T), DTI	No difference in amygdalar volumes, but lower FA & AD in subjects exposed to higher MPDS	No
8	Qiu et al. 2015	GUSTO	Humans	24 (12/12)	Mean 66.6 weeks	MPDS, EPDS at GW26	Amygdalar functional connectivity	rs-fMRI (1.5T)	Those exposed to higher levels of MPDS showed greater functional connectivity of the left amygdala	No
9	Posner et al. 2016		Humans	64 (27/37); 20 with exposure, 44 without	Mean 5.8 weeks	MPDS, CES-D & Perceived Stress Scale at GW34-37	Amygdalar functional & structural connectivity	rs-fMRI (3T), DTI	In newborns exposed to MPDS: bilateral, negative functional connectivity between amygdala and dorsal PFC; decreased structural connectivity between right amygdala & right ventral PFC	No
10	Qiu et al. 2017	GUSTO	Humans	Asian cohort: 168 (90/78); American cohort: 85 (50/35)	Mean ~ 40 weeks	MPDS, EPDS at GW26	$GPRS_{MDD}$, amygdalar volume	sMRI (1.5T)	Asian: Larger right amygdalar volume in subjects with high $GPRS_{MDD}$; American: Larger right amygdalar volume in subjects with low $GPRS_{MDD}$	No
11	Wen et al. 2017	GUSTO	Humans	235 (113/122)	Mean 4.6 years	MPDS, EPDS at GW26	Amygdalar volume and functional connectivity	sMRI (3T), DTI	Larger volume and higher FA in the right amygdala associated with greater prenatal maternal depressive symptoms in females	Yes
12	Acosta et al. 2019	FinnBrain	Humans	27 (14/13)	Mean 4 years	PSA, PRAQ-R2 at GW24 & GW34	Amygdalar volume, child behavioral problems	sMRI (3T), Child behavioural problems with the Strength and Difficulties Questionnaire	Higher PSA associated with larger left amygdalar volume in females and less behavioural problems	Yes

2.6 Maternal psychological distress and offspring hippocampus

2.6.1 Animal studies

Animal studies have shown that glucocorticoid treatment is associated with cognitive impairment and neurocellular changes in the hippocampus (Brown et al., 1999). Similarly, exposure to PS (also in the form of higher maternal corticosteroid concentrations) has been associated with learning difficulties, depressive and/or anxiogenic behaviour in the offspring and changes in hippocampal cell morphology (Weinstock, 2011, 2008) (Table 2). Lifelong reduction in neurogenesis and learning deficits in spatial tasks were observed in PS exposed rats (Lemaire et al., 2000). PS also affected the composition of dendritic arbor and excitatory spines and the volume of neuronal and glial cell numbers, as well as impaired neurogenesis and differentiation in rodent offspring hippocampi (Fujioka et al., 2006; Mychasiuk et al., 2011). Furthermore, PS guinea pig pups exhibited anxiety and neophobic behaviours, as well as reduced markers of myelination and reactive astrocytes (Bennett et al., 2015). Similar changes in neurodevelopment markers were observed in guinea pig foetuses earlier, but some of these effects were present only in males (Bennett et al., 2013). Another study observed that the number of hippocampal granule cells was lower in female PS rats, but not male rats, when compared to non-stressed control rats (Schmitz et al., 2002).

Overall, PS has long-term influence on the cell morphology of the hippocampus associated with cognitive and behavioural impairment. Moreover, some of these effects of PS seem to be sex-dependent (Weinstock, 2011). In males they are exhibited more often as learning deficits, and in females as anxious behaviour, which are possibly explained by the inhibition of neurogenesis and changes in cell morphology (Fride and Weinstock, 1988; Weinstock, 2011; Zagron and Weinstock, 2006). However, the timing and intensity of the stress, as well as the testing age of the offspring affect the outcome (Fujioka et al., 2006; Weinstock, 2011). These stress-induced deficits might not be permanent, as infantile postnatal stimulation has been seen to counteract the impairing effects of PS on hippocampal neurons (Lemaire et al., 2006).

2.6.2 Human studies

A considerable amount of literature has been published on hippocampal volumes and postnatal stress including maternal psychological distress, early life traumatic experiences, and all types of childhood maltreatment. A common feature in these studies associated with more postnatal stress is a reduced size of both hippocampi

with no sex differences (Dahmen et al., 2018; Killion and Weyandt, 2018; Marečková et al., 2018; Teicher et al., 2006), although contrary findings of no volume alteration have been reported (Lupien et al., 2011). The associations of hippocampal volumes and PPD are greatly understudied (Table 2). In a recent study, maternal trait anxiety in pregnancy was associated with smaller foetal left hippocampal volume (Wu et al., 2020). In newborns, no difference was found in hippocampal volumes after exposure to maternal prenatal anxiety, but at six months of age, reduced growth of both hippocampi was observed (Qiu et al., 2013). Of note, the result for the right hippocampal volume persisted after controlling for maternal postnatal symptoms (Qiu et al., 2013). In contrast, maternal prenatal depressive symptoms related to larger right hippocampal volumes in Asian newborns with a higher genetic risk for MDD in post hoc analyses, however, no associations were observed with hippocampal volumes in the American cohort of newborns (Qiu et al., 2017). In conclusion, although differences in time of observation exist, the effect of PPD on hippocampal volume seems to be growth-restricting in some studies (Qiu et al., 2013; Wu et al., 2020). However, evidence from one study suggests that the same risk alleles for psychopathology may function in an opposite manner depending on ethnicity (Qiu et al., 2017).

Table 2. Studies in animals and humans on the associations between maternal distress and offspring hippocampal morphology. Dopamine (DA), Prenatally stressed (PS), Prefrontal cortex (PFC), Caudate nucleus (Caud. N.), Nucleus accumbens (N. Acc.), Control (C), Hypothalamic-pituitary-adrenal axis (HPA axis), Postnatal days (P), Corticosteroid (COR), Myelin basic protein (MBP), Glial fibrillary acidic protein (GFAP), Prenatal psychological distress (PPD), Perceived Stress Scale (PSS), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State Anxiety Inventory (SSAI), Spielberger Trait Anxiety Inventory (STAI), Structural magnetic resonance imaging (sMRI), Gray matter (GM), White matter (WM), Deep gray matter (DGM).

	Author and year	Cohort if applicable	Species	Number (male/female)	Age at testing	Prenatal exposure	ROI	Method	Result	Sex difference
1	Fride & Weinstock 1988		Rat, albino Sabra	8 pups/litter (equal numbers)	6 months	Bell noise, flashing lights	Anxiogenic behaviour, lateralization of DA turnover rate	Plus maze, chromatography	Increased fearfulness after stress exposure in PS rats, PS increased DA turnover in PFC, but reduced it in Caud.N. & N. Acc., latter two only in females	Yes
2	Lemaire et al. 2000		Rat, Sprague-Dawley	PS 39, C 34, only males	Juvenile - old	Restraint stress, bright light	HPA axis activity, hippocampal cell morphology	Weight of adrenal glands, place navigation task, immunohistochemistry	PS exhibited greater decrease in hippocampal cell proliferation in all age groups, delayed learning & greater adrenal mass	-
3	Schmitz et al. 2002		Rat, Long-Evans	48 (not disclosed)	P75	Restraint stress	Numbers of hippocampal granule & pyramidal cells	Optical fractionator	PS females had reduced hippocampal volume & numbers of granule cells compared to controls	Yes
4	Fujioka et al. 2006		Rat, Sprague-Dawley	Not disclosed	P1, P15, P21, P31	Restraint stress	Morphological development of hippocampal neurons	Immunohistrochemistry, morphological analysis, electrophysiology	Short, mild PS enhanced neonatal neurogenesis, while long, severe PS impaired neuronal morphology	-
5	Lemaire et al. 2006		Rat, Wistar	Not disclosed, only males	4–26 months	Restraint stress, postnatal handling of pups by mothers	Hippocampal neurogenesis	Immunohistochemistry	PS decreased hippocampal cell proliferation in all age groups, but these effects were counteracted by neonatal handling	-
6	Zagron et al. 2006		Rat, Wistar	8-12 pups in each experiment (roughly equal)	P35	Maternal COR, adrenalectomy/ sham operation, restraint stress	Anxiogenic behaviour	Elevated plus maze, Morris water maze	Impairment of spatial learning in PS males. PS induced anxiogenic behaviour more in females than males, the behaviour was abolished by maternal adrenalectomy	Yes
7	Mychasiuk et al. 2011		Rat, Long-Evans	36 (roughly equal)	P21	Elevated platform, bright light	Hippocampal dendritic architecture, cell quantification	Stereological measures, Golgi-Cox morphological analysis	PS altered the dendritic arbor, the density of excitatory spines & volume of neuronal & glial cell numbers	No

	Author and year	Cohort if applicable	Species	Number (male/female)	Age at testing	Prenatal exposure	ROI	Method	Result	Sex difference
8	Bennett et al. 2015		Guinea pig	PS 41 (21/20), C 39 (20/19)	P18, P21	Strobe light	Anxiogenic behaviour, hippocampal MBP & GFAP (markers of plasticity)	Open-field test, object exploration test, immunohistochemistry	PS neonates exhibited higher levels of anxiety & neophobic behaviours, a decrease in MBP & GFAP	No
9	Qiu et al. 2013	GUSTO	Human	Baseline 175 (92/83), follow-up 42 (20/15)	Mean baseline 40.1 weeks, follow-up 66.4 weeks	Maternal prenatal anxiety, STAI at GW26	Hippocampal volume	sMRI (1.5T)	No associations between STAI scores and hippocampal volumes at baseline, but at 6 months the right hippocampus showed slower growth in subjects exposed to higher levels of maternal anxiety	No
10	Qiu et al. 2017	GUSTO	Human	Asian cohort: 168 (90/78); American cohort: 85 (50/35)	Mean ~ 40 weeks	MPDS, EPDS at GW 26	$GPRS_{MDD}$, amygdalar volume	sMRI (1.5T)	Asian: Larger right hippocampal volume in subjects with high $GPRS_{MDD}$; American: No association between hippocampal volumes & $GPRS_{MDD}$	No
11	Wu et al. 2020		Human	119 (67/52)	GW24-40	PPD measured with PSS, EPDS, SSAI & STAI at GW24-40	Fetal total brain, cortical GM, WM, DGM, cerebellum, brainstem & hippocampal volumes	sMRI (1.5T)	STAI scores associated with smaller left hippocampal volume, SSAI & STAI with increased cortical gyrification in the frontal & temporal lobes	No

2.7 Conclusions based on literature

Brain development is a complex process that consists of intricate and orderly events of intensive cell proliferation, migration, and transformation (Stiles and Jernigan, 2010). Growth of the deep subcortical structures and white matter is greater in mid-pregnancy, until which neurons are produced in most places, while growth of the cortex is greater in late pregnancy, when the migrating neurons arrive at their destinations (Stiles and Jernigan, 2010). With the extensive number of neurons and connections between them, the synapses are eventually pruned to maintain and strengthen the cells and networks that are most frequently used (Stiles and Jernigan, 2010). The brain is asymmetric at hemispheric, lobar, and brain unit levels, and these asymmetries are somewhat different in newborn and adult brains (Dean et al., 2018a; Giedd et al., 1999; Gilmore et al., 2007; Mark et al., 1999; Matsuzawa, 2001; Rajagopalan et al., 2011; Reiss et al., 1996). Despite the acquired knowledge on the human brain, the structural characteristics of the full-term newborn brain are yet unclear in terms of newborn age and sex. In addition, further elaboration of the associations between newborn growth metrics and brain volumes in full-term infants is needed.

Overall, the development and growth of the brain is region-, hemisphere-, and sex-specific (Tanaka et al., 2012). These developmental changes in brain tissues can be observed with an MRI starting from GW18 (Barkovich and Barkovich, 2019). Incidental findings are closely linked to brain MRI as they are common (Gupta et al., 2009). Incidental findings mostly consist of hemorrhages and cysts (A. Lind et al., 2010; Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004; Whitehead et al., 2013). Concerning hemorrhages, there are many known risk factors including gestational illnesses, obstetric factors, and mode of delivery (Gupta et al., 2009), but the risks by mode of delivery are inconsistent in studies (Benedetti, 1999; Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Towner et al., 1999; Whitby et al., 2004). In addition, the prevalence of the incidental findings varies notably between studies, and no consensus exists on how the family should be informed or how these findings should be followed.

The amygdala and the hippocampus are a part of a functional concept called the limbic system (McLachlan, 2009; Rajmohan and Mohandas, 2007). The amygdala is key to socioemotional cognition and memory, fear conditioning, as well as aggressive and anxiety-like behaviour, whereas the hippocampus is more involved in memory storing (McLachlan, 2009; Rajmohan and Mohandas, 2007). Both structures are influenced by the early environment, which interacts with many intrinsic factors (Buss et al., 2012b; Chen et al., 2015; Leuner and Gould, 2010; Ong et al., 2019; Roozenaal et al., 2009). Morphological changes have been observed in both structures after exposure to stress (Leuner and Gould, 2010; Roozenaal et al., 2009).

Maternal prenatal psychological distress (PPD) is one of the intrauterine exposures that may predispose the offspring to aberrant neurodevelopment (O'Donnell et al., 2014a; Van den Bergh et al., 2018). PPD most commonly refers to symptoms of anxiety and depression during pregnancy, but can also present as worries related to pregnancy (pregnancy-specific anxiety, PSA) (Emmanuel and St John, 2010). Comorbidity of these symptoms is common (Andersson et al., 2006; Kendler et al., 2007; Mathew et al., 2011; Middeldorp CM, Cath DC, Van Dyck R, 2005; Teixeira et al., 2009). The level of PPD varies during pregnancy and is influenced by maternal demographic factors (Baron et al., 2017; Figueiredo and Conde, 2011; Korja et al., 2018; Lee et al., 2007; Sutter-Dallay et al., 2012; Teixeira et al., 2009; Vänskä et al., 2011). Recent literature suggests that PPD impairs child neurodevelopment and increases the risk for later psychopathologies, especially anxiety and depression (O'Donnell et al., 2014a; Van Den Bergh et al., 2008). Changes in amygdalar and hippocampal volumes have been observed in individuals suffering from anxiety disorders, autism, and depression (De Bellis et al., 2000; Groen et al., 2010; Mosconi et al., 2009; Qin et al., 2014; Schumann et al., 2011, 2009, 2004; Videbech, 2004). Knowledge on how PPD, or its different types, may affect brain morphology is crucial in linking the possible predisposition of exposed children to later psychopathologies, and consequently, in developing preventative measures in the future.

Studies in humans have reported a positive effect of PPD on the right amygdalar volume in offspring (Acosta et al., 2019; Qiu et al., 2017; Wen et al., 2017). In children, this association has been significant only in females (Acosta et al., 2019; Wen et al., 2017). Animal studies have found PS to induce anxiogenic behaviour and nucleus-specific changes in the amygdala, which might be reflected differently in amygdalar volume and function (Ehrlich et al., 2015; Kraszpulski et al., 2006; Salm et al., 2004; Yang et al., 2008; Zohar and Weinstock, 2011). Human hippocampal growth seems to be restricted by PPD, although contradictory findings exist (Qiu et al., 2017, 2013; Wu et al., 2020). Similarly, in animals, PS related reductions in offspring hippocampal volume and changes in cell morphology have been observed, as well as problems in learning and behaviour (Bennett et al., 2015; Mychasiuk et al., 2011; Weinstock, 2011). In addition, PS exposure in animals has differential effects based on sex, including differences in amygdalar and hippocampal cell morphology, gene expression, and consequent behaviour (Weinstock, 2011; Zohar and Weinstock, 2011). However, due to the high variation in study variables (populations, maternal distress and offspring outcome measures), as well as inconsistent measurement time points, the effects of PPD on newborn amygdalar and hippocampal volumes remain disputed, as does the role of newborn sex.

Although it is yet unclear how PPD is transmitted to the foetus, the influence is most likely mediated by several factors – the effects of glucocorticoids and their

regulators on brain development is complex and seems to be further modified by genetic factors (Cottrell, 2009; Glover et al., 2010). Variations in (epi)genetics have differential effects on the developing brain as environmental conditions interplay with genetic susceptibility (Chen et al., 2015; Meaney et al., 2007; Ong et al., 2019). Additionally, the relevance of PPD might be time-sensitive depending on the stage of development during exposure (Buss et al., 2012b).Thus, investigating how the timing of PPD associates with offspring brain measures is beneficial in determining the overall effect of PPD on brain morphology.

3 Aims of the study

The first objective was to reveal the effects of basic newborn characteristics on brain volumetric measures. The second aim was to elucidate the prevalence and types, as well as possible clinical relevance, of incidental findings in our brain MRI study population. The first two studies were thus conducted to illustrate normal brain structure variation in a healthy newborn population. The third aim was to explore how different types and timings of maternal prenatal psychological distress may be associated with newborn amygdalar and hippocampal volumetric measures. A further aim was to see whether the associations between maternal prenatal distress and newborn amygdalar and hippocampal volumes were dependent on newborn sex.

The specific aims of the sub studies were:

I. To study how newborn age and sex affect total and lobar brain volumetric measures and asymmetry, and additionally, how newborn growth metrics associate with total and lobar brain volumes.

II. To describe incidental brain imaging findings in the newborn sample, and to investigate the prevalence and risk factors, as well as possible clinical implications of the incidental findings.

III. To investigate whether maternal prenatal psychological distress, as a combined assessment of depressive and anxiety symptoms, is associated with newborn amygdalar and/or hippocampal volumes, and if these relationships are moderated by newborn sex or timing of exposure.

IV. To explore the associations between second trimester pregnancy-specific anxiety and newborn amygdalar and hippocampal volumes, and the possibly modifying role of newborn sex.

4 Materials and methods

4.1 Subjects

The subjects were drawn from a larger participant pool of the FinnBrain Birth Cohort Study (Karlsson et al., 2018). The subjects consisted of pregnant women recruited from their first ultrasound visit at GW12 in South-Western Finland, referred to deliver at the Turku University Hospital. The recruitment occurred between December 2011 and April 2015 resulting in a total of 3,808 pregnant women and their soon to-be-born children. The number of younger, multiparous and smoking women, and the prevalence of preterm births were relatively lower in the cohort population than in the source population of women giving birth at the Turku University Hospital; otherwise the two populations resembled each other (Karlsson et al., 2018). Altogether 367 families discontinued the study during pregnancy, or between delivery and the three-month assessment due to a variety of reasons, of which the most frequently actively offered reason was lack of time (Karlsson et al., 2018). Other known reasons included miscarriage or stillbirth (n=35). The attrition analyses revealed that the women who did not respond to the GW34 distress questionnaire were younger and less often nulliparous, had shorter duration of gestation, lower educational and income levels, as well as smoked more frequently, and reported higher depressive symptom scores at GW14 than those who did respond to the GW34 questionnaires (Karlsson et al., 2018).

Based on willingness and availability, 189 Caucasian mother-newborn dyads were recruited to an MRI visit. Of the total, 180 scanning sessions were successful and produced structural MR images, but five had major motion artefacts and were excluded, reducing the total number of images to 175 (n=94 males, n=81 females). The inclusion and exclusion of individuals to and from sub studies I-IV are described in Figure 7. The enrollment to the study happened via a telephone call to the family. The purpose and protocol of the study was explained to the parent(s), after which they signed a written informed consent, as well as on behalf of their newborn.

A summary of the demographic data of the sub studies is presented in Table 3. Of the newborn participants, all but two were born full-term (born between GW37 and GW43). The two preterms were born at GW36 and two with no information available on gestational age. The study included singleton pregnancies only. All had

a birth weight over 2500 grams. Exclusion criteria for the newborns were severe perinatal complications with neurological consequences, previously diagnosed central nervous system anomaly, an abnormal finding in any previous MRI scan, and birth weight under 1500 grams. There were 19 newborns with mild asphyxia. One newborn underwent cardiopulmonary resuscitation (CPR) and respirator treatment and one had 4 points out of 10 in the 5 min Apgar.

Table 3. A summary of the descriptive characteristics of the subjects in studies I-IV. Male (M), Female (F), Central Nervous system (CNS).

Variable	Study I	Study II	Study III	Study IV
M ± SD (range)	N=68, M31/F37	N= 175, M94/F81	N=123, M69/F54	N=122, M68/F54
Newborn's age at scan (d)	305.8 ± 13.6 (276–339)	305.9 ± 7.4 (291–331)	305.2 ± 7.4 (291–325)	305.3 ± 7.4 (291–325)
Gestational age (d)	280.2 ± 7.5 (265–296)	279.3 ± 8.2 (254–296)	279 ± 7.8 (254–295)	279 ± 7.9 (254–295)
Birth weight (g)	3564.1 ± 429.6 (2530–4640)	3523.2 ± 434.8 (2530–4700)	3480.5 ± 431.8 (2530–4700)	3481.1 ± 431.7 (2530–4700)
Head circumference (cm)	35.2 ± 1.3 (32.5–37.5)	35.1 ± 1.3 (32.5–38.5)	35 ± 1.3 (32.5–37.5)	35 ± 1.3 (32.5–37.5)
Birth lenght (cm)	50.3 ± 1.7 (44–54)	50.5 ± 1.8 (44–56)	50.5 ± 1.9 (44–56)	50.5 ± 1.9 (44–56)
Maternal age (y)	30.2 ± 4.5 (21.5–30.2)	30.6 ± .2 (19.1–41.3)	30.2 ± 4.4 (19.1–41.3)	29.8 ± 4.4 (19–41)
Maternal prepregnancy BMI	24.3 ± 3.9 (18.8–24.3)	24.4 ± 4.1 (17.5–40.8)	24.1 ± 4 (17.5–38.4)	24.2 ± 3.9 (17.5–38.4)
Frequencies; total/yes (%)				
Birth complications	68/8 (11.7)	173/22 (12.7)	123/16 (13.3)	123/16 (13.3)
Birth before GW37 (GW36)	68/0 (0)	175/2 (1.1)	123/1 (0.8)	122/1 (0.8)
Prenatal alcohol/or nicotine consumption	68/20 (29.4)	167/49 (29.3)	120/36 (30)	119/35 (29.4)
Prenatal CNS affecting medication	68/6 (8.8)	166/12 (7.2)	123/9 (7.3)	118/8 (6.8)
Maternal education (low/middle/high)	1/41/24 (1.5/60.3/35.3)	47/51/71 (27.8/30.2/42)	34/38/49 (27.6/30.9/39.8)	33/38/51 (27/31.1/41.8)

Exclusion criteria for the mothers were alcohol or drug abuse, severe psychiatric disorders, epilepsy, or medication for psychosis. Obstetric information was retrieved from the Finnish Medical Birth register of the National Institute of Health and Welfare (www.thl.fi). Additional information was also gathered as a part of the FinnBrain Birth Cohort Study protocol, such as maternal pre-pregnancy body-mass-index, maternal age, monthly income, educational level, diagnosed medical conditions, CNS affecting medications, and substance use during pregnancy. No substance use other than alcohol and tobacco were reported. Regarding CNS

affecting medications, only serotonin and norepinephrine reuptake inhibitors or benzodiazepines were reported

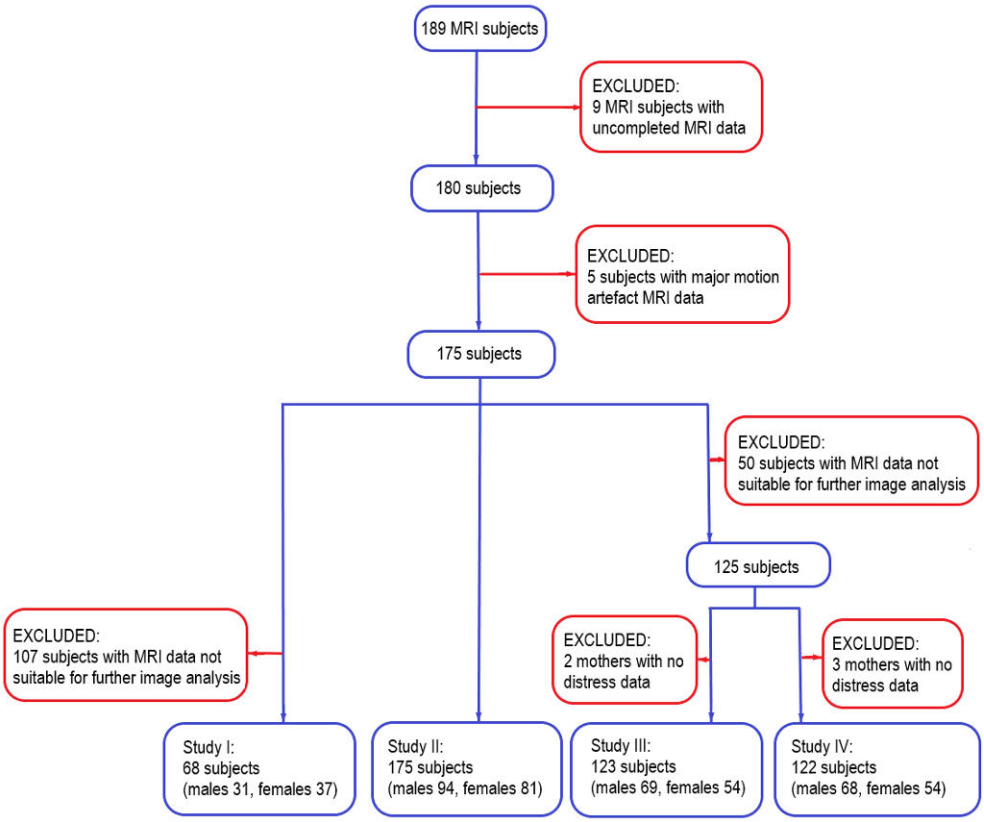

Figure 7. Inclusion and exclusion of subjects in sub studies I-IV. Author's illustration.

4.1.1 Study I

From the 175 imaged newborns, 68 (n=31 males, n=37 females) images had the requirements needed for the subsequent image analysis and were included into this sub study (Figure 7). One newborn had 4 out of 10 in 5 min Apgar and seven had mild asphyxia, although these characteristics were not considered as exclusion criteria. This sub study used the following obstetric information: newborn age at scan counted from due date and from birth date, head circumference, birth weight, and birth length.

4.1.2 Study II

A total of 175 newborns were included into this sub study after the primary exclusion of some subjects due to non-existent or bad-quality MR images (Figure 7). Out of 175 newborns, 125 (71 %) were born vaginally without assistance, 21 (12 %) with vacuum assisted extraction, and 29 (18 %) by c-section. Ninety-five (59 %) mothers had epidural and/or spinal anesthesia. Seventy-two (41 %) mothers out of 175 were primiparous.

Obstetric data used for this sub study consisted of the following: duration and mode of delivery, gestational age, use of anesthetics or oxytocin induction during delivery, mother's parity, possible episiotomy, gestational age at birth, child Apgar scores (1 min and 5 min), head circumference, birth weight, birth height, and pH of the umbilical cord. The modes of delivery were divided into three groups: 1) vaginal, 2) assisted deliveries (vacuum-assistance), and 3) c-sections (elective or emergency). Anesthetics were categorized into 1) epidural and spinal anesthesia and their combinations, and 2) all other anesthetic forms or no pain alleviation. Episiotomy was included as an indirect marker of increased pressure on the foetal skull during labour.

4.1.3 Studies III-IV

One hundred and twenty-five of 175 newborn MR images passed the quality control for further image analysis and were included into these sub studies (Figure 7). However, two mothers lacked the prenatal distress questionnaires for study III, and three mothers for study IV. Thus, 123 newborn-mother pairs were eligible for statistical analyses for study III and 122 for study IV. Sixteen newborns had mild asphyxia and one had 4 points out of 10 in 5 min Apgar. These individuals were grouped together as "birth complications" for sensitivity analyses. In addition, one newborn was born at GW36.3. Maternal gestational diabetes was included in sensitivity analyses as it may impair foetal neurodevelopment (Torres-Espínola et al., 2018). Maternal education was classified into three categories: 1) "low" representing educational attainment at maximum being high school graduation, 2) "middle" representing vocational schooling, and 3) "high" representing university level education.

4.1.4 Ethical considerations

The study was conducted according to the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK:31/180/2011).

4.2 Methods

4.2.1 Measures of maternal prenatal psychological distress

4.2.1.1 EPDS

Maternal depressive symptoms during pregnancy were measured at GWs 14, 24, and 34 with Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). Although originally developed for screening postnatal depression, EPDS is also validated for use during pregnancy (Bergink et al., 2011; Bunevicius et al., 2009; Rubertsson et al., 2011; Tendais et al., 2014). The 10 items of the EPDS cover the previous seven days on a total score range from 0 to 30. While no consensus on the most optimal EPDS cut-point for prenatal depression exists (Alvarado-Esquivel, 2014; Gibson et al., 2009; Rubertsson et al., 2011), a score of 10 or more has been employed to indicate clinically meaningful symptoms of depression in pregnancy (Vázquez and Míguez, 2019). However, no clinical cut-off scores were set for depressive symptoms in these sub studies as this would have excluded subjects with subclinical levels of these symptoms, which may be important in terms of the impact of PPD on foetal development. Nevertheless, for a better description of the study sample, the number of the mothers scoring above this threshold are listed in Table 4.

The number of missing data for EPDS was 3/123 at GW14, 1/123 at GW24, and 6/123 at GW34 (Table 4). If questionnaire data was missing in one of the timepoints, data was imputed by the MissForest method (Stekhoven and Buhlmann, 2012).

4.2.1.2 SCL-90

Maternal anxiety symptoms during pregnancy were measured at GWs 14, 24, and 34 with the anxiety subscale of Symptom Checklist 90 (SCL-90) (Deogratis et al., 1973). The anxiety subscale of SCL-90 is a standard tool for measuring anxiety (Bech et al., 2014; Deogratis et al., 1973) and widely used during the prenatal period (Adib-Rad et al., 2019; Kamel et al., 1999; Lin et al., 2017; Van den Heuvel et al., 2014). The SCL-90 anxiety subscale consists of 10 items, each on a five-point scale of distress (0-4) with a total score range of 0-40. As for EPDS, no established cut-off score exists for the SCL-90 anxiety subscale, however, a score higher than 10 has been used to indicate relevant symptoms of anxiety (Karlsson et al., 2018; Korja et al., 2017). If questionnaire data was missing in one of the timepoints, data was imputed by the MissForest method (Stekhoven and Buhlmann, 2012). As with depressive symptoms, no clinical cut-off scores were set for anxiety symptoms to

avoid exclusion of individuals with milder symptoms, but the mothers exceeding the cut-off score are likewise listed in Table 4 to better describe the sample.

The number of missing data for the SCL-90 anxiety subscale was 3/123 at GW14, 1/123 at GW24, and 6/123 at GW34 (Table 4). If questionnaire data was missing in one of the timepoints, data was imputed by the MissForest method (Stekhoven and Buhlmann, 2012).

4.2.1.3 PRAQ-R2

Maternal pregnancy-specific anxiety (PSA) was measured at GW24 with Pregnancy-Related Anxiety Questionnaire Revised 2 (PRAQ-R2). PRAQ-Revised (PRAQ-R), a shortened version of the original PRAQ (Bergh, 1990), is a commonly used questionnaire to measure anxiety during pregnancy in primiparous women (Huizink et al., 2004). A rephrased version PRAQ-R2 was successfully created to expand the applicability also to multiparous women (Huizink et al., 2016), and it has good to excellent reliability overall and at a subscale level (Arch, 2013; Brunton et al., 2019). PRAQ-R2 has ten items with a range of five answers from "definitely not true" to "definitely true", which form a total score range of 10-50. The items in PRAQ-R2 can be ordered into three subscales: 1) Fear of giving birth (three items), 2) Worries about bearing a physically or mentally handicapped child (four items), and 3) Concern about own appearance (three items) (Huizink et al., 2016). No clinical cut-off score has been established for PRAQ-R2, however, the highest quintile has been used to indicate the mothers having the most symptoms in the whole Finnbrain Cohort, with a threshold of 34 points or more (Karlsson et al., 2018). Although this threshold was not used in the current sub studies, the number of individuals scoring above this threshold are listed in Table 4 for additional descriptive information.

The number of missing data for PRAQ-R2 was three (Table 4). These individuals were excluded from the analyses.

4.2.1.4 Composite distress score

SCL-90 and EPDS scores were combined to create an overall continuous distress score because this study sample was drawn from the general population and the frequency of subjects with clinical depression and anxiety was expectedly low. However, to further describe the study populations, the number of individuals exceeding 10 points in the EPDS or SCL-90 anxiety subscale, indicating clinically meaningful symptoms of depression or anxiety, have been listed (Table 4). The SCL-90 and EPDS scores were standardized (mean=0, SD=1) for each scale and then summed. This overall distress score was calculated for each gestational timepoint (GW14: SCL1+EPDS1, GW24: SCL2+EPDS2, GW34: SCL3+EPDS3).

Table 4. Descriptive information of the maternal distress questionnaires in studies III-IV. In the column on the right p-values of Mann-Whitney U tests for sex differences in the sample. *Significant results (p<0.05); Gestational week (GW); Symptom Checklist -90, anxiety subscale (SCL-90, range of total sum score 0-40); Edinburgh Postnatal Depression Scale (EPDS, range of total sum score 0-30); Pregnancy-related Anxiety Questionnaire Revised 2 (PRAQ-R2, range of total sum score 0-50).

		M ± SD (range) (N of imputed symptom scores)			
Time point	**Distress questionnaire**	**All subjects**	**Males**	**Females**	***p***
GW14	SCL-90 score	3.53 ± 4.50 (0–19) (3)	3.40 ± 4.13 (0–16)	3.68 ± 5.04 (0–19)	0.558
	EPDS score	5.46 ± 5.15 (0–25) (3)	5.40 ± 4.78 (0–21)	5.54 ± 5.63 (0–25)	0.788
	SCL 1 + EPDS 1	1.28E-16 ± 1.92 (-1.84–6.43) (6)	-0.04 ± 1.76 (-1.84–6.43)	0.05 ± 2.12 (-1.84–6.43)	0.695
GW24	SCL-90 score	4.56 ± 5.32 (0–28) (1)	4.78 ± 5 (0–19)	4.27 ± 5.73 (0–28)	0.274
	EPDS score	5.58 ± 5.35 (0–25) (1)	5.66 ± 5.14 (0–23)	5.48 ± 5.66 (0–25)	0.645
	SCL 2 + EPDS 2	3.47E-18 ± 1.85 (-1.90–5.78) 6)	0.06 ± 1.77 (-1.90–5.78)	-0.07 ± 1.96 (-1.90–5.78)	0.403
	PRAQ score	24.09 ± 7.84 (10–46) (0)	25.55 ± 7.74 (11–46)	22.24 ± 7.63 (10–40)	0.008*
GW34	SCL-90 score	3.44 ± 4.12 (0–19) (6)	3.67 ± 3.67 (0–12)	3.15 ± 4.66 (0–19)	0.101
	EPDS score	5.48 ± 4.95 (0–20) (6)	5.66 ± 4.89 (0–17)	5.25 ± 5.06 (0–20)	0.574
	SCL 3 + EPDS 3	5.38E-17 ± 1.84 (-1.94–6.71) (12)	0.09 ± 1.67 (-1.94–6.71)	0.12 ± 2.01 (-1.94–6.71)	0.230
	Frequencies *(%)*				
GW14	SCL cut-off score ≥ 10	16 (13)	6 (8.7)	10 (18.5)	
	EPDS cut-off score ≥ 10	16 (13)	8 (11.6)	8 (14.8)	
GW24	SCL cut-off score ≥ 10	21 (17)	12 (17.4)	9 (16.7)	
	EPDS cut-off score ≥ 10	26 (21.1)	15 (21.7)	11 (20.4)	
	PRAQ-R2 score ≥ 34 (highest quintile)	21 (17.2)	13 (19.1)	8 (14.8)	
GW34	SCL cut-off score ≥ 10	12 (9.6)	7 (10.1)	5 (9.3)	
	EPDS cut-off score ≥ 10	23 (18.7)	13 (18.8)	10 (18.5)	

4.2.2 Special features of newborn MRI

MRI is a secure and commonly used method to investigate the developing human brain. Pediatric MR imaging is, however, accompanied with several challenges due

to the sensitivity to motion of the MRI method and the different composition of the newborn brain tissue compared to adults (Figure 8). Even the simple act of breathing or blinking, creates motion artefacts in the MR images of newborns, as their light-weight bodies transmit the movement easily to their heads. As studies on healthy newborns are done without anesthesia for ethical reasons, as well as to avoid potential complications, some of the following described methods are applied (Edwards and Arthurs, 2011). First, before positioning the newborn into the scanner, he or she is fed with (breast)milk to induce a period of natural sleep (Antonov et al., 2017). Second, a vacuum mattress is usually wrapped around him or her to reduce limb movements and to create a safer feeling for the baby (Antonov et al., 2017). Third, the scanner produces an intensive acoustic noise (Foster et al., 2000), so the newborn is provided with sufficient hearing protection (ear wax and muffs), which are put into place before or after feeding (Edwards and Arthurs, 2011). Finally, due to the sensitive nature of the imaging protocol, good collaboration and trust with the parent(s) is essential.

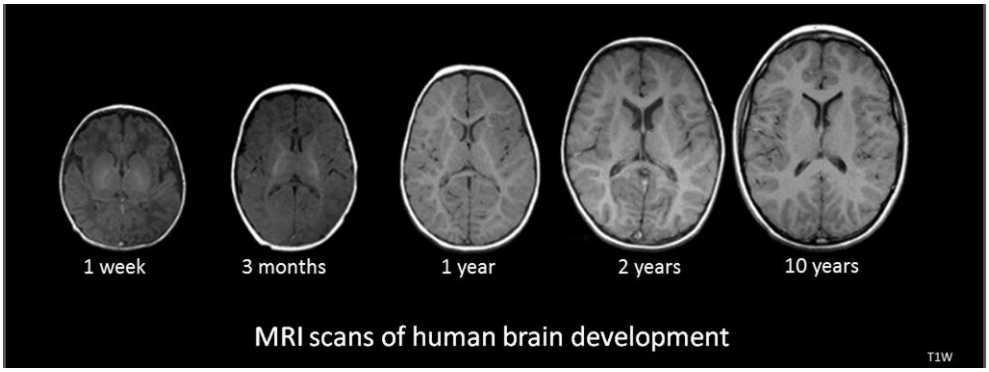

Figure 8. The human brain MRI (T1-weighted) in coronal planes at different ages. The increase in contrast is clearly visible over time. Image based on public domain: http://www.pediatricmri.nih.gov/nihpd/info/image_gallery.html#

The processing of the acquired MR images presents several challenges. The composition of the newborn brain differs from those of older individuals as it lacks most of the lipid rich myelin of WM and dense cellular structure of a mature brain GM, but at the same time contains more water (Makropoulos et al., 2018). Consequently, the contrast of GM/WM in MR images is inverted (Makropoulos et al., 2018), as the difference between GM and WM is very fine (Figure 8). Further, the small head size and shorter scanning periods create lower contrast-to-noise ratio (Makropoulos et al., 2018). Additionally, the variation of brain structure and shape is extensive across different scan ages due to the rapid developmental changes in the tissues, therefore rendering the precise registration of images difficult (Makropoulos et al., 2018)

4.2.3 MRI acquisition

The MR imaging was performed solely for research purposes and without clinical indications. The MRI acquisition occurred between November 2012 and January 2016. The scanning was executed at the Medical Imaging Center of the Hospital District of Southwest Finland. A Siemens Magnetom Verio 3T scanner (Siemens Medical Solutions, Erlangen, Germany) was used for the 40-minute imaging protocol, which contained axial PD-T2-TSE (Dual-Echo Turbo Spin Echo) and sagittal 3D-T1 MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) sequences with isotropic 1.0 mm^3 voxels, with whole brain coverage. Repetition time (TR) time of 12,070 ms and effective Echo time (TE) of 13 ms and 102 ms were used in PD-T2 TSE sequence to produce both PD-weighted and T2-weighted images from the same acquisition. The total number of 1 mm thick slices was 128. TR of 1,900 ms, TE of 3.26 ms, and inversion time (TI) of 900 ms were used for 3D-T1-MPRAGE sequence. The total number of slices was 176. Sequence parameters were optimized so that "whisper" gradient mode could be used in PD-T2-TSE and 3D-T1 sequences to reduce acoustic noise during the scan.

The newborns underwent the MRI scans at two to five weeks after birth without anesthesia. The scanning occurred usually during a weekday afternoon or evening, although some scans were performed during the day on weekends as well. The families were received by an experienced radiographer, who reviewed the scanning protocol with them and verified the absence of incompatibilities regarding MRI (inner ear implants, pacemakers, or other metal devices or parts). Before being placed into the scanner, the newborn was fed with milk (breast milk or formula) and then swaddled into sleep, having a vacuum mattress wrapped around them to limit limb movements. If willing, the parents were able to be present in the scanning room throughout the scan and could stop the study at any point of the visit. Sufficient hearing protection (ear plugs or wax and earmuffs) was provided to both the parents and the newborn. The scanning session was observed visually by the radiographer through a window. Newborn vocal sounds (possible signs of awakening) were transmitted by a loudspeaker to the observation room. The radiographer also had a microphone contact with one of the parents for communication during the scan. The scanning session was ended if the newborn did not fall asleep before or during the scan.

All 175 brain images were reviewed by a pediatric neuroradiologist for possible incidental findings. When incidental findings were detected, the researchers informed the families about them in between one and four weeks after the MRI visit. All the families of the newborns with a finding were offered the option of a neurological examination and consultation by an experienced pediatric neurologist (see paragraph 4.2.4).

4.2.4 MR image segmentation

4.2.4.1 Study I

The data were analyzed in iBEAT (Dai et al., 2013), an open source toolbox for processing newborn brain images. After file conversion from dicom to analyze the format, the images were preprocessed, which included reorientation, and subject to N3 intensity non-uniformity correction. Then the skull was extracted with an iBEAT module and, if the extraction was incomplete, manual correction of the brain mask was done. Next, tissue segmentation, i.e., separation of GM and WM (and cerebrospinal fluid [CSF]), was performed. Finally, iBEAT labeled the different parts of the brain according to an infant-specific Automatic Anatomical Labeling (AAL) atlas. Total gray matter volume (TGM) was counted using the iBEAT segmented and AAL labeled data. While the cortical segmentation was performed successfully, the subcortical segmentation output contained parts of the WM and was thus excluded from the analyses.

Total brain volume (TBV) was calculated as a combination of all gray and white matter volumes, and intracranial volume (ICV) was calculated by adding CSF to TBV. Total cortical volume (TCV) was calculated by subtracting the subcortical parts from TGM. Lobar volumes were calculated using the AAL labeled data by combining the volumes of separate anatomical brain parts belonging to a particular lobe. Ratios of the gray and white matter and lobar volumes, in relation to total brain volumes, namely relative volumes, were also calculated for total white matter (TWM), TGM, TCV and lobar volumes so that TGM, TWM and TCV were expressed as relative to TBV, and lobar volumes to TGM as they contained only gray matter.

4.2.4.2 Studies III-IV

Construction of an unbiased population-specific template

The measurements used in the analyses were derived using fusion-based methods that rely on a labelled template. These methods depend on achieving good registrations between the subjects and the template. This is increasingly difficult to achieve the further the template is from the subjects in terms of similarity. Therefore, a template was constructed based on the subjects in this study; then the structures of interest were manually labelled, and a mask was extracted for use in estimating intracranial volume (ICV).

All 125 MRIs were used to construct a population-specific dual-contrast template (Figure 9). The template construction process has been previously published (Fonov et al., 2011). It is an iterative process that, given a set of MRI

volumes, constructs a template, which minimizes the mean squared intensity difference between the template and each subject's MRI, and minimizes the magnitude of all deformations used to map the template to each subject's MRI. This method was applied to the T1 scans. The T1 scans were linearly registered to the Montreal Neurological Institute (MNI)152 template. The average scaling from the native MRIs to the MNI 152 template was then computed, and the inverse used to scale the MNI 152 template to the average size of the study population, which served as an initial target for construction of the population-specific template. The iterative template construction procedure was then applied producing the T1 template, as well as non-linear transformations between each T1 and the T1 template. The T2 native scans were then registered to the T1 native scans, and the resulting transform was concatenated with the linear and non-linear transforms taking that T1 to the T1 template. These composite transformations were then used to map the T2 scans to template space, where they were averaged to create the T2 template.

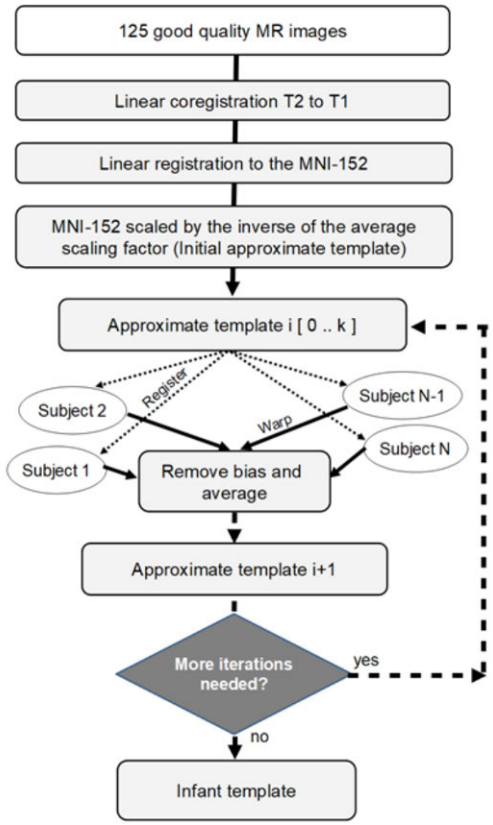

Figure 9. The construction of the infant template. Figure from (Acosta et al., 2020). Montreal Neurological Institute (MNI).

Labelling the template

The structures of interest, the amygdalae and hippocampi, were manually labelled on the dual-contrast template. To ensure the accuracy of the manual labelling, multiple warped variants of the template were produced (Figure 10), representing the morphological variability in the population, and each variant was manually labeled without the raters knowing that they were not actual subject data. Altogether 21 variants were produced, each a non-linear transformation of the template to overlay one of the subjects in the population. To construct these variants to reflect the morphological variation in the data, the non-linear transformations derived from the template construction process were used to cluster the subjects into 21 groups where the anatomical within-group variability was smaller than the inter-group variability. As the basis for clustering, the Jacobian was computed for the non-linear transform mapping each subject to the template. The values in the Jacobian were then extracted as a vector for each voxel within the template brain mask. These Jacobian vectors were then clustered using an equal combination of cosine similarity and Euclidean distance with Ward's clustering method (Ward, Jr, 1968), with the number of clusters chosen to be 21. Then, within each cluster, the sum-squared distance from each subject to each other subject was computed, and the subject with the minimum sum-squared distance was taken as the central-most subject of the cluster. The dual-contrast template constructed in the previous step was then warped to these 21 representative subjects, and provided for manual segmentation.

Segmentation was done following standard procedures (Hashempour et al., 2019). One template was first segmented by the primary rater, and subsequently by a senior rater, and externally reviewed by another senior rater. Once the first segmentation was deemed satisfactory, the other templates were then segmented.

The 21 manual segmentations were then warped back to the standard template, and each voxel was assigned a label based on the majority vote across all 21 manual segmentations. This yielded the final labels for the amygdalae and hippocampi on the standard template. The generalized conformity index (GCI) was calculated to determine the inter-rater agreement in spatial overlap for the newborn template (hippocampus: CGI= 0.76, amygdala: CGI= 0.70). CGI scores of 0.7–1.0 are regarded as excellent agreement between raters (Kouwenhoven et al., 2009; Visser et al., 2019)

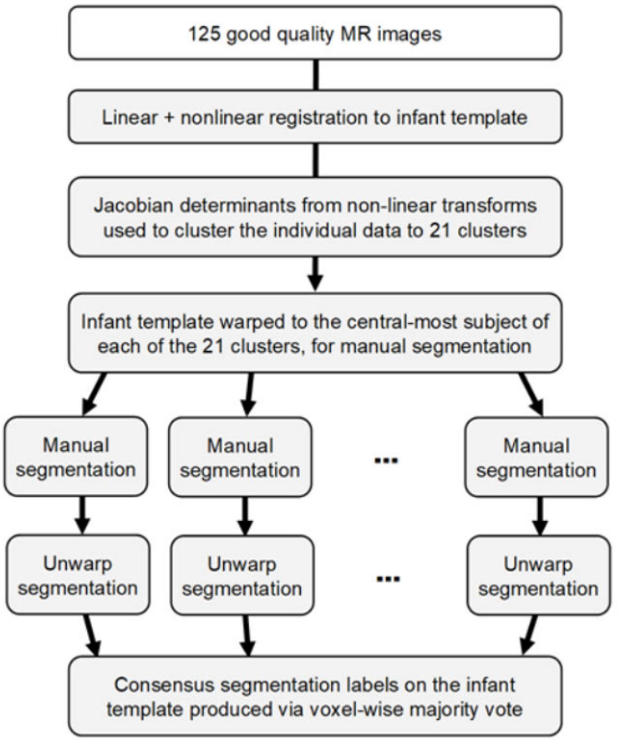

Figure 10. Labelling the infant template. Figure from (Acosta et al., 2020).

Labelling the subjects

Segmentation into left and right amygdalae and hippocampi was done for each subject using a label-fusion-based labeling technique based on Coupé et al. (2011), and further developed by Weier et al. (2014), and Lewis et al. (2019). The approach uses a population-specific template library. The library was constructed by clustering the deformation fields from the non-linear transforms produced during construction of the template and using the central-most subject of each cluster to construct the entries in the template library; this is similar to the method described above, but in this case, the clustering used a dilated mask of the amygdalae and hippocampi to capture the anatomical context of the nonlinear registration in that region of the brain, and the number of clusters was the square of the natural log of the number of subjects. The representative subject for each cluster was chosen as described above. This was done per hemisphere to accommodate hemispheric asymmetries. Thus, the template library represented the range of deformations of the hippocampi and amygdalae found in the population.

To create the library entry for a cluster, the non-linear transform for the central-most subject was used to warp the template together with the segmentation defined

on it, and this pair was added to the template library. The template library was thus a set of warped copies of the template together with their correspondingly warped segmentations. Once the template library had been created, each subject in the population was non-linearly registered to the n closest templates in the library (here, n=7), and the resulting transforms were used to warp their corresponding segmentations to the subject; the final labelling was then established via a patch-based label fusion. This was also done separately for each hemisphere. An example of such a labelling is shown in Figure 11. The volumes of each of the final labellings were then computed and scaled to native space based on the scaling factors in the subject's linear transforms.

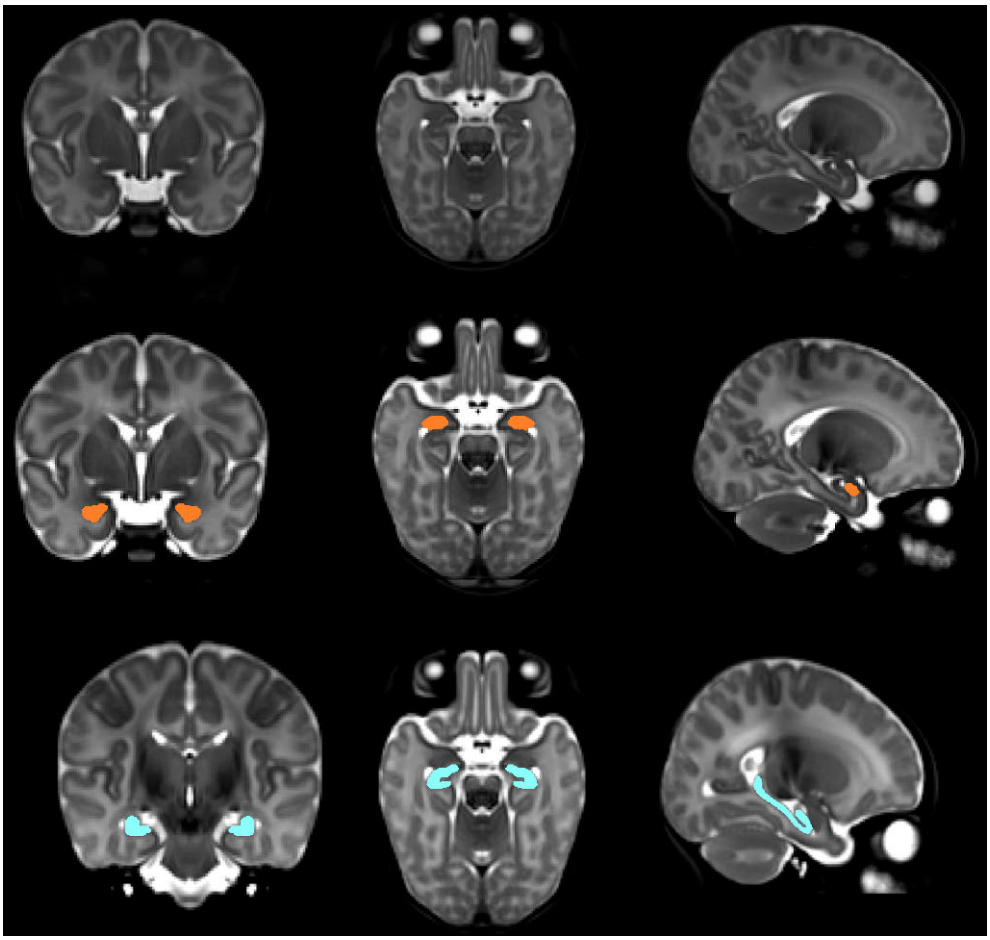

Figure 11. Example of the segmentation of the amygdala and hippocampus in a study subject. From left to right, coronal, axial and sagittal planes of the segmentations. The first row presents the newborn brain without segmentation. The second row presents the segmentation of the amygdala (orange color) and the third row the segmentation of the hippocampus (blue color).

4.2.5 Follow-up on neurological development (Study II)

A neurological assessment by a pediatric neurologist was offered to the newborns with incidental findings, and it comprised a detailed review of the child's health (clinical history and interview), developmental milestones, and possible abnormal symptoms. The pediatric neurologist performed a complete somatic and neurological examination for all the children using a standardized proforma of the Dubowitz neurological examination for children below 6 months (Dubowitz et al., 1998) and the Hammersmith Infant Neurological Examination (HINE) for all children (Haataja et al., 1999). Finally, the results of the neurological assessment and the findings of the MR images were discussed with the parents, who were given the opportunity also to contact the specialist after the visit. However, no family used this opportunity, and thus, it was concluded that the given information was sufficient.

4.2.6 Statistical methods

4.2.6.1 Study I

The IBM SPSS Statistics Version 23 was used for statistical analyses (Armonk, NY IBM Corp.). The normality of the data was checked by visual confirmation and with Shapiro–Wilk test. *P* values smaller than 0.05 were considered statistically significant, unless otherwise noted. A Bonferroni correction was applied for all the analyses including multiple comparisons to prevent possible Type I errors due to multiple tests.

Newborn age was calculated from both the due date and the actual birth date as the age varied between these dates. The associations between newborn age variables and brain volumes were analyzed using bivariate correlations and then controlled for sex with partial correlation. The relationships between newborn growth markers (head circumference, birth weight, and length) and brain volumes were studied with bivariate and partial correlations (controlling for sex and age).

To analyze sex differences in clinical variables, a parametric test (*t*-test) was used as the data was normally distributed. Sex differences in mean brain volumes were examined with the Independent samples *t*-test. Simple linear regression, including age-by-sex interaction, was run to examine associations between newborn age at scan (due date) and brain volumes, having sex as a fixed factor. After the exclusion of the newborns exposed to maternal antidepressant medication (N=5), the analyses were repeated, yielding similar results.

An asymmetry index (AI) (Dean et al., 2018a; Tanaka et al., 2012; Uematsu et al., 2012) was calculated to investigate total gray matter and lobar asymmetry using the formula ([left – right] / [left + right] × 100). Positive values represented leftward

(left > right) and negative values rightward asymmetry. The statistical significance of hemispheric asymmetry was calculated using a One sample *t*-test (testing against the reference value 0.00). If asymmetry was detected, sex differences were tested with Independent samples *t*-test. The association between asymmetry and age was investigated with simple linear regression with sex as a covariate. Finally, possible correlations within regional brain volumes were explored using bivariate correlations.

4.2.6.2 Study II

Statistical analyses were performed with SPSS version 23 (Armonk, N.Y., USA). Group comparisons for the categorical variables were determined with Chi-square test, and for continuous variables, with two-sample *t*-test (means and SDs) or nonparametric Wilcoxon rank-sum test (medians and median absolute deviation [MAD], scaled by a factor $k = 1.4826$) depending on the normality of the distribution of the data. Multiple comparison corrections were not performed due to the small sample size and the exploratory nature of the study. Odds ratios for putative risk factors of incidental findings were calculated by using Boschloo's test (Boschloo, 1970; Lydersen et al., 2009).

4.2.6.3 Studies III-IV

Statistical analyses were performed using the IBM SPSS Statistics Version 23 (Study III) and 26 (Study IV) (Armonk, N.Y., USA). Dependent variables used in the analyses were the relative (absolute volumes divided by ICV) volumes of the left and the right amygdala and hippocampus. The same analyses were repeated also for absolute amygdalar and hippocampal volumes, as controlling for ICV can have complex effects on results (Mills et al., 2016), but were not considered as a part of the main analyses. *P* values smaller than 0.05 were considered significant. Given the exploratory nature of the studies, uncorrected (for multiple comparisons) values were reported.

Associations between the continuous study variables (maternal and newborn health parameters, distress questionnaire scoring, and brain volumetric measures) were investigated with zero-order Pearson or Spearman correlations depending on the distribution of the data. Sex differences in continuous variables (mean volumetric measures, newborn age, head circumference, birthweight and length, maternal age, pre-pregnancy BMI, and distress scores) were analyzed with Independent samples *t*-test or Mann-Whitney U Test. Sex differences in categorial variables (birth complications, maternal prenatal substance and/or CNS affecting medication consumption, maternal education, and gestational illnesses) were investigated with

Chi-square Tests. Differences between distress scores at different pregnancy time points were analyzed with the Friedman test (Study III). General linear modelling (GLM) was used to investigate the relationships between maternal prenatal distress scores and newborn volumetric measures of the amygdalae and hippocampi. Distress score variables were not normally distributed, but as normality is not assumed for independent variables in regression, no adjustments were made. The analyses were also repeated with other newborn age variables (gestational age and postnatal age in days at scan) to test the consistency of the results.

In study III, the GLM analyses were performed in two parts: 1) the main effect model and 2) the interaction model. The first model (see Results, Model A in Table 7) explored the main effects of the distress scores on amygdalar and hippocampal volumes. The second model (Model B in Table 7) explored the interaction between sex and distress scores by adding an interaction variable (sex*distress score). Both models were tested separately for both sides of the amygdala and hippocampus and in each pregnancy time point (GW14, GW24 and GW34, respectively). Thus, altogether 24 tests were performed. Covariates were added stepwise into the analyses: step 1) newborn age at scan (days counted from estimated due date) and newborn sex; step 2) maternal prenatal medication (CNS-affecting medication), substance use (alcohol or tobacco), and maternal education; step 3) gestational diabetes and birth complications (asphyxia, CRP, respirator treatment, 5 min Apgar score under five). Steps 2 and 3 were regarded as sensitivity analyses. Additional sensitivity analyses were conducted excluding the only preterm born, all newborns with birth complications and mothers with prenatal CNS affecting medication (n=25, n=15 males, n=10 females). The main effect models for the whole sample were also performed separately in males and females as *post-hoc* analyses to further describe the results yielded in the interaction model.

In study IV, the GLM analyses were also performed in two parts: the first part (Model A) investigated the main effect of mid pregnancy (GW24) PRAQ-R2-score on the volumetric measures of amygdalae and hippocampi in the whole group; in the second part (Model B), the same analysis was repeated but separately in males and females to explore potential differences between sexes (see Results, Table 7). Covariates were added stepwise into the analyses. In the first step of each part, newborn total age (gestational age + days counted from birth), birthweight, maternal BMI, and maternal education were included. In the second step, the EPDS+SCL composite distress score of GW24 was added as a potential confounder. The birthweights were adjusted to gestational age to investigate if there were large differences between individuals referring to small- or large-for-gestational-age conditions. All newborns, except one, were found to be appropriate weight for gestational age, thus the original birthweight value was used. The median value was used to replace the missing values of birthweight (n=1) and maternal BMI (n=2).

The most common education level (3) high) was used to replace the missing values in maternal education (n=2, male n=1). As a confirmation, five sets of sensitivity analyses were run, where the following groups were individually removed from the analyzed sample: individuals exposed to maternal prenatal CNS affecting medication and/or substance use, as well as individuals with birth complications and, in addition, individuals with mothers who had gestational diabetes and/or hypertension or pre-eclampsia.

5 Results

5.1 Associations of age and sex with brain volumes and asymmetry in newborns

5.1.1 Brain volumetric measures and brain interregional correlations

The mean brain volumetric measures are presented in Figure 12 and Table 5.TGM between hemispheres did not differ (Table 5). All the total volumes, ICV, TBV, TWM, TCV, correlated strongly with each other ($R > 0.8$, $p < 0.001$), as well as TGM with each of the hemispheric TGM ($R > 0.9$, $p < 0.001$).

Regarding lobar volumes, frontal lobe formed the largest part of TGM, then the occipital lobe, temporal lobe and parietal lobe (Figure 13). There was high interlobar correlation between all the lobes ($R > 0.7$, $p < 0.001$). Temporal regions showed the strongest correlations with all the other lobes ($R > 0.8$, $p < 0.001$). TGM correlated strongly with all lobar volumes ($R > 0.9$, $p < 0.001$). Poor correlation was observed between TWM and the frontal/parietal lobes, as well as TCV, and the parietal lobe ($R < 0.2$, $p > 0.1$).

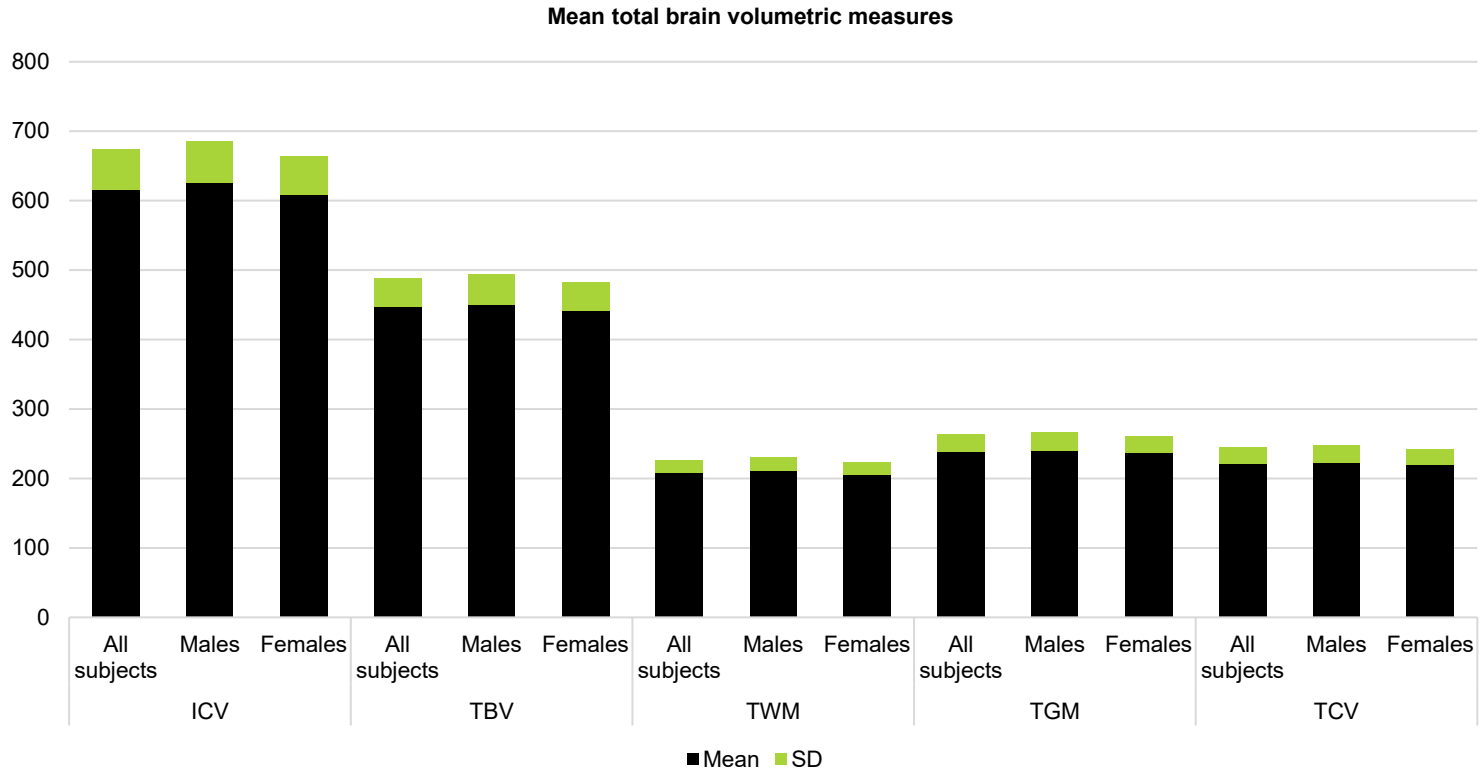

Figure 12. Mean total brain volumes (ml) of all subjects, males, and females. Total cortical volume (TCV), total white matter volume (TWM), Total brain volume (TBV), Intracranial volume (ICV).

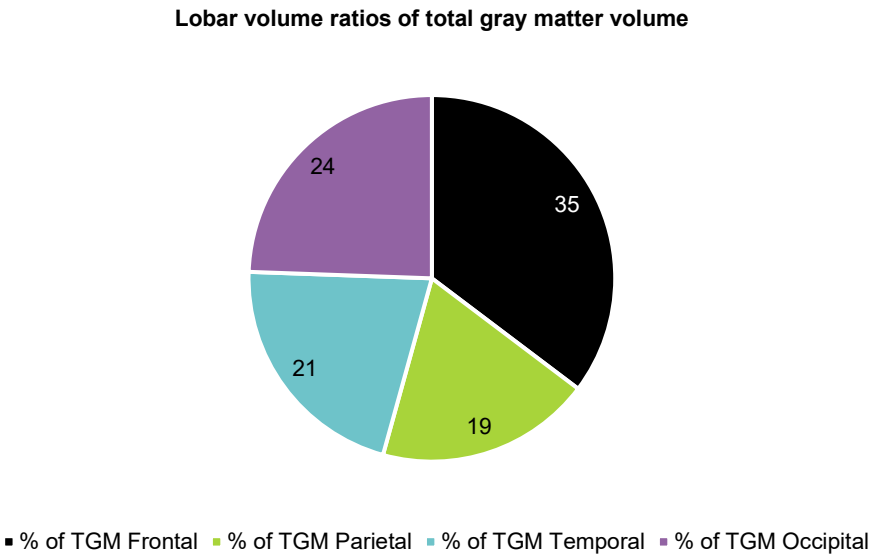

Figure 13. Pie chart of the lobar volume ratios of total gray matter volume (TGM).

5.1.2 Brain asymmetry and its association with newborn sex and age

In the whole sample, the absolute volumes of left parietal (p=0.003), left occipital, and right temporal (p<0.001, Bonferroni corrected for multiple comparisons) lobes were larger than their counterparts (Figure 14 and Figure 15). No asymmetry was detected in the frontal lobe. Results were similar with relative volumes and when controlled with sex. Age did not associate with the degree of asymmetry.

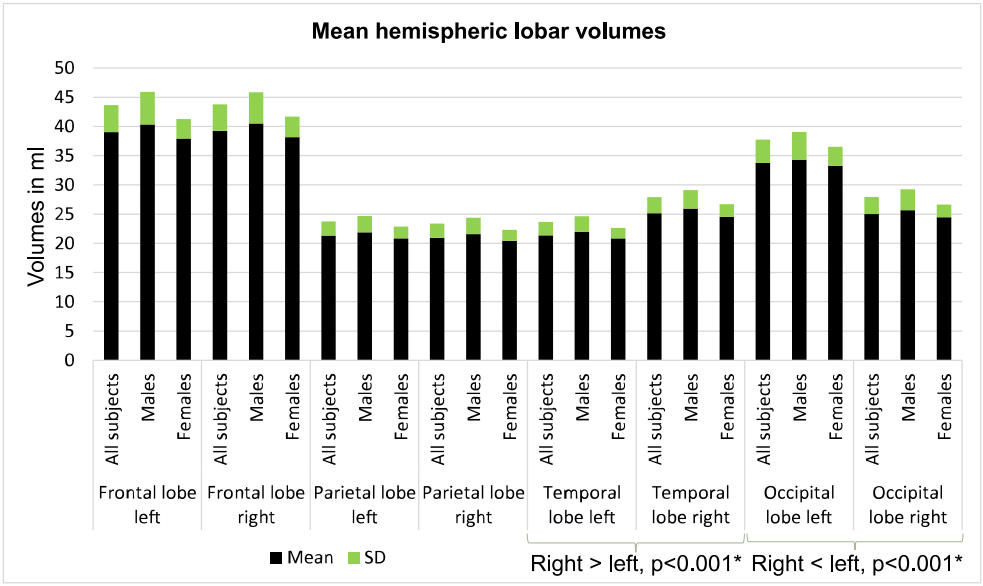

Figure 14. Mean hemispheric lobar volumes of all subjects, males, and females. *Bonferroni corrected for multiple comparisons.

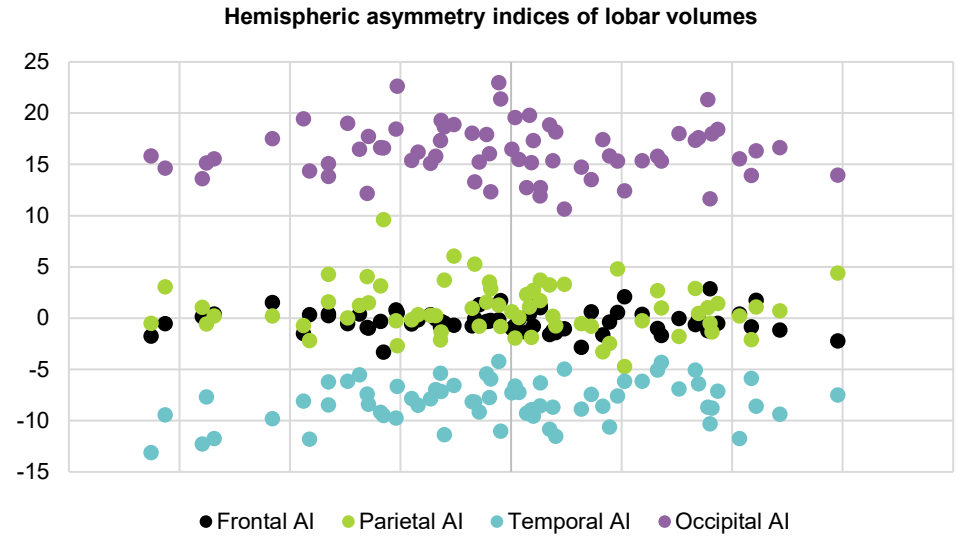

Figure 15. A scatter plot of the hemispheric asymmetry indices (AI) of lobar volumes. Positive values represent leftward asymmetry (left > right) and negative values rightward asymmetry (right > left).

5.1.3 Sex differences in brain volumetric measures

Males had greater absolute total volumes of frontal, parietal and temporal lobes, as well as the right hemispheric TGM (Table 5). Females, in turn, had greater total and left parietal lobe volume, right temporal lobe volume, and TGM. None of these results persisted after Bonferroni correction for multiple comparisons.

5.1.4 Brain volumetric measures and newborn age

No correlations between absolute brain volumetric measures and newborn age were observed in the whole sample, but relative volumes of TGM and TCV correlated positively with age (Table 5). In the subgroups defined by sex, the same associations with relative volumes were present, and additionally, age correlated negatively with TWM in both sex groups. In females, frontal and occipital lobe volumes also showed a positive correlation with age. The results were the same for both calculated age variables. All the results survived Bonferroni correction (p<0.003), except some results in females (TWM, TCV, left and right frontal lobe volume, total and left occipital lobe volumes) (Table 5).

5.1.5 Brain volumetric measures and newborn growth metrics

After controlling for sex and age, the majority of the correlations between brain volumetric measures and newborn growth markers were with head circumference: positive correlations with absolute ICV, TBV, TWM (R>0.3, p<0.01), TCV, total and left frontal lobe volumes, as well as with all relative volumes of the frontal lobe (R>0.2, p<0.05); and, additionally, negative correlations with relative occipital lobe volumes (R< -0.2, p<0.05). Birth length correlated positively with absolute TWM (R=0.269, p=0.029). The correlation with TWM (R=0.340, p=0.005) was the only one to survive Bonferroni correction (p <0.006).

Table 5. The associations of mean brain volumetric measures and newborn sex and age. Relative volume of TBV was calculated in relation to ICV. Relative total volumes of grey and white matter were derived from relating absolute volumes to TBV and lobar absolute volumes to TGM. Independent samples *t* test was used with normally distributed values and Mann–Whitney *U* test with non-normally distributed values for sex differences. *Only statistically significant ($p < 0.05$) sex differences are listed and marked; – non-significant results. Correlations with newborn age: a) R>0.5, $p<0.001$, b) R>0.4, $p<0.01$, c) R< -0.4, $p<0.01$, d) R>0.3, $p<0.05$. Total brain volume (TBV), intracranial volume (ICV), total gray matter volume (TGM); ** Associations with age that survived the Bonferroni correction for multiple comparisons.

	Mean absolute volumes				**Mean relative volumes**			
Cerebral structures	All (n=68), cm^3 (SD)	Males ($n = 31$), cm^3 (SD)	Females ($n = 37$), cm^3 (SD)	Sex difference *p*	All (n=68)	Males ($n = 31$)	Females ($n = 37$)	Sex difference *p*
ICV	616 (58.0)	625.7 (60.7)[a**]	608.2 (55.2)	–				
TBV	446 (41.7)	450.8 (43.6)[a**]	442.6 (40.3)	–	0.72 (0.03)	0.72 (0.02)	(0.73 (0.03)	–
TWM	208 (18.4)	211.1 (18.7)	205.3 (18.0)	–	0.47 (0.01)	0.47 (0.01)[c**]	0.46 (0.01)[c]	–
TGM	238 (24.8)	240.6 (26.2)	237. 4 (23.8)	–	0.60 (0.01)[a**]	0.60 (0.01)[a**]	0.61 (0.01)[a**]	0.027*
Left	119 (12.4)	122.3 (14.9)	116.6 (9.2)	–	0.27 (0.01)[a**]	0.27 (0.01)[a**]	0.27 (0.01)[a**]	–
Right	119 (12.4)	122.7 (15.0)	116.4 (9.0)	0.044*	0.27 (0.01)[b**]	0.27 (0.01)[a**]	0.27 (0.01)	–
TCV	221 (23.6)	222.0 (25.0)[a**]	219.8 (22.6)	–	0.49 (0.01)[a**]	0.49 (0.01)[a**]	0.50 (0.01)[b]	–
Frontal lobe	78.3 (9.1)	80.8 (10.9)	76.1 (6.8)	0.040*	0.33 (0.01)	0.33 (0.01)	0.33 (0.01)[b**]	–
Left	39.0 (4.6)	40.3 (5.6)	37.9 (3.3)	–	0.17 (0.01)	0.17 (0.01)	0.16 (0.01)[b]	–
Right	39.2 (4.6)	40.5 (5.3)	38.2 (3.5)	0.041*	0.17 (0.01)	0.17 (0.01)	0.16 (0.01)[b]	–
Parietal lobe	42.3 (4.7)	43.4 (5.5)	41.3 (3.7)	–	0.18 (0.01)	0.18 (0.01)	0.18 (0.01)	0.021*
Left	21.3 (2.4)	21.9 (2.8)	20.9 (2.0)	–	0.09 (0.01)	0.09 (0.01)	0.09 (0.01)	0.017*
Right	20.9 (2.4)	21.6 (2.8)	20.4 (1.9)	–	0.09 (0.01)	0.09 (0.00)	0.09 (0.00)	
Temporal lobe	46.5 (5.0)	47.9 (5.8)	45.4 (3.9)	0.041*	0.19 (0.01)	0.19 (0.01)	0.20 (0.00)	–
Left	21.4 (2.3)	22.0 (2.7)	20.9 (1.8)	0.049*	0.09 (0.01)	0.09 (0.00)	0.09 (0.00)	–
Right	25.2 (2.8)	25.9 (3.2)	24.5 (2.2)	0.042*	0.11 (0.01)	0.11 (0.00)	0.11 (0.00)	0.021*
Occipital lobe	53.7 (6.3)	54.8 (7.6)	52.7 (4.8)	–	0.23 (0.01)	0.23 (0.01)	0.22 (0.01)[d]	–
Left	33.8 (4.0)	34.3 (4.7)	33.3 (3.2)	–	0.14 (0.01)	0.14 (0.01)	0.14 (0.01)[d]	–
Right	25.0 (2.9)	25.7 (3.6)	24.5 (2.2)	–	0.11 (0.01)	0.11 (0.01)	0.11 (0.01)	–

5.2 Prevalence and risk factors of incidental findings in brain MRIs of healthy newborns

5.2.1 Prevalence of incidental findings

Out of 175 brain MR images, 13 had incidental findings (n=6 males, n=7 females). Hence, the prevalence of all incidental findings was 7.4 % (Figure 16). All the newborns with incidental findings were born vaginally and four of these were vacuum assisted deliveries, resulting in a 19 % prevalence of incidental findings in this group. The incidental findings consisted of 12 (6.9 %) hemorrhages, three (1.7 %) cysts, and combinations of these two (Figure 16). Regarding hemorrhages, only subdural (SDH) and intraparenchymal (IPH) hemorrhages were observed, and SDH was the most prevalent finding (n=10, 5.7 %) compared to IPH (n=4, 2.3 %).

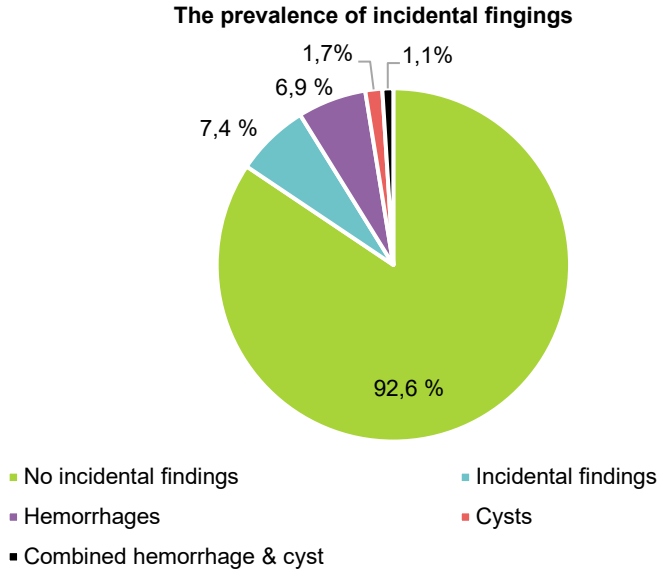

Figure 16. Pie chart of the prevalence of incidental findings in the study population.

SDHs were mostly located in the posterior fossa (n=10), but simultaneous occurrence of occipital (n=3) and temporal (n=3) SDH, as well as the combination of all these three (n=2) was observed (Figure 17). Only one individual presented with an isolated temporal SDH. Two subjects with SDH in the posterior fossa had also cerebellar parenchymal hemorrhage and cyst-related caudothalamic parenchymal hemorrhage. In addition, the findings included one individual caudothalamic IPH, one caudothalamic cyst, and one caudothalamic cyst combined with a parenchymal

hemorrhage. As cysts as an isolated finding are very common in normal brain development, the one individual with this finding was excluded from further analyses.

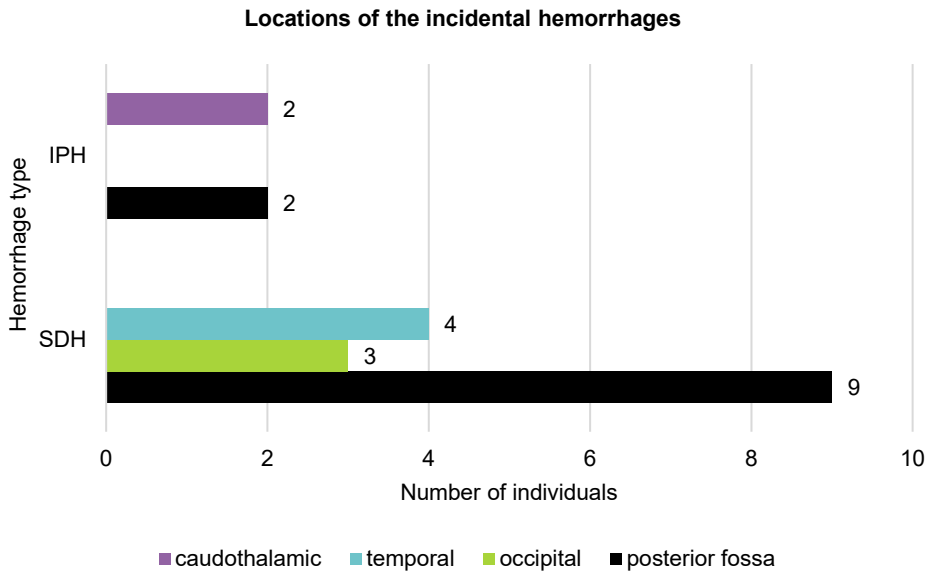

Figure 17. The locations of the incidental hemorrhages in the study population. Intraparenchymal hemorrhage (IPH), subdural hemorrhage (SDH).

5.2.2 Risk factors for hemorrhages

Within this sample, while vacuum-assisted delivery fell short of significance as a risk factor for hemorrhages in general (odds ratio, OR, 3.4; 95% Cl [0.92;11.7], p=0.059), it presented as a risk factor for SDH (OR, 4.7; 95% Cl [1.18;18.9], p=0.032), especially temporal SDH, as three out of four of them occurred in vacuum-assisted deliveries (OR=20.7, 95%Cl [2.2;378], p=0.008) in primiparous women with episiotomy. However, primiparity did not present as a risk factor for hemorrhages in the whole sample (OR 1.47, 95%Cl [0.44;4.9], p>0.05). Hemorrhages in the posterior fossa were mainly associated with vaginal deliveries without assistance. There were no incidental findings in the c-section group. Other newborn or obstetric variables (birth weight and height, newborn age, gestational age, duration of delivery, maternal age, anesthetics, Apgar scores, oxytocin induction, and maternal parity) had no relation to the occurrence of incidental findings. Age at scanning was not controlled in the risk factor calculations due to small group sizes, however, no significant age differences were detected between the

individuals with (median 23 [5.9] days) and without (median 26 [7.4] days) incidental findings in the risk factor analysis.

5.2.3 Neurological evaluation of clinical significance

All newborns with incidental findings underwent a standard stay on the maternity ward (average 3.1 days [0;6]) and a discharge from the hospital. One newborn with cerebellar IPH had had acute surveillance due to breathing difficulties, which were considered to be caused by an infection.

All 13 newborns with incidental findings were offered a follow-up appointment by a pediatric neurologist, to which 11 newborns attended and two families declined, one of them explaining the control was not necessary due to multiple check-ups at the Finnish well-baby clinics over the first year of life. Newborn age at the examination varied due to scheduling issues (age 7 to 54 weeks, mean 16.6 weeks). Acknowledging this, two different, age-appropriate assessment protocols were used to guarantee comparability, the Dubowitz proforma and HINE.

At the time of the examination, none of the newborns had clinically identifiable, significant neurological symptoms or deficits in their development, and their general health was normal. Of the children evaluated with Dubowitz proforma (N=9), none had clinically significant deviation in the scoring or deviant items, five had no deviant items, and four had one deviant item (mainly mild truncal hypotony), which is considered common (i.e. present in one third of the population, Dubowitz et al., 1998). All the children examined with HINE (Haataja et al., 1999) had normal cranial nerve function, 10 exhibited fully normal, and one mildly delayed motor milestones. This same child also had mild problems in social behaviour. Posture, movement, tone, and reflexes were assessed resulting in median optimality HINE score of 65, which falls within the normal variation of the score amongst normally developing children. To summarize, no evident delay in the neurological development or behaviour was observed in the examined children.

5.3 Associations of maternal prenatal psychological distress with newborn amygdalar and hippocampal volumes and roles of timing of exposure and newborn sex

5.3.1 Intercorrelations of the study variables

No significant difference was found between the cross-sectional SCL+EPDS ($Q=1.29$, $p=0.524$) and EPDS sum scores ($Q=0.84$, $p=0.635$) in different time points or between sexes. However, SCL-90 scores were highest at GW24 compared to other

trimesters (Q=18.48, $p<0.001$). The composite scores SCL+EPDS1 through 3 were all highly intercorrelated (Table 6). Regarding brain volumetric measures, ICV correlated positively with both absolute volumes of the amygdalae and hippocampi. These three absolute volumes were also greater in males than females (ICV $p<0.001$; left amygdala $p=0.024$; right amygdala $p<0.001$, left hippocampus $p=0.004$, right hippocampus $p=0.032$), however, when corrected with ICV, only the finding of the right amygdala persisted ($p=0.030$). Newborn total age and age at scan correlated positively with absolute right volumes of the amygdala and hippocampus, with no significant correlation on the left side (Table 6). Due to the correlations of volumetric measures with ICV and newborn age, brain volumes were adjusted to ICV and newborn age was used as a control variable.

Table 6. Correlations between study variables in studies III-IV. Edinburgh Postnatal Depression Scale (EPDS), Symptom Checklist 90, anxiety subscale (SCL-90), Pregnancy-related Anxiety Questionnaire Revised 2 (PRAQ-R2), Gestational week (GW), Body Mass Index (BMI), Intracranial volume (ICV), Correlation coefficient (R).

			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	EPDS + SCL GW14	R	1,000														
		p															
2	EPDS + SCL GW24	R	0,805	1,000													
		p	<0.001											R			
3	EPDS + SCL GW34	R	0,707	0,818	1,000												
		p	<0.001	<0.001										1,0			
4	PRAQ sum at GW24	R	0,531	0,579	0,571	1,000								0,9			
		p	<0.001	<0.001	<0.001									0,8			
5	Age at scan (due date)	R	0,124	0,088	0,031	0,023	1,000							0,7			
		p	0,173	0,332	0,735	0,798								0,6			
6	Newborn total age at scan	R	0,148	0,106	0,051	0,040	0,982	1,000						0,5			
		p	0,102	0,245	0,576	0,665	<0.001							0,4			
7	Gestational age	R	0,010	0,013	-0,007	-0,072	0,489	0,495	1,000					0,3			
		p	0,914	0,891	0,941	0,431	<0.001	<0.001						0,2			
8	Birth weight	R	-0,109	-0,098	-0,039	-0,013	0,198	0,197	0,384	1,000				0,1			
		p	0,231	0,281	0,666	0,884	0,028	0,028	<0.001					0,0			
9	Mother's age	R	-0,295	-0,232	-0,111	-0,032	0,002	-0,014	-0,060	-0,091	1,000						
		p	0,001	0,010	0,224	0,728	0,980	0,877	0,507	0,321							
10	Mother's BMI	R	-0,054	-0,039	-0,040	0,034	-0,071	-0,083	-0,006	0,163	0,187	1,000					
		p	0,557	0,674	0,660	0,714	0,437	0,362	0,948	0,072	0,040						
11	ICV	R	-0,051	-0,067	0,005	0,003	0,403	0,418	0,081	0,392	0,041	0,145	1,000				
		p	0,577	0,462	0,960	0,970	0,000	0,000	0,371	0,000	0,654	0,112					
12	Left amygdala	R	-0,093	-0,137	-0,083	-0,028	0,170	0,166	0,121	0,227	-0,009	0,052	0,52	1,000			
		p	0,307	0,131	0,363	0,763	0,058	0,064	0,178	0,011	0,918	0,573	<0.001				
13	Left hippocampus	R	-0,043	-0,024	0,072	0,027	0,125	0,116	0,038	0,193	0,005	-0,003	0,529	0,438	1,000		
		p	0,639	0,793	0,426	0,769	0,166	0,199	0,671	0,032	0,958	0,976	<0.001	<0.001			
14	Right amygdala	R	0,024	0,051	0,010	0,002	0,215	0,237	0,148	0,248	-0,001	0,144	0,544	0,671	0,298	1,000	
		p	0,788	0,576	0,914	0,981	0,016	0,008	0,099	0,005	0,995	0,115	<0.001	<0.001	0,001		
15	Right hippocampus	R	0,035	0,052	0,075	0,028	0,273	0,277	0,110	0,226	-0,026	-0,003	0,608	0,402	0,748	0,369	1,000
		p	0,697	0,571	0,410	0,760	0,002	0,002	0,222	0,012	0,779	0,970	<0.001	<0.001	<0.001	<0.001	

5.3.2 Maternal distress composite scores at different time points and newborn sex in relation to newborn amygdalar and hippocampal volumes

The first part of the analysis (main effect) showed no significant associations between SCL+EPDS composite scores and the relative volumes of the amygdala and hippocampus at any time point (Model A, Table 7).

The second part of the analysis, consisting of the sex-interaction term, revealed significant associations between the interaction term by SCL2+EPDS2 and relative left and right amygdalar volumes, which presented as more negative in males than females. This relationship remained after the addition of control variables (Model B, Table 7). However, in the sensitivity analyses for birth complications and gestational diabetes, the results for the relative volumes of amygdala did not persist. Both parts one and two of analyses with the sensitivity analyses were repeated with the other newborn age variable (gestational age + days after birth), and they yielded similar results for the amygdala. No significant relationships were observed between sex-by-SCL+EPDS composite scores and hippocampal volumes (Table 7). The analyses run for consistency with absolute amygdalar and hippocampal volumes generated corresponding results.

The main and interaction analyses were also performed after exclusion of the one preterm-born, birth complications, and maternal CNS affecting medication (n=25, n=15 males, n=10 females). In the main effect model, SCL2+EPDS2 associated with right amygdalar volume, but was no longer significant after adding control variables. In the sex-interaction model, both SCL1+EPDS1 and SCL2+EPDS2 associated more negatively with the male left amygdalar volume than female, remaining significant after controlling for other variables. The association with SCL3+EPDS3 was not significant nor were any significant associations found regarding the hippocampus.

As a post hoc test, including the whole sample, the main effect model analyses were done separately in both sex groups to test the significant sex interactions in amygdalar volumes. The results were consistent as SCL2+EPDS2 related negatively to left amygdalar volume in males persisting with all the control variables (Table 7). No significant findings were detected in females, however, a trend between SCL2+EPDS2 and larger right amygdala was observed (Table 7).

Table 7. Results from the general linear model analyses of the association between prenatal maternal distress and newborn brain volumetric measures. *Significant (p<0.05) uncorrected results. Study III results are adjusted for newborn sex, newborn age at scan counted from due date. Study IV results are adjusted for newborn total age, birthweight, maternal education, and BMI; results for all subjects are also adjusted for newborn sex. Edinburgh Postnatal Depression Scale (EPDS), Symptom Checklist 90, anxiety subscale (SCL-90), Gestational week (GW), Pregnancy-related Questionnaire Revised 2 (PRAQ-R2), Intracranial volume (ICV), Amygdala (AG), Central nervous system (CNS). a) results p< 0.05 after controlling for maternal education, maternal prenatal CNS affecting medication and substance use (left AG *p*=0.035, right AG *p*=0.048), but *p*>0.05 after controlling for birth complications and gestational diabetes (left AG *p*=0.057, right AG *p*=0.099); b) *p* < 0.05 controlling for second trimester EPDS+SCL composite score (*p*=0.036) as well as maternal prenatal CNS affecting medication (*p*=0.019) and substance use (*p*=0.008), but *p* > 0.05 controlling for birth complications (*p*=0.055), gestational diabetes (*p*=0.137) and hypertension/pre-eclampsia (*p*=0.148); c) *p*<0.05 after controlling for gestational diabetes (*p*=0.019).

				Brain structure											
Subjects	**Study**	**Statistical model**	**Distress variable**	**Left amygdala/ICV**			**Right amygdala/ICV**			**Left hippocampus/ICV**			**Right hippocampus/ICV**		
				Adj R^2	β	*p*	Adj R^2	β	*p*	Adj R^2	β	*p*	Adj R^2	β	*p*
ALL	III	Model A	EPDS+SCL GW14	-0.02	-1.30E-6	0.586	0.02	1.80E-6	0.461	-0.01	-5.10E-6	0.478	-0.01	2.10E-6	0.757
			EPDS+SCL GW24	0.01	-3.00E-7	0.223	0.02	1.20E-6	0.623	-0.01	6.20E-7	0.934	-0.01	3.90E-6	0.577
			EPDS+SCL GW34	-0.02	-2.10E-6	0.401	0.02	3.10E-7	0.905	2.00E-3	8.00E-6	0.291	-0.01	4.60E-6	0.506
	IV	Model A	PRAQ GW24	-0.04	-4.70E-8	1.000	0.01	2.20E-7	0.724	0.01	-4.00E-7	0.825	0.00	-1.90E-6	0.274
	III	Model B	sex*EPDS+SCL GW14	-0.02	5.50E-	0.252	0.02	6.20E-6	0.203	-0.01	-8.00E-6	0.548	-0.02	-9.10E-6	0.496
			sex*EPDS+SCL GW24	0.02	1.00E-5	0.042*[a]	0.05	1.10E-5	0.029*[a]	-0.02	-9.40E-6	0.536	-0.020	-2.10E-6	0.881
			sex*EPDS+SCL GW34	4.00E-3	7.70E.6	0.126	0.04	9.60E-6	0.061	2.00E-3	-1.60E.5	0.306	-0.02	-2.80E-6	0.840
MALES	III	Post hoc	EPDS+SCL GW14	-0.06	-4.73E-6	0.302	0.07	2.26E-8	0.996	-0.05	9.93E-6	0.466	-0.02	1.37E-5	0.208
			EPDS+SCL GW24	0.01	-1.08E-	0.026*	0.08	-1.71E-6	0.704	-0.01	2.22E-5	0.127	-0.03	1.27E-5	0.278
			EPDS+SCL GW34	-0.02	-7.13E-6	0.131	0.09	-1.85E-6	0.669	0.05	3.35E-5	0.016*	-0.02	1.11E-5	0.323
	IV	Model B	PRAQ GW24	-0.04	-1.0E-6	0.143	-0.04	-7.50E-7	0.381	0.01	2.50E-6	0.314	-0.08	-5.80E-7	0.789
FEMALES	III	Post hoc	EPDS+SCL GW14	-0.01	2.95E-6	0.366	-0.06	5.88E-6	0.117	0.051	-9.40E-6	0.359	0.06	-9.52E-7	0.928
			EPDS+SCL GW24	0.01	3.95E-6	0.262	-0.02	7.84E-6	0.052	0.04	-3.81E-6	0.732	0.07	5.90E-6	0.605
			EPDS+SCL GW34	0.01	2.54E-6	0.446	-0.04	5.60E-6	0.144	-0.05	-1.09E-8	0.999	-0.02	2.82E-6	0.803
	IV	Model B	PRAQ GW24	0.06	1.80E-6	0.039*[b]	-0.03	1.40E-6	0.153	0.07	-3.00E-6	0.266	0.09	-3.40E-6	0.220[c]

5.4 Pregnancy-specific anxiety at mid gestation and newborn amygdalar and hippocampal volumes

5.4.1 Correlations between variables

The relative volumes of right and left amygdala were strongly, positively intercorrelated, as well as relative right amygdala and hippocampus (Table 6). The relative left amygdalar and hippocampal volumes were mildly positively intercorrelated, but no significant correlation was observed between the right and left hippocampal volumes or the right amygdalar and left hippocampal volumes. Newborn age correlated positively with gestational age and birth weight. Maternal age was positively correlated with maternal pre-pregnancy BMI and negatively with SCL+EPDS composite score at GW24 (Table 6).

5.4.2 Sex differences in maternal pregnancy-specific anxiety and brain volumetric measures

The absolute amygdalar and hippocampal volumes were greater in males than females ($p<0.05$), but only the result for the right amygdala persisted after volume correction for ICV ($p=0.032$). The mothers of males had higher GW24 PRAQ-R2 scores than the mothers of females (Table 4). No difference between sexes was observed in GW24 SCL+EPDS composite scores (Table 4).

5.4.3 Pregnancy-specific anxiety as a predictor of newborn amygdalar and hippocampal volumes

In the first part of the analyses, the main effect model performed with the whole sample yielded no significant associations between GW24 PRAQ-R2 and newborn amygdalar or hippocampal volumes (Model A, Table 7).

In the second part, when the analyses were performed separately for males and females, no significant results were detected in males. However, in females, GW24 PRAQ-R2 associated positively with the left relative amygdalar volume, even after controlling for GW24 SCL+EPDS composite score (Model B, Table 7). The analyses with other newborn age variables (gestational age, postnatal age in days at scan) yielded similar results. The results persisted in the sensitivity analyses after the removal of exposure to maternal prenatal CNS affecting medication and substance use, but became insignificant after controlling for birth complications, gestational diabetes, and /or hypertension or pre-eclampsia. However, after the exclusion of gestational diabetes, a negative association between PRAQ-R2 and relative right hippocampal volume appeared in females (Table 7).

6 Discussion

6.1 Newborn brain volumetric measures, asymmetry, and newborn age and sex

The first aim of this thesis was to explore the structural characteristics of the newborn brain and how they relate to newborn age and sex, as well as to body size (Study I, Table 8). Our results are consistent with previous findings of the foetal leftward hemispheric asymmetry equalizing by term age (Andescavage et al., 2016), as no asymmetry was detected in TGM volume. There was significant rightward lobar asymmetry in the temporal lobe, which is also in line with previous findings (Dean et al., 2018a; Mark et al., 1999; Matsuzawa, 2001; Rajagopalan et al., 2011; Tanaka et al., 2012; Utsunomiya et al., 1999). We also observed leftward asymmetry in the parietal and occipital lobes. Leftward occipital asymmetry has been reported before in foetal and newborn brains (Gilmore et al., 2007; Rajagopalan et al., 2011), but no reported studies of parietal asymmetry exists in young populations. However, in adults, the left side of the parietal lobe has been described to be larger than the right (Pujol et al., 2002). Together, the lobar asymmetry in the newborn brain seems to correspond to that of an adult.

Just as gyrification proceeds in an orderly manner during pregnancy by gradually separating the lobes from each other, the brain lobes continue developing postnatally, following hemisphere and region-specific growth trajectories that are dependent on sex and age (Giedd et al., 1999; Lenroot et al., 2007b; Matsuzawa, 2001; Tanaka et al., 2012). For this same reason, we observed no association of hemispheric lobar asymmetry within the narrow age range of our study, or by sex, as these differences occur only later on in childhood, as the maturation of hierarchically high-order functional regions lasts longer than that of regions with low-order functionality (Matsuzawa, 2001; Tanaka et al., 2012).

While some studies have detected larger absolute brain volumetric measures in male newborns and children compared to females (Dean et al., 2018a; Gilmore et al., 2007; Knickmeyer et al., 2016; Ruigrok et al., 2014; van Soelen et al., 2010), in this sample, no sex differences in the total brain volumes were found (ICV, TBV, TWM, TCV), but absolute volumes of the right TGM, frontal, parietal, and temporal lobes were greater in males than females. However, after correcting for brain size, these associations changed showing greater volumes of TGM, parietal and temporal lobes

in females. Similarly, greater gray matter to white matter ratio in females has been previously detected in children and young adults (Koolschijn and Crone, 2013). In fact, a meta-analysis of brain studies concluded that sexual dimorphism stems from regional volume and density differences, although newborns and young children were under represented in the population (Ruigrok et al., 2014). However, the results of the sex difference might be modified by correction to brain size as was observed in our study and in others, where the sex difference disappeared after correction for ICV (Dean et al., 2018b; Gilmore et al., 2007). Overall, later in development, males tend to have larger brains than females (Ruigrok et al., 2014), however, this may not present as apparent in the gross volumes of the newborn brain, which is lacking the strong molding effect of sex hormones. Although modest, our results suggest that slight sex differences might exist regionally also in the newborn brain.

After the exponential growth of GM and WM during pregnancy, the postnatal growth trajectories of GM and WM diverge. While GM continues to grow fast until late childhood, early teenage years, WM growth speed subdues after the first two years of life and continues over several years, until reaching its peak of remodeling in adulthood (approximately at 30 years of age) (Lebel and Deoni, 2018; Mills et al., 2016). In our study, newborn age predicted larger relative volumes of TGM and TCV, as well as smaller volume of TWM in both males and females. These findings support previous evidence of early life brain growth being driven mostly by GM (Knickmeyer et al., 2008), the negative association with WM reflecting the slower growth speed of WM. Overall, our results are in line with previous literature linking longer gestation with larger brain volumes (Bora et al., 2014; Holland et al., 2014; Munakata et al., 2013; Peterson, 2000; van Soelen et al., 2010).

Newborns with a greater head circumference had also larger absolute volumes of ICV, TBV, TWM, and TCV. Additionally, larger head size related positively to absolute and relative frontal lobe volumes, and negatively to relative occipital lobe volumes. Similarly, Munakata et al. (2013) found volumes of GM and the cerebrum to positively associate with head circumference, but not with WM volume, possibly due to a different population consisting of also late-preterm subjects. While no correlation between birth weight or length and brain volumetric measures was observed, after controlling for sex, birth length associated positively with TWM, although no sex differences were detected in newborn growth metrics. No previous reports of birth length associating with brain volumes exists in full-term individuals, but findings on birth weight are contradictory as some have found it to predict larger brain volumes (Knickmeyer et al., 2016), while others observed no connection with brain volumes (van Soelen et al., 2010). In conclusion, the influences of newborn growth metrics on brain volumetric measures are still partly unclear, but still important to assess, particularly regarding the analyses to be performed in populations with growth affecting prenatal conditions.

6.2 MRI in the newborn and incidental findings

As MRI is gaining popularity in newborn imaging, and the technologies advance and the image quality and resolution become more accurate, more incidental findings are likely to be detected in future studies. Related to this, our second aim was to assess the prevalence and characteristics of the incidental brain MRI findings in our healthy study population. The prevalence of incidental findings in our sample was 7.4 % and that of hemorrhages 6.9 % (Study II), which correspond to the lower end of the prevalence reported in other studies (A. Lind et al., 2010; Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004; Whitehead et al., 2013) (Table 8). The variance in the frequency may be explained by differences in study populations (delivery treatment), imaging time point, and the strength of the MR field. Imaging right after birth and the use of a more powerful MR field most likely increase the chance of detecting birth related hemorrhages (Looney et al., 2007; Rooks et al., 2008; Whitby et al., 2004). Although SDH was the most prevalent finding, the 3T field used in our study may have contributed to the higher number of detected IPHs. In addition to imaging related variables, variation in delivery treatment protocols and peripartum care may have created differences in the occurrence of hemorrhages.

The ratio of different delivery methods was similarly distributed in the study population as in the Finnish national delivery statistics (Vuori and Gissler, n.d.), the sample thus providing a good representation of the Finnish population. From the pool of the many obstetric and newborn variables, only vaginal and vacuum-assisted deliveries had a significant risk increasing effect on the prevalence of incidental hemorrhages, when compared to c-section, which supports the current literature (Looney et al., 2007; Rooks et al., 2008; Sirgiovanni et al., 2014; Tavani et al., 2003; Whitby et al., 2004). Although, no risk of intracranial hemorrhage was associated with c-section, its precedence over other delivery methods based on this is not advised, as the incidental findings are likely clinically irrelevant, and as other benefits of vaginal delivery are undisputed.

The newborns with incidental findings did not present any clinical symptoms or deficits at any point in the postnatal period, and their general health and neurological status were normal at their follow-up appointments. Based on these observations, incidental findings seem to have no relevant clinical significance, nor do they need to be considered in current delivery treatment guidelines. However, with the increasing amount of MRI performed in pediatric research, the protocol for informing about the incidental findings should be solid with sufficient guidance and support provided to the families to prevent possible parental distress that might impair the parent-child relationship (Waisbren, 2003).

6.3 The sex-dependent associations between newborn amygdalar and hippocampal volumes, and maternal prenatal psychological distress

The third aim of this thesis was to investigate the relationships between maternal PPD and newborn amygdalar and hippocampal volumes, and whether they are moderated by newborn sex (Table 8). No main effects of PPD on amygdalar and hippocampal volumes were detected with either PPD exposure, i.e. the composite measurement of depressive and anxiety symptoms, or the more specific measure of pregnancy-specific anxiety. The most striking result was that sex moderated the effect of PPD on newborn amygdalar volumes. More specifically, exposure to higher PPD in mid pregnancy, either depressive or general anxiety symptoms, or pregnancy-specific anxiety (PSA), associated with volume variations of the left amygdala, presenting smaller volumes in males (Study III) and larger volumes in females (Study IV). These results further support existing evidence suggesting that males and females are differentially susceptible to PPD. Thus far, the observed effect of PPD on newborn amygdalar volume has been growth inducing, especially on the right side, but without any sex-dependency (Qiu et al., 2017). Then again, in older children, larger right amygdalar volumes in females after exposure to PPD have been observed (Acosta et al., 2019; Wen et al., 2017). Thus, this is the first study to report a sexually dimorphic influence of PPD on the left amygdalar volume in newborns. Of note, after controlling for birth complications and gestational diabetes, the results concerning the left amygdala fell short of statistical significance (Study III and IV), as well as after controlling for gestational hypertension (Study IV), possibly due to the large number of covariates or the currently unknown effects of birth complications and gestational illnesses on brain development. In addition, although no main effects of PPD on hippocampal volumes were observed, the exclusion of individuals exposed to gestational diabetes revealed that higher PSA associated with smaller right hippocampal volumes in females (Study IV). In previous studies, no sex-specific effect has been observed in hippocampal volumes after exposure to maternal general anxiety, however, the literature describes either reduced volume of the left hippocampus already in foetuses at GW24 to GW40 (Wu et al., 2020), or that of the right hippocampus in newborns (Wang et al., 2018), but slower growth of the right hippocampus at six months of age (Qiu et al., 2013). The smaller volume of the right hippocampus was observed only in individuals with both the genetic susceptibility (genetic variants with increased risk for MDD) and exposure to PPD (Wang et al., 2018). Thus, the evidence suggests that PPD has some potentially sexually dimorphic volume reducing effects on the hippocampus.

Animal experiments have plunged further into the offspring amygdalar and hippocampal cytoarchitecture and revealed prenatal stress exposure to decrease cell proliferation in both structures (Kawamura et al., 2006) and to stimulate microglial changes, impair synaptic maturation, axonal growth and myelination, as well as to alter dendritic structure in the hippocampus (Delpech et al., 2016; Mychasiuk et al.,

2011; Wei et al., 2015). The decrease in cell proliferation was observed at the embryonic stage (Kawamura et al., 2006) and could partially explain the temporary early life deceleration in growth of several amygdalar nuclei observed in another study (Kraszpulski et al., 2006) that later turned to enlargement of the lateral amygdala through increased cell numbers. Thus, as brain development is a dynamic process, the influence of prenatal stress might be reflected differently on the brain volumes depending on the stage of development. Similar neurocellular events might underlie the observed volumetric changes found in humans. Furthermore, as previous research has shown, these alterations in cell morphology and volume may change over time due to development, and are further influenced by postnatal experiences, the final outcomes of which might be seen only later in life. For instance, childhood maltreatment has been associated with bilateral hippocampal volume reduction in adults but not in children (Woon and Hedges, 2008), implying these changes may develop after the active growth period is over.

A number of studies have linked elevated maternal distress in mid pregnancy with offspring brain morphology (Acosta et al., 2019; Buss et al., 2010; Lebel et al., 2016; Qiu et al., 2017, 2013; Rifkin-Graboi et al., 2013; Sandman et al., 2015; Wen et al., 2017). Consistent with this, we observed the strongest associations between PPD and newborn amygdalar volumes with mid pregnancy PPD, however, in further sensitivity analyses, significant relationships were observed also in early pregnancy with maternal depressive and general anxiety symptoms. One possible explanation is that, there are different symptoms trajectories during pregnancy (Korja et al., 2018), and changing the sample by excluding some subjects may accentuate some symptom trajectories over others. Furthermore, considering the great intra- and inter-individual variation of PPD in symptom type and intensity during pregnancy, the effects of PPD on neurodevelopment are most likely equally variant as the different trajectories of PPD.

To the best of our knowledge, we are the first to report on the effects of PSA on newborn amygdalar and hippocampal volumes. Whereas the effect of maternal prenatal depressive symptoms and general anxiety was more negative on the male left amygdalar volume compared to females (Study III), the association of PSA and newborn amygdalar volumes was positive on the left amygdalar volume and apparent only in females (Study IV). Because PSA and other symptoms of PPD differ in symptom dimensions and gestational trajectory, as well as in the prediction of child outcomes (Blackmore et al., 2016; Huizink et al., 2003, 2002), it has been suggested that PSA be considered a separate symptom entity (Huizink et al., 2004). Considering this, as well as our results, these different distress symptom dimensions might indeed have differential effects on the newborn brain, depending on offspring sex. Moreover, the fact that the negative association with female right hippocampus was observed only after exposure to PSA, albeit only after removing gestational diabetes, further suggests that the effect of PSA differs from other distress exposures.

Table 8. Summary of the sub studies. Region of interest (ROI), Total gray matter volume (TGM), Incidental findings (IF), Maternal prenatal psychological distress (PPD), Edinburgh Postnatal Depression Scale (EPDS), Symptom Checklist 90, anxiety subscale (SCL-90), gestational week (GW), Pregnancy-related Anxiety Questionnaire Revised 2 (PRAQ-R2), Pregnancy-specific anxiety (PSA).

	Study I	**Study II**	**Study III**	**Study IV**
Hypothesis	Newborn age and sex affect brain volumetric measures & asymmetry	Prevalence and risk factors of incidental findings	The relation of maternal prenatal psychological distress and newborn brain volumetric measures is sex-dependent	Pregnancy-specific anxiety associates with newborn brain volumetric measures
Brain ROI	Total gray and white matter, lobar volumes	Intracranial incidental findings	Amygdala, hippocampus	Amygdala, hippocampus
Main covariate(s)	Newborn sex, age & growth metrics	Mode of delivery	EPDS + SCL-90 sum score at GW 14, 24 and 34; newborn sex	PRAQ-R2 score at GW24; newborn sex
Results	Greater age predicted larger brain volumes. No sex differences in total brain volumes, but modest differences in lobar volumes, females having greater relative TGM in parietal and temporal lobes. Lobar asymmetry similar in both sexes: rightward in temporal and leftward in parietal & occipital lobes. Larger head size predicted larger total brain volumes.	Prevalence of IF 7.4% (n=13/175). Vaginal delivery a risk factor for IF. Vaccuum-assisted delivery a risk factor for subdural hemorrhages.	Sex moderated the association of PPD at GW24 and amygdalar volumes presenting as more negative in males compared to females. No associations between PPD and hippocampal volumes.	In the subgroup of females, PSA related positively to left amygdalar volume. In sensitivity analyses, PSA associated negatively with female right hippocampal volume.

6.4 Possible mechanisms for the mediating effect of newborn sex

Why sex seems to predispose the offspring brain differently to PPD still remains unresolved. Besides the fact that brain development itself has sex-dependent features, the mediating effect of sex is most probably the result of a multitude of variables. As described before, studies have linked PPD with changes in maternal and offspring HPA activity, which may contribute to alterations in neurodevelopment after exposure to PPD. Sexual dimorphism in HPA related gene expression has been observed in rats, specifically in the expression of CRH, its receptor (CRHR2) and binding protein (CRH-BP). The elevated anxiety exhibited by PS rats, when exposed to stress, is marked by an up-regulation of CRH mRNA and down-regulation of CRHR2 mRNA in the female amygdala, and a down-regulation of both CRH-BP and CRHR2 mRNA in the male amygdala (Iwasaki-Sekino et al., 2009; Zohar and Weinstock, 2011). These members of the CRH family have not been studied in human newborns exposed to PPD, but in adults with major depression, schizophrenia, and bipolar disorder, reduced expression of CRH-BP has been detected (Herringa et al., 2006).

In addition, the sex differences in the regional expression of corticosteroid receptors, have been observed both in the hippocampus, as well as in the placenta, along with differences in the expression of 11-β-HSD-2. The female foetus' placenta is more adaptive, reducing the exposure of the foetus to maternal cortisol by upregulating 11-β-HSD-2 and downregulating GR (Clifton, 2010). However, if this protective barrier is diminished or neutralized, such as when exposed to PPD (O'Donnell et al., 2012), more cortisol gets transmitted to the foetus. Simulating this, female guinea pigs exposed to dexamethasone prenatally presented higher GR mRNA levels in the hippocampus, and higher basal and stimulated plasma cortisol levels, while males had elevated MR mRNA, decreased plasma cortisol levels, and increased plasma testosterone (Liu et al., 2001). As female guinea pigs already normally exhibit higher corticosteroid receptor expression in the hippocampus during pregnancy (Owen and Matthews, 2003), further stimulation with maternal cortisol might alter the developmental course of the structure.

Furthermore, glucocorticoids reduce female glycogen levels in the placenta, but not male levels resulting in differential energy availability (O'Connell et al., 2013). These effects may also be significantly interacted by sex hormones (Liu et al., 2001; Lombardo et al., 2012) and placental sex chromosomes (Bale, 2016). Through a complex system the X-linked gene *O*-linked-N-acetylglucosamine transferase (OGT) stabilizes chromatin (Bale, 2016). The amount of OGT is lower in male than female placentas because it escapes X inactivation resulting in levels two-fold higher in female placentas (Bale, 2016). In addition, prenatal stress decreases OGT levels

depressing the level even further in male placentas (Bale, 2016). By a proposed hypothesis, due to a more instable state of male chromatin caused by the low levels of OGT, males are more susceptible to prenatal stress (Bale, 2016). The reduction of OGT in PS rats has also been connected with lower placental levels of testosterone (through downregulation of a gene) and a dysmasculinised phenotype resembling more that of control females than males (Bale, 2016; Morgan and Bale, 2011). In addition to sexual dimorphism in the placenta, the function of rat neonatal hippocampal microglia has been observed to be sexually dimorphic, with females having more activity in phagocytic function, as well as gene expression, than males, even though the same number of cells were born and died in both sexes (Nelson et al., 2017). In summary, the evidence suggests the modifying effect of sex is mediated through several pathways, starting from sex-specific developmental trajectories, through differential functioning of the placenta that might partially contribute to an altered activity of the HPA axis in the offspring, which, in turn, may interact with the amygdala and hippocampus possibly changing their morphology.

6.5 Clinical significance of the findings

In previous research, exposure to PPD has been linked to alterations in brain morphology, more developmental problems, and a higher risk for psychiatric disorders in the offspring (Van den Bergh and Marcoen, 2004). The investigation of these links has led researchers to observe sex-dependent alterations in the amygdala and the hippocampus related to PPD. These sexually dimorphic amygdalar and hippocampal alterations are likely significant as these structures are intertwined with the pathophysiology of many psychiatric disorders, some of which have a relevant sex bias in their prevalence (Bale and Epperson, 2015; Davis and Pfaff, 2014). For instance, women suffer at least twice as often from anxiety disorders (generalized anxiety, panic disorder, obsessive-compulsive disorder, and social phobia) than do men (Brown, 2001), whereas the prevalence of autism and ADHD is higher in males (Bale and Epperson, 2015; Davis and Pfaff, 2014). The reasons underpinning the volumetric changes in the limbic system associated with PPD remain largely unsolved. Understanding these mechanisms behind the observed sex differences and sex-specific susceptibility would enable the creation of preventative protocols, which promote beneficial brain development when applied at the right time. Shown by a previous experiment, the prevention of PPD decreased depressive symptoms in postpartum women (Kozinszky et al., 2012), thus reducing the exposure to maternal distress and ameliorating the early environment of the newborn. Reducing distress exposure is critical as maternal postnatal distress has also been associated with changes in amygdalar and cortical morphology (Lebel et al., 2016; Wen et al., 2017). However, thus far no studies investigating these preventative methods on child brain

development exist. In animal studies, it has been observed that the effects associated with prenatal stress exposure have been revoked by postnatal stimulation (Lemaire et al., 2006). Although there are no corresponding studies in humans, this could also be considered as a possible treatment approach in human offspring that are known to have been exposed to maternal PPD.

Existing evidence links PPD to alterations on either the right or the left side of the limbic structures. However, researchers struggle to explain the causal mechanisms behind the variation of hemispheric side in observations. Importantly, these alterations in structure may have functional implications. Based on previous research, the functions of the right and left amygdala differ from each other in fear learning and/or threat processing. In fMRI studies investigating reactions to fearful faces, the right amygdala has exhibited greater activation than the left (Noesselt et al., 2005). Researchers have theorized that the right side responds automatically and faster to all new visual stimuli generating overall arousal, while the left side has a more selective response and may be more reactive to emotional stimuli of different degrees (Gläscher and Adolphs, 2003; Hardee et al., 2008). Further, greater left amygdalar activation has been described when study subjects have encountered fears that are envisioned and apprehended but never experienced (Phelps et al., 2001). Interestingly, eight-month-old children with a larger left amygdala volume were more likely to disengage from fearful faces to a suddenly appearing lateral distractor, but the distraction was not observed with happy or neutral faces (Tuulari et al., in press). The results suggest that early life socioemotional traits relate to the volumetric variation of the left amygdala. To summarize, our observation of the sex-dependent left amygdalar volume variation coupled with the knowledge on the close connection of the left amygdala and (early) socioemotional and fear learning traits, suggest there may be a link between PPD exposure and sex-specific susceptibility to psychopathology through alterations in amygdalar morphology.

6.6 Strengths and limitations

There are several shared strengths in the sub studies. Importantly, the individuals were imaged soon after birth to prevent the confounding effects of postnatal factors, which has been a noted limitation in a few previous studies. The age variance was nevertheless broad enough to justify the age-volume correlation analyses for Study I. In addition, all the newborns in Study I and most of newborns in Studies II through IV were term-born, minimizing the complex and possibly confounding effects of prematurity and other pregnancy complications. Moreover, the same scanner and scanning protocol were used for all individuals. The sample size was relatively large in all sub studies, although it was too modest for epidemiological evaluations in

Study II and did not enable reliable trajectory models of maternal distress symptoms over the pregnancy (Korja et al., 2017) in Study III.

Some common limitations are of note to mention. For instance, brain volumetric measures are a gross, yet robust, parameter to evaluate brain growth and brain development, as volumetric differences do not directly reveal the functional development of the nervous system. Further, it was not possible to explore the cytoarchitecturally different regions of amygdala and hippocampus (see paragraphs 2.1.2.1., 2.1.2.2.), which might have region-specific responses in volume after PPD, as it has been observed in the rat amygdala (Kraszpulski et al., 2006; Salm et al., 2004). In addition, the data included only Finnish, mostly full-term, newborns and the results may thus not be generalizable to other newborn groups or nationalities. Furthermore, the attrition of subjects was not random but based on unreturned distress questionnaire data (Karlsson et al., 2018), and assumingly, the families, with a mother experiencing more distress symptoms, had a lower attendance rate at the MR visits than families with less symptoms. Consequently, this might have diluted some effects that otherwise might have been observable. The small number of mothers with clinically significant symptoms of depression or anxiety, might have also had a similar influence. As these studies are cross-sectional, the possible functional or behavioural correlates remain to be studied in the future. Finally, the narrow age range also inhibited further investigation of growth trajectories and potential sex differences in the growth patterns, as some structures might have had accelerated "catch up" growth in earlier born children. In the following paragraphs, some additional sub study specific strengths and limitations are described.

Study II provided an accurate estimate of the prevalence of incidental findings in a representative Finnish term-born population as symptom-based selection bias did not occur. Our scanning protocol included T1 weighted images, which show hypoxia (direct indicator of brain damage) unlike Susceptibility weighted imaging (SWI), which is better suited for intraparenchymal microhemorrhages (Dogan et al., 2018). The study did not cover the time right after birth, the relatively late imaging time point was a limitation, as the delivery associated hemorrhages may have already diminished after three weeks postpartum due to resorption (Rooks et al., 2008; Whitby et al., 2004). However, an even greater prevalence (26 %) has been reported before in a sample with a similar scan age to ours (Looney et al., 2007). The imaging, as well as the neurological evaluation were performed only once, thus the resorption of the hemorrhages or the absence of future developmental problems could not be confirmed.

In Studies III and IV, including both amygdalar and hippocampal volumes, was essential as these structures are closely related and very few newborn studies have yet reported findings on these volumes, especially in relation to PSA, which has not been studied before as an exposure in newborn brain morphology. Moreover, using

a composite score of depressive and anxiety symptoms in Study III, may better simulate the overall distress in pregnant populations as these symptoms are often comorbid (Andersson et al., 2006; Kendler et al., 2007; Mathew et al., 2011; Middeldorp CM, Cath DC, Van Dyck R, 2005). However, Studies III and IV were also subjects to certain limitations. Maternal distress data was based on self-reporting questionnaires and although these are widely validated and accepted measures, no objective indicators of distress were included. In addition, although maternal distress was measured in three time points in Study III, PSA was measured only once in Study IV, and as a consequence, additional information on the relevance of the timing of the exposure cannot be provided; however, the results of Study III support the importance of mid gestation as a sensitive time for the developing brain to be exposed to PPD. As in the previous sub studies, the newborns were scanned only once, and consequently, no causal relations between PPD and postnatal brain growth can be generated. Furthermore, genetic influence, which might present as differential susceptibility to volumetric changes, could not be taken into account in these designs, nor other biological markers, for instance related to glucocorticoid activity or immunological mechanisms. Finally, as the nature of these studies was exploratory, no corrections for multiple comparisons were made.

7 Conclusions

7.1 Main findings

First, the lobar asymmetry of the newborn brain was similar in both sexes and resembled that of adults being rightward in the temporal lobe and leftward in the parietal and occipital lobes. While age did not associate with asymmetry, it expectedly reflected the different growth trajectories of gray and white matter by predicting larger gray matter volume and smaller white matter volume. Gross sex differences were not detected in brain volumetric measures, but the data suggested that subtle sexual dimorphism is seen regionally.

Second, the prevalence of incidental findings was 7.4 % and that of hemorrhages 6.9 %. Only subdural and intraparenchymal hemorrhages, as well as cysts, were observed. Of these, subdural hemorrhages were the most common finding. Vaginal and vacuum-assisted deliveries proved to be risk factors for intracranial hemorrhages, while no association with c-section was found. Despite the incidental findings, the neurological and overall development of the subjects was normal in the follow-up examination supporting evidence of benign incidental findings having little clinical significance.

Third, maternal prenatal psychological distress in mid pregnancy associated with the newborn left amygdalar volume in a sex-dependent way. Maternal prenatal depressive and general anxiety symptoms related to smaller left amygdalar volume in males compared to females. Greater pregnancy-specific anxiety (PSA) associated with larger left amygdalar volume in females. Additionally, the sensitivity analysis suggested a negative association between PSA and the female right hippocampal volume.

In conclusion, our results on newborn brain characteristics are in line with previous studies and expand our understanding of newborn brain asymmetry and sex differences. Incidental findings in newborn MR imaging are relatively common, however, mostly harmless. Our data from two studies suggests that greater maternal prenatal psychological distress induces sex-specific volumetric changes in the offspring left amygdala, possibly predisposing the offspring to psychopathology.

7.2 Implications for future research

The results of Study I expand our understanding on normal variation in the newborn brain structures, which, in turn, facilitates the planning of future exposure or case-control studies in newborns. Study II provided insight on how common, and on the other hand, benign, incidental findings are. This information helps to plan protocols for MR research settings, which will have to deal with incidental findings, however, the variation in their occurrence remains still partly elusive. For pediatric brain studies in general, combining both structural, including diffusion tensor imaging, and functional MR imaging with multiple scanning time points would gain a more accurate assessment of brain development. The amount of the data is many times reduced by technical difficulties, thus standardized scanning protocols adjusted to the top should be implemented. Considering normal variation in brain structures, epidemiology of incidental findings and the possible relevance of their location and size on child outcomes, larger sample sizes are crucial as are thorough background information characterizations. Moreover, the addition of newborns with peripartum complications or excessive crying due to pain could shed new light on the prevalence of incidental findings. Defining the appearance of incidental hemorrhages by the variation of blood coagulation and the timeline, by which incidental hemorrhages are absorbed postnatally, could help optimize the timing of control scans.

To the best of our knowledge, Study III, is the first reported study that used a composite score of maternal distress as an exposure to the foetal brain. It remains to be seen if this method is profitable in the future, in terms of having a more comprehensive measurement tool for PPD. For determining this, it would be useful to study different symptom subgroups with varying levels of depressive and anxiety symptoms, for instance mothers reporting only high EPDS or high SCL-90 anxiety, or both. This way, the relevance of the timing to exposure, such as mid gestation, could also be investigated in more detail. In the future, however, it might be sensible to explore the prenatal maternal distress symptom trajectory models, which track the symptoms over the whole pregnancy, to explore what type of distress is the most meaningful (consistently low, consistently high, moderate, moderate and decreasing, and moderate and increasing levels) for offspring brain development. Additionally, the combination of different measurements, both subjective and objective, would be beneficial to gain a wholesome understanding of the influence of PPD on the offspring brain. For instance, given the links between PPD and offspring HPA axis function, markers of the HPA activity would provide more correlates to brain measures. Furthermore, as emphasized in other studies (Ong et al., 2019; Qiu et al., 2017; Wang et al., 2018), genetic and epigenetic variation in the offspring, as well as gene-environment interaction have modifying effects on the relationship between PPD and offspring brain structures, and the risk for psychopathology and thus, these factors should be considered in future research. Additionally, if studying other than

newborns, postnatal maternal distress and other early-life exposures should always be considered. Finally, longitudinal human studies that investigate the effects of PPD prevention or treatment on offspring brain structure, as well as the incidence of developmental problems and psychiatric disorders in the offspring, are needed.

Acknowledgements

This work was carried out as a part of the FinnBrain Birth Cohort Study in the Turku Brain and Mind Center, at the University of Turku during 2015-2020.

I am sincerely thankful to my supervisors Adjunct Professor Noora Scheinin and Professor Hasse Karlsson for their expertise and guidance during this process. I truly admire your academic experience, perception, and achievements. I especially thank you for always making time to answer my many questions, even during your vacation time, which helped keep the thesis moving along. More than that, thank you for sharing your wealth of knowledge. You certainly have made me learn an immeasurable amount. I also appreciate the encouragement, positivity, and support you gave me throughout these years.

I am very grateful to have Professor Soili Lehto as my opponent and want to thank her for accepting the invitation. My high appreciation also goes to my reviewers, Adjunct Professor Marjo Metsäranta and Adjunct Professor Juha Salmitaival. Thank you for taking the time for reviewing my thesis and getting me through the review process. Your insights truly improved the thesis as a whole. I am likewise thankful to Claudia Buss and the other members of my follow-up committee for their participation and insights.

I wish to thank my unofficial supervisor Jetro, who has supported and guided me greatly during this process. Your expertise and guidance have carried me far in the small world of brain segmentation, and further still in the bigger world of research. I would like to also thank my co-author, Venla Kumpulainen, who did excellent work with the second published article. My collaborators in Canada, John D. Lewis, Vladimir S. Fonov, D. Louis Collins, and Alan Evans, thank you for using your segmentation wizardry to make this project work. Further on the subject of wizardry, an especially warm thank you to the FinnBrain statistician, Juho Pelto, on whose statistical prowess I relied ever so consistently. Thank you for your patience and thank you for helping me get these projects done. I am also very thankful for the help Niloofar Hashempour provided on the brain segmentation images. Finally, and though I lack the space to thank you in a truly personal way, I want to warmly express gratitude to all my co-authors: Linnea Karlsson, Riitta Parkkola, Tuire Lähdesmäki, Jani Saunavaara, Harri Merisaari, and Henriette Acosta. Your many comments,

discussions, and insights ensured that these papers got published. It was not always easy, but they are out there now.

A special thanks goes to radiographer Kristiina Kuvaja and the rest of the skillful staff of the Department of Radiology at Turku University Hospital, whose professional touch enabled the imaging of the newborns by their experience in MR imaging and excellent communication with the families. I want to express my gratitude to all the FinnBrain families, without whom this work would not have been possible.

A heartily thank you also to all my research colleagues at FinnBrain Birth Cohort Study. You have proved that science can be something much more than just staring at stats sheets alone and redoing analyses over and over again. The lunches shared, as well as the trips, cruises, and parties spent together are a definitive proof of your unparalleled team spirit and I am happy to have been part of it. I would also like to thank the rest of the FinnBrain team, including the data manager, Teemu Kemppainen, as well as the research coordinators, Katja Tervahartiala, and Eija Jossandt for their hard work for FinnBrain.

Thank you, all my friends, and colleagues, for your sympathy and support during the testing times. You reminded me of the life outside of research and gave me energy to continue my battle by distracting me with phone calls, talks over lunch, walks, lazy weekend brunches, exercise, and dinners. Thank you, Sini and Keso, for always welcoming me into your home during my research related visits in Turku. I truly enjoyed your company. I am also thankful to Headspace for making my brain better prepared for intellectual tasks and for unwinding it after a long day of work.

My dear family. Thank you for being there for me and cheering me on when I hit a rough patch. As most of you have been through the same, I appreciated how you were able to relate to my situation and to be compassionate. You have all along been my inspiration. I am also truly grateful to Tricia Shulist, whose expertise in academic writing improved my dissertation greatly, and got my comma usage to a whole other level. Finally, my partner in crime, my beloved Patrick. I am extremely grateful to have you by my side. Your relentless support, understanding, and self-esteem boosting words of courage coupled with my stubbornness have gotten me where I am today.

This work was financially supported by Maire Taponen Foundation, Finnish State Grants for Clinical Research, Juho Vainio Foundation, Turku University Foundation, and Finnish Medical Foundation.

04.09.2020
Satu J. Lehtola

References

Aanes, S., Bjuland, K.J., Skranes, J., Løhaugen, G.C.C., 2015. Memory function and hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults. Neuroimage 105, 76–83. https://doi.org/10.1016/j.neuroimage.2014.10.023

Åberg, K., Norman, M., Pettersson, K., Ekéus, C., 2016. Vacuum extraction in fetal macrosomia and risk of neonatal complications: a population-based cohort study. Acta Obstet. Gynecol. Scand. 95, 1089–1096. https://doi.org/10.1111/aogs.12952

Acosta, H., Kantojärvi, K., Hashempour, N., Pelto, J., Scheinin, N., Lehtola, S., Lewis, J., Fonov, V., Collins, D., Evans, A., Parkkola, R., Lähdesmäki, T., Saunavaara, J., Karlsson, L., Merisaari, H., Paunio, T., Karlsson, H., Tuulari, J., 2020. Partial Support for an Interaction Between a Polygenic Risk Score for Major Depressive Disorder and Prenatal Maternal Depressive Symptoms on Infant Right Amygdalar Volumes. Cereb. Cortex bhaa158. https://doi.org/10.1093/cercor/bhaa158

Acosta, H., Tuulari, J.J., Scheinin, N.M., Hashempour, N., Rajasilta, O., Lavonius, T.I., Pelto, J., Saunavaara, V., Parkkola, R., Lähdesmäki, T., Karlsson, L., Karlsson, H., 2019. Maternal Pregnancy-Related Anxiety Is Associated With Sexually Dimorphic Alterations in Amygdala Volume in 4-Year-Old Children. Front. Behav. Neurosci. 13, 175. https://doi.org/10.3389/fnbeh.2019.00175

Aden, P., Paulsen, R.E., Mæhlen, J., Løberg, E.M., Goverud, I.L., Liestøl, K., Lømo, J., 2011. Glucocorticoids dexamethasone and hydrocortisone inhibit proliferation and accelerate maturation of chicken cerebellar granule neurons. Brain Res. 1418, 32–41. https://doi.org/10.1016/j.brainres.2011.08.053

Adib-Rad, H., Basirat, Z., Faramarzi, M., Mostafazadeh, A., Bijani, A., 2019. Psychological distress in women with recurrent spontaneous abortion: A case-control study. Turk Jinekoloji ve Obstet. Dern. Derg. 16, 151–157. https://doi.org/10.4274/tjod.galenos.2019.88899

Alvarado-Esquivel, 2014. Validation of the Edinburgh Postpartum Depression Scale in a Population of Adult Pregnant Women in Mexico. J. Clin. Med. Res. 6, 374–378. https://doi.org/10.14740/jocmr1883w

Anacker, C., Cattaneo, A., Luoni, A., Musaelyan, K., Zunszain, P.A., Milanesi, E., Rybka, J., Berry, A., Cirulli, F., Thuret, S., Price, J., Riva, M.A., Gennarelli, M., Pariante, C.M., 2013. Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. Neuropsychopharmacology 38, 872–883. https://doi.org/10.1038/npp.2012.253

Andersson, L., Sundström-Poromaa, I., Bixo, M., Wulff, M., Bondestam, K., Åström, M., 2003. Point prevalence of psychiatric disorders during the second trimester of pregnancy: A population-based study. Am. J. Obstet. Gynecol. 189, 148–154. https://doi.org/10.1067/mob.2003.336

Andersson, L., Sundström-Poromaa, I., Wulff, M., Åström, M., Bixo, M., 2006. Depression and anxiety during pregnancy and six months postpartum: a follow-up study. Acta Obstet. Gynecol. Scand. 85, 937–944. https://doi.org/10.1080/00016340600697652

Andescavage, N.N., du Plessis, A., McCarter, R., Serag, A., Evangelou, I., Vezina, G., Robertson, R., Limperopoulos, C., 2016. Complex Trajectories of Brain Development in the Healthy Human Fetus. Cereb. Cortex 27, 5274–5283. https://doi.org/10.1093/cercor/bhw306

Antonov, N.K., Ruzal-Shapiro, C.B., Morel, K.D., Millar, W.S., Kashyap, S., Lauren, C.T., Garzon, M.C., 2017. Feed and Wrap MRI Technique in Infants. Clin. Pediatr. (Phila). https://doi.org/10.1177/0009922816677806

Arch, J.J., 2013. Pregnancy-specific anxiety: Which women are highest and what are the alcohol-related risks? Compr. Psychiatry 54, 217–228. https://doi.org/10.1016/j.comppsych.2012.07.010

Arnold, S.E., Trojanowski, J.Q., 1996. Human fetal hippocampal development: I. Cytoarchitecture, myeloarchitecture, and neuronal morphologic features. J. Comp. Neurol. 367, 274–92. https://doi.org/10.1002/(SICI)1096-9861(19960401)367:2<274::AID-CNE9>3.0.CO;2-2

Bale, T.L., 2016. The placenta and neurodevelopment: Sex differences in prenatal vulnerability. Dialogues Clin. Neurosci. 18, 459–464.

Bale, T.L., Epperson, C.N., 2015. Sex differences and stress across the lifespan. Nat. Neurosci. 18, 1413–1420. https://doi.org/10.1038/nn.4112

Barkovich, M.J., Barkovich, A.J., 2019. MR Imaging of Normal Brain Development. Neuroimaging Clin. N. Am. https://doi.org/10.1016/j.nic.2019.03.007

Baron, E., Bass, J., Murray, S.M., Schneider, M., Lund, C., 2017. A systematic review of growth curve mixture modelling literature investigating trajectories of perinatal depressive symptoms and associated risk factors. J. Affect. Disord. https://doi.org/10.1016/j.jad.2017.07.046

Bayrampour, H., Ali, E., McNeil, D.A., Benzies, K., MacQueen, G., Tough, S., 2016. Pregnancy-related anxiety: A concept analysis. Int. J. Nurs. Stud. 55, 115–130. https://doi.org/10.1016/j.ijnurstu.2015.10.023

Bech, P., Bille, J., Møller, S.B., Hellström, L.C., Stergaard, S.D., 2014. Psychometric validation of the Hopkins Symptom Checklist (SCL-90) subscales for depression, anxiety, and interpersonal sensitivity. J. Affect. Disord. 160, 98–103. https://doi.org/10.1016/j.jad.2013.12.005

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An Inventory for Measuring Depression. Arch. Gen. Psychiatry 4, 561–571. https://doi.org/10.1001/archpsyc.1961.01710120031004

Benedetti, T.J., 1999. Birth injury and method of delivery. N. Engl. J. Med. https://doi.org/10.1056/NEJM199912023412308

Bennett, G.A., Palliser, H.K., Saxby, B., Walker, D.W., Hirst, J.J., 2013. Effects of prenatal stress on fetal neurodevelopment and responses to maternal neurosteroid treatment in guinea pigs. Dev. Neurosci. 35, 416–426. https://doi.org/10.1159/000354176

Bennett, G.A., Palliser, H.K., Shaw, J.C., Walker, D., Hirst, J.J., 2015. Prenatal Stress Alters Hippocampal Neuroglia and Increases Anxiety in Childhood. Dev. Neurosci. 37, 533–545. https://doi.org/10.1159/000437302

Bennett, H.A., Einarson, A., Taddio, A., Koren, G., Einarson, T.R., 2004. Depression during Pregnancy: Overview of Clinical Factors. Clin. Drug Investig. 24, 157–179. https://doi.org/10.2165/00044011-200424030-00004

Bergh, B. Van den, 1990. The influence of maternal emotions during pregnancy on fetal and neonatal behavior. Pre- Peri-Nat. Psychol. J. 5, 119–130.

Bergink, V., Kooistra, L., Lambregtse-van den Berg, M.P., Wijnen, H., Bunevicius, R., van Baar, A., Pop, V., 2011. Validation of the Edinburgh Depression Scale during pregnancy. J. Psychosom. Res. 70, 385–389. https://doi.org/10.1016/j.jpsychores.2010.07.008

Binda, V., Figueroa-Leigh, F., Olhaberry, M., 2019. Antenatal and postnatal depressive symptoms: Association with quality of mother–infant interaction. Infant Behav. Dev. 57, 101386. https://doi.org/10.1016/j.infbeh.2019.101386

Blackmore, E.R., Gustafsson, H., Gilchrist, M., Wyman, C., G O'Connor, T., 2016. Pregnancy-related anxiety: Evidence of distinct clinical significance from a prospective longitudinal study. J. Affect. Disord. 197, 251–258. https://doi.org/10.1016/j.jad.2016.03.008

Bock, J., Wainstock, T., Braun, K., Segal, M., 2015. Stress In Utero: Prenatal Programming of Brain Plasticity and Cognition. Biol. Psychiatry 78, 315–326. https://doi.org/10.1016/j.biopsych.2015.02.036

Bora, S., Pritchard, V.E., Chen, Z., Inder, T.E., Woodward, L.J., 2014. Neonatal cerebral morphometry and later risk of persistent inattention/hyperactivity in children born very preterm. J. Child Psychol. Psychiatry 55, 828–838. https://doi.org/10.1111/jcpp.12200

Boschloo, R.D., 1970. Raised conditional level of significance for the 2 × 2-table when testing the equality of two probabilities. Stat. Neerl. 24, 1–9. https://doi.org/10.1111/j.1467-9574.1970.tb00104.x

Brannigan, R., Cannon, M., Tanskanen, A., Huttunen, M.O., Leacy, F.P., Clarke, M.C., 2019. The association between subjective maternal stress during pregnancy and offspring clinically diagnosed psychiatric disorders. Acta Psychiatr. Scand. 139, 304–310. https://doi.org/10.1111/acps.12996

Brown, C.S., 2001. Depression and anxiety disorders. Obstet. Gynecol. Clin. North Am. 28, 241–268. https://doi.org/10.1016/S0889-8545(05)70199-6

Brown, E.S., Rush, A.J., McEwen, B.S., 1999. Hippocampal remodeling and damage by corticosteroids: Implications for mood disorders. Neuropsychopharmacology 21, 474–484. https://doi.org/10.1016/S0893-133X(99)00054-8

Brunton, R., Dryer, R., Saliba, A., Kohlhoff, J., 2019. Re-examining pregnancy-related anxiety: A replication study. Women and Birth 32, e131–e137. https://doi.org/10.1016/j.wombi.2018.04.013

Brunton, R.J., Dryer, R., Krägeloh, C., Saliba, A., Kohlhoff, J., Medvedev, O., 2018. The pregnancy-related anxiety scale: A validity examination using Rasch analysis. J. Affect. Disord. 236, 127–135. https://doi.org/10.1016/j.jad.2018.04.116

Bunevicius, A., Kusminskas, L., Pop, V.J., Pedersen, C.A., Bunevicius, R., 2009. Screening for antenatal depression with the Edinburgh Depression Scale. J. Psychosom. Obstet. Gynecol. 30, 238–243. https://doi.org/10.3109/01674820903230708

Buss, C., Davis, E., Muftuler, L.T., Head, K., Sandman, C., 2010. High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6-9-year-old children. Psychoneuroendocrinology 35, 141–153. https://doi.org/10.1016/j.psyneuen.2009.07.010

Buss, C., Davis, E.P., Hobel, C.J., Sandman, C.A., 2011. Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. Stress 14, 665–676. https://doi.org/10.3109/10253890.2011.623250

Buss, C., Davis, E.P., Shahbaba, B., Pruessner, J.C., Head, K., Sandman, C.A., 2012a. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc. Natl. Acad. Sci. 109, E1312–E1319. https://doi.org/10.1073/pnas.1201295109

Buss, C., Entringer, S., Wadhwa, P.D., 2012b. Fetal Programming of Brain Development: Intrauterine Stress and Susceptibility to Psychopathology. Sci. Signal. 5, pt7–pt7. https://doi.org/10.1126/scisignal.2003406

Capron, L.E., Glover, V., Pearson, R.M., Evans, J., O'Connor, T.G., Stein, A., Murphy, S.E., Ramchandani, P.G., 2015. Associations of maternal and paternal antenatal mood with offspring anxiety disorder at age 18 years. J. Affect. Disord. 187, 20–26. https://doi.org/10.1016/j.jad.2015.08.012

Chan, W.Y., Lorke, D.E., Tiu, S.C., Yew, D.T., 2002. Proliferation and apoptosis in the developing human neocortex. Anat. Rec. 267, 261–276. https://doi.org/10.1002/ar.10100

Chen, L., Pan, H., Tuan, T.A., Teh, A.L., MacIsaac, J.L., Mah, S.M., McEwen, L.M., Li, Y., Chen, H., Broekman, B.F.P., Buschdorf, J.P., Chong, Y.S., Kwek, K., Saw, S.M., Gluckman, P.D., Fortier, M. V, Rifkin-Graboi, A., Kobor, M.S., Qiu, A., Meaney, M.J., Holbrook, J.D., 2015. Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism influences the association of the methylome with maternal anxiety and neonatal brain volumes. Dev. Psychopathol. 27, 137–150. https://doi.org/10.1017/S0954579414001357

Cheong, J.L.Y., Hunt, R.W., Anderson, P.J., Howard, K., Thompson, D.K., Wang, H.X., Bear, M.J., Inder, T.E., Doyle, L.W., 2008. Head Growth in Preterm Infants: Correlation With Magnetic

Resonance Imaging and Neurodevelopmental Outcome. Pediatrics 121, e1534–e1540. https://doi.org/10.1542/peds.2007-2671

Clifton, V.L., 2010. Review: Sex and the Human Placenta: Mediating Differential Strategies of Fetal Growth and Survival. Placenta 31, S33–S39. https://doi.org/10.1016/j.placenta.2009.11.010

Cottrell, E.C., 2009. Prenatal stress, glucocorticoids and the programming of adult disease. Front. Behav. Neurosci. 3. https://doi.org/10.3389/neuro.08.019.2009

Coupé, P., Manjón, J. V, Fonov, V., Pruessner, J., Robles, M., Collins, D.L., 2011. Patch-based segmentation using expert priors: Application to hippocampus and ventricle segmentation. Neuroimage 54, 940–954. https://doi.org/10.1016/j.neuroimage.2010.09.018

Cowell, W., Deyssenroth, M., Chen, J., Wright, R.J., 2020. Maternal stress in relation to sex-specific expression of placental genes involved in nutrient transport, oxygen tension, immune response, and the glucocorticoid barrier. Placenta 96, 19–26. https://doi.org/10.1016/j.placenta.2020.05.004

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of Postnatal Depression: Development of the 10-item Edinburgh Postnatal Depression scale. Br. J. Psychiatry 150, 782–786. https://doi.org/10.1192/bjp.150.6.782

Da Costa, D., Larouche, J., Dritsa, M., Brender, W., 1999. Variations in stress levels over the course of pregnancy: Factors associated with elevated hassles, state anxiety and pregnancy-specific stress. J. Psychosom. Res. 47, 609–621. https://doi.org/10.1016/S0022-3999(99)00064-1

Dahmen, B., Puetz, V.B., Scharke, W., von Polier, G.G., Herpertz-Dahlmann, B., Konrad, K., 2018. Effects of Early-Life Adversity on Hippocampal Structures and Associated HPA Axis Functions. Dev. Neurosci. 40, 13–22. https://doi.org/10.1159/000484238

Dai, Y., Shi, F., Wang, L., Wu, G., Shen, D., 2013. iBEAT: A Toolbox for Infant Brain Magnetic Resonance Image Processing. Neuroinformatics 11, 211–225. https://doi.org/10.1007/s12021-012-9164-z

Davis, E., Glynn, L., Schetter, C., Hobel, C., Chicz-Demet, A., Sandman, C., 2007. Prenatal exposure to maternal depression and cortisol influences infant temperament. J. Am. Acad. Child Adolesc. Psychiatry 46, 737–746. https://doi.org/10.1097/chi.0b013e318047b775

Davis, E.P., Pfaff, D., 2014. Sexually dimorphic responses to early adversity: implications for affective problems and autism spectrum disorder. Psychoneuroendocrinology 49, 11–25. https://doi.org/10.1016/j.psyneuen.2014.06.014

De Bellis, M.D., Casey, B.., Dahl, R.E., Birmaher, B., Williamson, D.E., Thomas, K.M., Axelson, D.A., Frustaci, K., Boring, A.M., Hall, J., Ryan, N.D., 2000. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biol. Psychiatry 48, 51–57. https://doi.org/10.1016/S0006-3223(00)00835-0

Dean, D.C., Planalp, E.M., Wooten, W., Schmidt, C.K., Kecskemeti, S.R., Frye, C., Schmidt, N.L., Goldsmith, H.H., Alexander, A.L., Davidson, R.J., 2018a. Investigation of brain structure in the 1-month infant. Brain Struct. Funct. 223, 1953–1970. https://doi.org/10.1007/s00429-017-1600-2

Dean, D.C., Planalp, E.M., Wooten, W., Schmidt, C.K., Kecskemeti, S.R., Frye, C., Schmidt, N.L., Goldsmith, H.H., Alexander, A.L., Davidson, R.J., 2018b. Correction to: Investigation of brain structure in the 1-month infant. Brain Struct. Funct. 223, 3007–3009. https://doi.org/10.1007/s00429-018-1643-z

Delpech, J.-C., Wei, L., Hao, J., Yu, X., Madore, C., Butovsky, O., Kaffman, A., 2016. Early life stress perturbs the maturation of microglia in the developing hippocampus. Brain. Behav. Immun. 57, 79–93. https://doi.org/10.1016/j.bbi.2016.06.006

Deogratis, L.R., Lipman, R.S., Covi, L., 1973. SCL-90: An Outpatient Psychiatric Rating Scale-Preliminary Report. Psychopharmacol Bull. 9, 13–28.

Dickerson, P.A., Lally, B.E., Gunnel, E., Birkle, D.L., Salm, A.K., 2005. Early emergence of increased fearful behavior in prenatally stressed rats. Physiol. Behav. 86, 586–593. https://doi.org/10.1016/j.physbeh.2005.08.025

Dogan, M.S., Koc, G., Doganay, S., Dogan, S., Özdemir, A., Korkmaz, L., Coskun, A., 2018. Evaluation of symmetrical increased echogenicity of bilateral caudothalamic grooves detected on

cranial ultrasonography by comparing with susceptibility-weighted imaging. Radiol. Medica 123, 434–440. https://doi.org/10.1007/s11547-018-0861-z

Dubowitz, L., Mercuri, E., Dubowitz, V., 1998. An optimality score for the neurologic examination of the term newborn. J. Pediatr. 133, 406–416. https://doi.org/10.1016/S0022-3476(98)70279-3

Dunkel Schetter, C., Tanner, L., 2012. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. Curr. Opin. Psychiatry 25, 141–148. https://doi.org/10.1097/YCO.0b013e3283503680 [doi]

Edwards, A.D., Arthurs, O.J., 2011. Paediatric MRI under sedation: is it necessary? What is the evidence for the alternatives? Pediatr. Radiol. 41, 1353–1364. https://doi.org/10.1007/s00247-011-2147-7

Ehrlich, D.E., Neigh, G.N., Bourke, C.H., Nemeth, C.L., Hazra, R., Ryan, S.J., Rowson, S., Jairam, N., Sholar, C.A., Rainnie, D.G., Stowe, Z.N., Owens, M.J., 2015. Prenatal stress, regardless of concurrent escitalopram treatment, alters behavior and amygdala gene expression of adolescent female rats. Neuropharmacology 97, 251–258. https://doi.org/10.1016/j.neuropharm.2015.05.012

Ekéus, C., Högberg, U., Norman, M., 2014. Vacuum assisted birth and risk for cerebral complications in term newborn infants: a population-based cohort study. BMC Pregnancy Childbirth 14, 36. https://doi.org/10.1186/1471-2393-14-36

Elshazzly, M., Lopez, M.J., Reddy, V., Caban, O., 2019. Embryology, Central Nervous System, StatPearls. StatPearls Publishing.

Emmanuel, E., St John, W., 2010. Maternal distress: concept analysis. J. Adv. Nurs. 66, no-no. https://doi.org/10.1111/j.1365-2648.2010.05371.x

Ewing-Cobbs, L., Prasad, M., Kramer, L., Louis, P.T., Baumgartner, J., Fletcher, J.M., Alpert, B., 2000. Acute neuroradiologic findings in young children with inflicted or noninflicted traumatic brain injury. Child's Nerv. Syst. 16, 25–34. https://doi.org/10.1007/s003810050006

Field, T., 2017. Prenatal anxiety effects: A review. Infant Behav. Dev. 49, 120–128. https://doi.org/10.1016/j.infbeh.2017.08.008

Figueiredo, B., Conde, A., 2011. Anxiety and depression symptoms in women and men from early pregnancy to 3-months postpartum: Parity differences and effects. J. Affect. Disord. 132, 146–157. https://doi.org/10.1016/j.jad.2011.02.007

Fisher, J., Cabral de Mello, M., Patel, V., Rahman, A., Tran, T., Holton, S., Holmes, W., 2012. Prevalence and determinants of common perinatal mental disorders in women in low- and lower-middle-income countries: a systematic review. Bull. World Health Organ. 90, 139-149H. https://doi.org/10.2471/BLT.11.091850

Fonov, V., Evans, A.C., Botteron, K., Almli, C.R., McKinstry, R.C., Collins, D.L., Brain Development Cooperative Group, 2011. Unbiased average age-appropriate atlases for pediatric studies. Neuroimage 54, 313–327. https://doi.org/10.1016/j.neuroimage.2010.07.033

Fontein-Kuipers, Y., Ausems, M., Budé, L., Van Limbeek, E., De Vries, R., Nieuwenhuijze, M., 2015. Factors influencing maternal distress among Dutch women with a healthy pregnancy. Women and Birth 28, e36–e43. https://doi.org/doi.org/10.1016/j.wombi.2015.02.002

Foster, J.R., Hall, D.A., Summerfield, A.Q., Palmer, A.R., Bowtell, R.W., 2000. Sound-Level Measurements and Calculations of Safe Noise Dosage During EPI at 3 T. J. Magn. Reson. Imaging 12, 157–163. https://doi.org/10.1002/1522-2586(200007)12:1<157::AID-JMRI17>3.0.CO;2-M

Fride, E., Weinstock, M., 1988. Prenatal stress increase anxiety related behavior and alters cerebral lateralization of dopamine activity. Life Sci. 42, 1059–1065. https://doi.org/10.1016/0024-3205(88)90561-9

Frodl, T., Meisenzahl, E.M., Zetzsche, T., Born, C., Jäger, M., Groll, C., Bottlender, R., Leinsinger, G., Möller, H.-J., 2003. Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. Biol. Psychiatry 53, 338–344. https://doi.org/10.1016/s0006-3223(02)01474-9

Fujioka, A., Fujioka, T., Ishida, Y., Maekawa, T., Nakamura, S., 2006. Differential effects of prenatal stress on the morphological maturation of hippocampal neurons. Neuroscience 141, 907–915. https://doi.org/10.1016/j.neuroscience.2006.04.046

Gabaeff, S.C., 2013. Investigating the possibility and probability of perinatal subdural hematoma progressing to chronic subdural hematoma, with and without complications, in neonates, and its potential relationship to the misdiagnosis of abusive head trauma. Leg. Med. 15, 177–192. https://doi.org/10.1016/j.legalmed.2012.12.003

Gavin, N.I., Gaynes, B.N., Lohr, K.N., Meltzer-Brody, S., Gartlehner, G., Swinson, T., 2005. Perinatal Depression. Obstet. Gynecol. 106, 1071–1083. https://doi.org/10.1097/01.AOG.0000183597.31630.db

Ge, X., Shi, Y., Li, J., Zhang, Z., Lin, X., Zhan, J., Ge, H., Xu, J., Yu, Q., Leng, Y., Teng, G., Feng, L., Meng, H., Tang, Y., Zang, F., Toga, A.W., Liu, S., 2015. Development of the human fetal hippocampal formation during early second trimester. Neuroimage 119, 33–43. https://doi.org/10.1016/j.neuroimage.2015.06.055

Gibb, R., Kolb, B., 2018. The Neurobiology of Brain and Behavioral Development, The Neurobiology of Brain and Behavioral Development. Elsevier. https://doi.org/10.1016/C2015-0-00695-5

Gibson, J., McKenzie-McHarg, K., Shakespeare, J., Price, J., Gray, R., 2009. A systematic review of studies validating the Edinburgh Postnatal Depression Scale in antepartum and postpartum women. Acta Psychiatr. Scand. 119, 350–364. https://doi.org/10.1111/j.1600-0447.2009.01363.x

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: A longitudinal MRI study [2]. Nat. Neurosci. https://doi.org/10.1038/13158

Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A.C., Vauss, Y.C., Hamburger, S.D., Kaysen, D., Rapoport, J.L., 1996. Quantitative Magnetic Resonance Imaging of Human Brain Development: Ages 4–18. Cereb. Cortex 6, 551–559. https://doi.org/10.1093/cercor/6.4.551

Gilles, F.H., Nelson, M.D., 2012. The Developing Human Brain Growth and Adversities. Mac Keith Press. Print.

Gilmore, J.H., Lin, W., Prastawa, M.W., Looney, C.B., Sampath, Y., Vetsa, K., Knickmeyer, R.C., Evans, D.D., Smith, J.K., Robert, M., Lieberman, J.A., Gerig, G., 2007. Regional Gray Matter Growth, Sexual Dimorphism, and Cerebral Asymmetry in the Neonatal Brain 27, 1255–1260. https://doi.org/10.1523/JNEUROSCI.3339-06.2007.Regional

Girard, N., Raybaud, C., du Lac, P., 1991. MRI study of brain myelination - PubMed. J. Neuroradiol. 18, 291–307.

Gladstone, G.L., Parker, G.B., Mitchell, P.B., Malhi, G.S., Wilhelm, K.A., Austin, M.P., 2005. A Brief Measure of Worry Severity (BMWS): Personality and clinical correlates of severe worriers. J. Anxiety Disord. 19, 877–892. https://doi.org/10.1016/j.janxdis.2004.11.003

Gläscher, J., Adolphs, R., 2003. Processing of the Arousal of Subliminal and Supraliminal Emotional Stimuli by the Human Amygdala. J. Neurosci. 23, 10274–10282. https://doi.org/10.1523/jneurosci.23-32-10274.2003

Glover, V., O'Connor, T.G., O'Donnell, K., 2010. Prenatal stress and the programming of the HPA axis. Neurosci. Biobehav. Rev. 35, 17–22. https://doi.org/10.1016/j.neubiorev.2009.11.008

Graham, A.M., Rasmussen, J.M., Entringer, S., Ben Ward, E., Rudolph, M.D., Gilmore, J.H., Styner, M., Wadhwa, P.D., Fair, D.A., Buss, C., 2019. Maternal Cortisol Concentrations During Pregnancy and Sex-Specific Associations With Neonatal Amygdala Connectivity and Emerging Internalizing Behaviors. Biol. Psychiatry 85, 172–181. https://doi.org/10.1016/j.biopsych.2018.06.023

Green, J.M., Kafetsios, K., Statham, H.E., Snowdon, C.M., 2003. Factor Structure, Validity and Reliability of the Cambridge Worry Scale in a Pregnant Population. J. Health Psychol. 8, 753–764. https://doi.org/10.1177/13591053030086008

Grigoriadis, S., VonderPorten, E.H., Mamisashvili, L., Tomlinson, G., Dennis, C.-L., Koren, G., Steiner, M., Mousmanis, P., Cheung, A., Radford, K., Martinovic, J., Ross, L.E., 2013. The Impact of Maternal Depression During Pregnancy on Perinatal Outcomes. J. Clin. Psychiatry 74, e321–e341. https://doi.org/10.4088/JCP.12r07968

Groen, W., Teluij, M., Buitelaar, J., Tendolkar, I., 2010. Amygdala and Hippocampus Enlargement During Adolescence in Autism. J. Am. Acad. Child Adolesc. Psychiatry 49, 552–560. https://doi.org/10.1016/j.jaac.2009.12.023

Gross, C., Zhuang, X., Stark, K., Ramboz, S., Oosting, R., Kirby, L., Santarelli, L., Beck, S., Hen, R., 2002. Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. Nature 416, 396–400. https://doi.org/10.1038/416396a

Guo, J.Y., Isohanni, M., Miettunen, J., Jääskeläinen, E., Kiviniemi, V., Nikkinen, J., Remes, J., Huhtaniska, S., Veijola, J., Jones, P.B., Murray, G.K., 2016. Brain structural changes in women and men during midlife. Neurosci. Lett. 615, 107–12. https://doi.org/10.1016/j.neulet.2016.01.007

Gupta, S.N., Kechli, A.M., Kanamalla, U.S., 2009. Intracranial Hemorrhage in Term Newborns: Management and Outcomes. Pediatr. Neurol. 40, 1–12. https://doi.org/10.1016/j.pediatrneurol.2008.09.019

Haataja, L., Mercuri, E., Regev, R., Cowan, F., Rutherford, M., Dubowitz, V., Dubowitz, L., 1999. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J. Pediatr. 135, 153–161. https://doi.org/10.1016/S0022-3476(99)70016-8

Hardee, J.E., Thompson, J.C., Puce, A., 2008. The left amygdala knows fear: laterality in the amygdala response to fearful eyes. Soc. Cogn. Affect. Neurosci. 3, 47–54. https://doi.org/10.1093/scan/nsn001

Hashempour, N., Tuulari, J.J., Merisaari, H., Lidauer, K., Luukkonen, I., Saunavaara, J., Parkkola, R., Lähdesmäki, T., Lehtola, S.J., Keskinen, M., Lewis, J.D., Scheinin, N.M., Karlsson, L., Karlsson, H., 2019. A Novel Approach for Manual Segmentation of the Amygdala and Hippocampus in Neonate MRI. Front. Neurosci. 13, 1025. https://doi.org/10.3389/fnins.2019.01025

Hensch, T.K., 2004. Critical Period Regulation. Annu. Rev. Neurosci. 27, 549–579. https://doi.org/10.1146/annurev.neuro.27.070203.144327

Herman, J.P., Ostrander, M.M., Mueller, N.K., Figueiredo, H., 2005. Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. Prog. Neuro-Psychopharmacology Biol. Psychiatry 29, 1201–1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Herringa, R.J., Roseboom, P.H., Kalin, N.H., 2006. Decreased amygdala CRF-binding protein mRNA in post-mortem tissue from male but not female bipolar and schizophrenic subjects. Neuropsychopharmacology 31, 1822–1831. https://doi.org/10.1038/sj.npp.1301038

Holcomb, W.L., Stone, L.S., Lustman, P.J., Gavard, J.A., Mostello, D.J., 1996. Screening for depression in pregnancy: Characteristics of the beck depression inventory. Obstet. Gynecol. 88, 1021–1025. https://doi.org/10.1016/S0029-7844(96)00329-8

Holland, D., Chang, L., Ernst, T.M., Curran, M., Buchthal, S.D., Alicata, D., Skranes, J., Johansen, H., Hernandez, A., Yamakawa, R., Kuperman, J.M., Dale, A.M., 2014. Structural Growth Trajectories and Rates of Change in the First 3 Months of Infant Brain Development. JAMA Neurol. 71, 1266. https://doi.org/10.1001/jamaneurol.2014.1638

Hong, H.S., Lee, J.Y., 2018. Intracranial hemorrhage in term neonates. Child's Nerv. Syst. 34, 1135–1143. https://doi.org/10.1007/s00381-018-3788-8

Huizink, A.C., Delforterie, M.J., Scheinin, N.M., Tolvanen, M., Karlsson, L., Karlsson, H., 2016. Adaption of pregnancy anxiety questionnaire–revised for all pregnant women regardless of parity: PRAQ-R2. Arch. Womens. Ment. Health 19, 125–132. https://doi.org/10.1007/s00737-015-0531-2

Huizink, A.C., Mulder, E.J.H., Robles de Medina, P.G., Visser, G.H.A., Buitelaar, J.K., 2004. Is pregnancy anxiety a distinctive syndrome? Early Hum. Dev. 79, 81–91. https://doi.org/10.1016/j.earlhumdev.2004.04.014

Huizink, A.C., Robles De Medina, P.G., Mulder, E.J.H., Visser, G.H.A., Buitelaar, J.K., 2003. Stress during pregnancy is associated with developmental outcome in infancy. J. Child Psychol. Psychiatry Allied Discip. 44, 810–818. https://doi.org/10.1111/1469-7610.00166

Huizink, A.C., Robles De Medina, P.G., Mulder, E.J.H., Visser, G.H.A., Buitelaar, J.K., 2002. Psychological Measures of Prenatal Stress as Predictors of Infant Temperament. J. Am. Acad. Child Adolesc. Psychiatry 41, 1078–1085. https://doi.org/10.1097/00004583-200209000-00008

Humphrey, T., 1968. The development of the human amygdala during early embryonic life,. J. Comp. Neurol. 132, 135–165. https://doi.org/10.1002/cne.901320108

Humphrey, T., 1967. The development of the human hippocampal fissure. J. Anat 101, 655–676.

Ingstrup, K.G., Schou Andersen, C., Ajslev, T.A., Pedersen, P., Sørensen, T.I.A., Nohr, E.A., 2012. Maternal Distress during Pregnancy and Offspring Childhood Overweight. J. Obes. 2012, 1–7. https://doi.org/10.1155/2012/462845

Insausti, R., Amaral, D.G., 2012. Hippocampal Formation, in: The Human Nervous System. Elsevier Inc., pp. 896–942. https://doi.org/10.1016/B978-0-12-374236-0.10024-0

Iwasaki-Sekino, A., Mano-Otagiri, A., Ohata, H., Yamauchi, N., Shibasaki, T., 2009. Gender differences in corticotropin and corticosterone secretion and corticotropin-releasing factor mRNA expression in the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala in response to footshock stress or psychological stress in rats. Psychoneuroendocrinology 34, 226–237. https://doi.org/10.1016/j.psyneuen.2008.09.003

Jacobson, L., Sapolsky, R., 1991. The Role of the Hippocampus in Feedback Regulation of the Hypothalamic-Pituitary-Adrenocortical Axis. Endocr. Rev. 12, 118–134. https://doi.org/10.1210/edrv-12-2-118

Jalbrzikowski, M., Larsen, B., Hallquist, M.N., Foran, W., Calabro, F., Luna, B., 2017. Development of White Matter Microstructure and Intrinsic Functional Connectivity Between the Amygdala and Ventromedial Prefrontal Cortex: Associations With Anxiety and Depression. Biol. Psychiatry 82, 511–521. https://doi.org/10.1016/j.biopsych.2017.01.008

Jhawar, B.S., Ranger, A., Steven, D., Del Maestro, R.F., Cohen, A.R., McComb, J.G., Humphreys, R.P., Hill, A., 2003. Risk factors for intracranial hemorrhage among full-term infants: A case-control study. Neurosurgery 52, 581–590. https://doi.org/10.1227/01.NEU.0000047819.33177.72

Jones, S.L., Dufoix, R., Laplante, D.P., Elgbeili, G., Patel, R., Chakravarty, M.M., King, S., Pruessner, J.C., 2019. Larger Amygdala Volume Mediates the Association Between Prenatal Maternal Stress and Higher Levels of Externalizing Behaviors: Sex Specific Effects in Project Ice Storm. Front. Hum. Neurosci. 13, 144. https://doi.org/10.3389/fnhum.2019.00144

Kamel, H.S., Ahmed, H.N., Eissa, M.A., Abol-Oyoun, A.-S.M., 1999. Psychological and Obstetrical Responses of Mothers Following Antenatal Fetal Sex Identification. J. Obstet. Gynaecol. Res. 25, 43–50. https://doi.org/10.1111/j.1447-0756.1999.tb01121.x

Karlsson, L., Nousiainen, N., Scheinin, N.M., Maksimow, M., Salmi, M., Lehto, S.M., Tolvanen, M., Lukkarinen, H., Karlsson, H., 2017. Cytokine profile and maternal depression and anxiety symptoms in mid-pregnancy—the FinnBrain Birth Cohort Study. Arch. Womens. Ment. Health 20, 39–48. https://doi.org/10.1007/s00737-016-0672-y

Karlsson, L., Tolvanen, M., Scheinin, N.M., Uusitupa, H.-M., Korja, R., Ekholm, E., Tuulari, J.J., Pajulo, M., Huotilainen, M., Paunio, T., Karlsson, H., 2018. Cohort Profile: The FinnBrain Birth Cohort Study (FinnBrain). Int. J. Epidemiol. 47, 15-16j. https://doi.org/10.1093/ije/dyx173

Katsu, Y., Iguchi, T., 2016. Cortisol, in: Handbook of Hormones. Elsevier, pp. 533-e95D-2. https://doi.org/10.1016/B978-0-12-801028-0.00231-2

Kawamura, T., Chen, J., Takahashi, T., Ichitani, Y., Nakahara, D., 2006. Prenatal stress suppresses cell proliferation in the early developing brain. Neuroreport 17, 1515–1518. https://doi.org/10.1097/01.wnr.0000236849.53682.6d

Kendler, K.S., Gardner, C.O., Gatz, M., Pedersen, N.L., 2007. The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. Psychol. Med. 37, 453–462. https://doi.org/10.1017/S0033291706009135

Kier, E.L., Kim, J.H., Fulbright, R.K., Bronen, R.A., 1997. Embryology of the Human Fetal Hippocampus: MR Imaging, Anatomy, and Histology. AJNR Am J Neuroradiol 18, 525–532.

Killion, B.E., Weyandt, L.L., 2018. Brain structure in childhood maltreatment-related PTSD across the lifespan: A systematic review. Appl. Neuropsychol. Child 1–15. https://doi.org/10.1080/21622965.2018.1515076

Knickmeyer, R.C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J.K., Hamer, R.M., Lin, W., Gerig, G., Gilmore, J.H., 2008. A Structural MRI Study of Human Brain Development from Birth to 2 Years. J. Neurosci. 28, 12176–12182. https://doi.org/10.1523/JNEUROSCI.3479-08.2008

Knickmeyer, R.C., Xia, K., Lu, Z., Ahn, M., Jha, S.C., Zou, F., Zhu, H., Styner, M., Gilmore, J.H., 2016. Impact of Demographic and Obstetric Factors on Infant Brain Volumes: A Population Neuroscience Study. Cereb. Cortex 5, 187. https://doi.org/10.1093/cercor/bhw331

Koelewijn, J.M., Sluijs, A.M., Vrijkotte, T.G.M., 2017. Possible relationship between general and pregnancy-related anxiety during the first half of pregnancy and the birth process: a prospective cohort study. BMJ Open 7, e013413. https://doi.org/10.1136/bmjopen-2016-013413

Koolschijn, P.C.M.P., Crone, E.A., 2013. Sex differences and structural brain maturation from childhood to early adulthood. Dev. Cogn. Neurosci. 5, 106–118. https://doi.org/10.1016/j.dcn.2013.02.003

Korhonen, M., Luoma, I., Salmelin, R., Tamminen, T., 2014. Maternal depressive symptoms: Associations with adolescents' internalizing and externalizing problems and social competence. Nord. J. Psychiatry 68, 323–332. https://doi.org/10.3109/08039488.2013.838804

Korja, R., Nolvi, S., Grant, K.A., McMahon, C., 2017. The Relations Between Maternal Prenatal Anxiety or Stress and Child's Early Negative Reactivity or Self-Regulation: A Systematic Review. Child Psychiatry Hum. Dev. 48, 851–869. https://doi.org/10.1007/s10578-017-0709-0

Korja, R., Nolvi, S., Kataja, E.-L., Scheinin, N., Junttila, N., Lahtinen, H., Saarni, S., Karlsson, L., Karlsson, H., 2018. The courses of maternal and paternal depressive and anxiety symptoms during the prenatal period in the FinnBrain Birth Cohort study. PLoS One 13, e0207856. https://doi.org/10.1371/journal.pone.0207856

Kouwenhoven, E., Giezen, M., Struikmans, H., 2009. Measuring the similarity of target volume delineations independent of the number of observers - IOPscience. Phys Med Biol. 54, 2863–2873. https://doi.org/10.1088/0031-9155/54/9/018

Kozinszky, Z., Dudas, R.B., Devosa, I., Csatordai, S., Tóth, É., Szabó, D., Sikovanyecz, J., Barabás, K., Pál, A., 2012. Can a brief antepartum preventive group intervention help reduce postpartum depressive symptomatology? Psychother. Psychosom. 81, 98–107. https://doi.org/10.1159/000330035

Kraszpulski, M., Dickerson, P.A., Salm, A.K., 2006. Prenatal stress affects the developmental trajectory of the rat amygdala. Stress 9, 85–95. https://doi.org/10.1080/10253890600798109

Krispin, E., Aviram, A., Salman, L., Chen, R., Wiznitzer, A., Gabbay-Benziv, R., 2017. Cup detachment during vacuum-assisted vaginal delivery and birth outcome. Arch. Gynecol. Obstet. 296, 877–883. https://doi.org/10.1007/s00404-017-4507-5

Lebel, C., Deoni, S., 2018. The development of brain white matter microstructure. Neuroimage 182, 207–218. https://doi.org/10.1016/j.neuroimage.2017.12.097

Lebel, C., Walton, M., Letourneau, N., Giesbrecht, G.F., Kaplan, B.J., Dewey, D., 2016. Prepartum and Postpartum Maternal Depressive Symptoms Are Related to Children's Brain Structure in Preschool. Biol. Psychiatry 80, 859–868. https://doi.org/10.1016/j.biopsych.2015.12.004

LeDoux, J.E., 2000. Emotion Circuits in the Brain. Annu. Rev. Neurosci. 23, 155–184. https://doi.org/10.1146/annurev.neuro.23.1.155

Lee, A.M., Lam, S.K., Sze Mun Lau, S.M., Chong, C.S.Y., Chui, H.W., Fong, D.Y.T., 2007. Prevalence, course, and risk factors for antenatal anxiety and depression. Obstet. Gynecol. 110, 1102–1112. https://doi.org/10.1097/01.AOG.0000287065.59491.70

Leigh, B., Milgrom, J., 2008. Risk factors for antenatal depression, postnatal depression and parenting stress. BMC Psychiatry 8, 24. https://doi.org/10.1186/1471-244X-8-24

Lemaire, V., Koehl, M., Le Moal, M., Abrous, D.N., 2000. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc. Natl. Acad. Sci. U. S. A. 97, 11032–11037.

Lemaire, V., Lamarque, S., Le Moal, M., Piazza, P.-V., Abrous, D.N., 2006. Postnatal stimulation of the pups counteracts prenatal stress-induced deficits in hippocampal neurogenesis. Biol. Psychiatry 59, 786–792. https://doi.org/10.1016/j.biopsych.2005.11.009

Lenroot, R.K., Gogtay, N., Al., E., 2007a. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36, 1065–1073. https://doi.org/10.1016/J.NEUROIMAGE.2007.03.053

Lenroot, R.K., Gogtay, N., Greenstein, D.K., Wells, E.M., Wallace, G.L., Clasen, L.S., Blumenthal, J.D., Lerch, J., Zijdenbos, A.P., Evans, A.C., Thompson, P.M., Giedd, J.N., 2007b. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage 36, 1065–1073. https://doi.org/10.1016/j.neuroimage.2007.03.053

Leuner, B., Gould, E., 2010. Structural plasticity and hippocampal function. Annu. Rev. Psychol. 61, 111–140. https://doi.org/0.1146/annurev.psych.093008.100359

Levesque, R.J.R., 2011. Externalizing and Internalizing Symptoms, in: Encyclopedia of Adolescence. Springer New York, pp. 903–905. https://doi.org/10.1007/978-1-4419-1695-2_539

Levin, J.S., 1991. The factor structure of the pregnancy anxiety scale - PubMed. J. Heal. Soc. Behav. 32, 368–381.

Levitt, N.S., Lindsay, R.S., Holmes, M.C., Seckl, J.R., 1996. Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. Neuroendocrinology 64, 412–418. https://doi.org/10.1159/000127146

Lewis, J.D., Fonov, V.S., Collins, D.L., Evans, A.C., Tohka, J., Brain Development Cooperative Group and the Pediatric Imaging, Neurocognition, and Genetics Study, 2019. Cortical and subcortical T1 white/gray contrast, chronological age, and cognitive performance. Neuroimage 196, 276–288. https://doi.org/10.1016/j.neuroimage.2019.04.022

Lin, Y., Hu, W., Xu, J., Luo, Z., Ye, X., Yan, C., Liu, Z., Tong, S., 2017. Association between temperature and maternal stress during pregnancy. Environ. Res. 158, 421–430. https://doi.org/10.1016/j.envres.2017.06.034

Lind, A., Lapinleimu, H., Korkman, M., Lehtonen, L., Parkkola, R., Haataja, L., 2010. Five-year follow-up of prematurely born children with postnatally developing caudothalamic cysts. Acta Paediatr. Int. J. Paediatr. 99, 304–307. https://doi.org/10.1111/j.1651-2227.2009.01530.x

Lind, A, Lapinleimu, H., Korkman, M., Lehtonen, L., Parkkola, R., Haataja, L., Group, S., 2010. Five-year follow-up of prematurely born children with postnatally developing caudothalamic cysts 20, 304–307. https://doi.org/10.1111/j.1651-2227.2009.01530.x

Liu, L., Li, A., Matthews, S.G., 2001. Maternal glucocorticoid treatment programs HPA regulation in adult offspring: sex-specific effects. Am. J. Physiol. Metab. 280, E729–E739. https://doi.org/10.1152/ajpendo.2001.280.5.E729

Lombardo, M. V., Ashwin, E., Auyeung, B., Chakrabarti, B., Taylor, K., Hackett, G., Bullmore, E.T., Baron-Cohen, S., 2012. Fetal testosterone influences sexually dimorphic gray matter in the human brain. J. Neurosci. 32, 674–680. https://doi.org/10.1523/JNEUROSCI.4389-11.2012

Looney, C.B., Smith, J.K., Merck, L.H., Wolfe, H.M., Chescheir, N.C., Hamer, R.M., Gilmore, J.H., 2007. Intracranial hemorrhage in asymptomatic neonates: Prevalence on MR images and relationship to obstetric and neonatal risk factors. Radiology 242, 535–541. https://doi.org/10.1148/radiol.2422060133

Luo, J., Luo, Y., Zeng, H., Reis, C., Chen, S., 2019. Research Advances of Germinal Matrix Hemorrhage: An Update Review. Cell. Mol. Neurobiol. 39, 1–10. https://doi.org/10.1007/s10571-018-0630-5

Lupien, S., Parent, S., Evans, A., Tremblay, R., Zelazo, P., Corbo, V., Pruessner, J., Séguin, J., 2011. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to

maternal depressive symptomatology since birth. Proc. Natl. Acad. Sci. U. S. A. 108, 14324–14329. https://doi.org/10.1073/pnas.1105371108

Lydersen, S., Fagerland, M.W., Laake, P., 2009. Recommended tests for association in 2×2 tables. Stat. Med. 28, 1159–1175. https://doi.org/10.1002/sim.3531

Madhavanprabhakaran, G.K., Kumar, K.A., Ramasubramaniam, S., Akintola, A.A., 2013. Effects of pregnancy related anxiety on labour outcomes: A prospective cohort study. J. Res. Nurs. Midwifery 2, 96–103. https://doi.org/10.14303/JRNM.2013.061

Madigan, S., Oatley, H., Racine, N., Fearon, R.M.P., Schumacher, L., Akbari, E., Cooke, J.E., Tarabulsy, G.M., 2018. A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socioemotional Development. J. Am. Acad. Child Adolesc. Psychiatry 57, 645-657.e8. https://doi.org/10.1016/j.jaac.2018.06.012

Mai, J.K., Paxinos, G. (Eds.), 2011. The Human Nervous System, edited by Juergen K. Mai, and George Paxinos. Saint Louis: Elsevier Science & Technology., Third. ed. Elsevier Science & Technology.

Makropoulos, A., Counsell, S.J., Rueckert, D., 2018. A review on automatic fetal and neonatal brain MRI segmentation. Neuroimage 170, 231–248. https://doi.org/10.1016/j.neuroimage.2017.06.074

Malt, E.A., Juhasz, K., Malt, U.F., Naumann, T., 2016. A Role for the Transcription Factor Nk2 Homeobox 1 in Schizophrenia: Convergent Evidence from Animal and Human Studies. Front. Behav. Neurosci. 10. https://doi.org/10.3389/fnbeh.2016.00059

Marečková, K., Mareček, R., Bencurova, P., Klánová, J., Dušek, L., Brázdil, M., 2018. Perinatal stress and human hippocampal volume: Findings from typically developing young adults. Sci. Rep. 8, 4696. https://doi.org/10.1038/s41598-018-23046-6

Mark, L.P., Daniels, D.L., Naidich, T.P., Hendrix, L.E., 1999. Limbic connections. AJNR. Am. J. Neuroradiol. 16, 1303–1306.

Mastorakos, G., Ilias, I., 2003. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum, in: Annals of the New York Academy of Sciences. New York Academy of Sciences, pp. 136–149. https://doi.org/10.1196/annals.1290.016

Mathew, A.R., Pettit, J.W., Lewinsohn, P.M., Seeley, J.R., Roberts, R.E., 2011. Co-morbidity between major depressive disorder and anxiety disorders: shared etiology or direct causation? Psychol. Med. 41, 2023–2034. https://doi.org/10.1017/S0033291711000407

Matsuzawa, J., 2001. Age-related Volumetric Changes of Brain Gray and White Matter in Healthy Infants and Children. Cereb. Cortex 11, 335–342. https://doi.org/10.1093/cercor/11.4.335

Matthey, S., Phillips, J., White, T., Glossop, P., Hopper, U., Panasetis, P., Petridis, A., Larkin, M., Barnett, B., 2004. Routine psychosocial assessment of women in the antenatal period: frequency of risk factors and implications for clinical services. Arch. Womens. Ment. Health 7, 223–229. https://doi.org/10.1007/s00737-004-0064-6

McLachlan, R.S., 2009. A brief review of the anatomy and physiology of the limbic system. Can. J. Neurol. Sci. 36 Suppl 2, S84-87.

Meaney, M.J., Szyf, M., Seckl, J.R., 2007. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. Trends Mol. Med. 13, 269–277. https://doi.org/10.1016/j.molmed.2007.05.003

Middeldorp CM, Cath DC, Van Dyck R, B. DI, 2005. The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies. - PubMed - NCBI. Psychol Med. 611–624. https://doi.org/10.1017/s003329170400412x

Mills, K.L., Goddings, A.L., Herting, M.M., Meuwese, R., Blakemore, S.J., Crone, E.A., Dahl, R.E., Güroğlu, B., Raznahan, A., Sowell, E.R., Tamnes, C.K., 2016. Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. Neuroimage 141, 273–281. https://doi.org/10.1016/j.neuroimage.2016.07.044

Misri, S., Abizadeh, J., Sanders, S., Swift, E., 2015. Perinatal Generalized Anxiety Disorder: Assessment and Treatment. J. Women's Heal. 24, 762–770. https://doi.org/10.1089/jwh.2014.5150

Moors, M., Bose, R., Johansson-Haque, K., Edoff, K., Okret, S., Ceccatelli, S., 2012. Dickkopf 1 mediates glucocorticoid-induced changes in human neural progenitor cell proliferation and differentiation - PubMed. Toxicol Sci. 125, 488–495. https://doi.org/10.1093/toxsci/kfr304

Morgan, C.P., Bale, T.L., 2011. Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. J. Neurosci. 31, 11748–11755. https://doi.org/10.1523/JNEUROSCI.1887-11.2011

Mosconi, M.W., Cody-Hazlett, H., Poe, M.D., Gerig, G., Gimpel-Smith, R., Piven, J., 2009. Longitudinal study of amygdala volume and joint attention in 2- to 4-year-old children with autism. Arch. Gen. Psychiatry 66, 509–516. https://doi.org/10.1001/archgenpsychiatry.2009.19

Muller, F., O'Rahilly, R., 2006. The amygdaloid complex and the medial and lateral ventricular eminences in staged human embryos. J. Anat. 208, 547–564. https://doi.org/10.1111/j.1469-7580.2006.00553.x

Munakata, S., Okada, T., Okahashi, A., Yoshikawa, K., Usukura, Y., Makimoto, M., Hosono, S., Takahashi, S., Mugishima, H., Okuhata, Y., 2013. Gray matter volumetric MRI differences late-preterm and term infants. Brain Dev. 35, 10–16. https://doi.org/10.1016/j.braindev.2011.12.011

Murphy Jr, G.M., Inger, P., Mark, K., Lin, J., Morrice, W., Gee, C., Gan, S., Korp, B., 1987. Volumetric asymmetry in the human amygdaloid complex - PubMed. J Hirnforsch 28, 281–289.

Murray, D., Cox, J.L., 1990. Screening for depression during pregnancy with the edinburgh depression scale (EDDS). J. Reprod. Infant Psychol. 8, 99–107. https://doi.org/10.1080/02646839008403615

Mychasiuk, R., Gibb, R., Kolb, B., 2011. Prenatal bystander stress induces neuroanatomical changes in the prefrontal cortex and hippocampus of developing rat offspring. Brain Res. 1412, 55–62. https://doi.org/10.1016/j.brainres.2011.07.023

Nelson, L.H., Warden, S., Lenz, K.M., 2017. Sex differences in microglial phagocytosis in the neonatal hippocampus. Brain. Behav. Immun. 64, 11–22. https://doi.org/10.1016/j.bbi.2017.03.010

Nieuwenhuys, R., Voogd, J., van Huijzen, C., 2008. The Human Central Nervous System, The Human Central Nervous System. Springer Berlin Heidelberg, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-34686-9

Nikolić, I., Kostović, I., 1986. Development of the lateral amygdaloid nucleus in the human fetus: transient presence of discrete cytoarchitectonic units. Anat. Embryol. (Berl). 174, 355–360. https://doi.org/10.1007/bf00698785

Nishikuni, K., Ribas, G.C., 2013. Study of fetal and postnatal morphological development of the brain sulci: Laboratory investigation. J. Neurosurg. Pediatr. 11, 1–11. https://doi.org/10.3171/2012.9.PEDS12122

Noesselt, T., Driver, J., Heinze, H.J., Dolan, R., 2005. Asymmetrical activation in the human brain during processing of fearful faces. Curr. Biol. 15, 424–429. https://doi.org/10.1016/j.cub.2004.12.075

Nolvi, S., Karlsson, L., Bridgett, D.J., Korja, R., Huizink, A.C., Kataja, E.L., Karlsson, H., 2016. Maternal prenatal stress and infant emotional reactivity six months postpartum. J. Affect. Disord. 199, 163–170. https://doi.org/10.1016/j.jad.2016.04.020

O'Connell, B.A., Moritz, K.M., Walker, D.W., Dickinson, H., 2013. Treatment of pregnant spiny mice at mid gestation with a synthetic glucocorticoid has sex-dependent effects on placental glycogen stores. Placenta 34, 932–940. https://doi.org/10.1016/j.placenta.2013.06.310

O'Connor, T.G., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., Glover, V., 2005. Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. Biol. Psychiatry 58, 211–217. https://doi.org/10.1016/j.biopsych.2005.03.032

O'Donnell, K.J., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T.G., Glover, V., 2012. Maternal prenatal anxiety and downregulation of placental 11ß-HSD2. Psychoneuroendocrinology 37, 818–826. https://doi.org/10.1016/j.psyneuen.2011.09.014

O'Donnell, K.J., Glover, V., Barker, E.D., O'Connor, T.G., 2014a. The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev. Psychopathol. 26, 393–403. https://doi.org/10.1017/S0954579414000029

O'Donnell, K.J., Glover, V., Holbrook, J.D., O'Connor, T.G., 2014b. Maternal prenatal anxiety and child brain-derived neurotrophic factor (BDNF) genotype: Effects on internalizing symptoms from 4 to 15 years of age. Dev. Psychopathol. 26, 1255–1266. https://doi.org/10.1017/S095457941400100X

Ong, M., Tuan, T.A., Poh, J., Teh, A.L., Chen, L., Pan, H., MacIsaac, J.L., Kobor, M.S., Chong, Y.S., Kwek, K., Saw, S.M., Godfrey, K.M., Gluckman, P.D., Fortier, M. V., Karnani, N., Meaney, M.J., Qiu, A., Holbrook, J.D., 2019. Neonatal amygdalae and hippocampi are influenced by genotype and prenatal environment, and reflected in the neonatal DNA methylome. Genes, Brain Behav. 18, e12576. https://doi.org/10.1111/gbb.12576

Østgård, H.F., Løhaugen, G.C.C., Bjuland, K.J., Rimol, L.M., Brubakk, A.-M., Martinussen, M., Vik, T., Håberg, A.K., Skranes, J., 2014. Brain Morphometry and Cognition in Young Adults Born Small for Gestational Age at Term. J. Pediatr. 165, 921-927.e1. https://doi.org/10.1016/j.jpeds.2014.07.045

Owen, D., Matthews, S.G., 2003. Glucocorticoids and Sex-Dependent Development of Brain Glucocorticoid and Mineralocorticoid Receptors. Endocrinology 144, 2775–2784. https://doi.org/10.1210/en.2002-0145

Padilla, N., Alexandrou, G., Blennow, M., Lagercrantz, H., Ådén, U., 2015. Brain Growth Gains and Losses in Extremely Preterm Infants at Term. Cereb. Cortex 25, 1897–1905. https://doi.org/10.1093/cercor/bht431

Passamonti, L., Fairchild, G., Fornito, A., Goodyer, I., Nimmo-Smith, I., Hagan, C., Calder, A., 2012. Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. PLoS One 7, e48789–e48789. https://doi.org/10.1371/journal.pone.0048789

Pedraza, O., Bowers, D., Gilmore, R., 2004. Asymmetry of the hippocampus and amygdala in MRI volumetric measurements of normal adults. J. Int. Neuropsychol. Soc. 10, 664–678. https://doi.org/10.1017/S1355617704105080

Peterson, B.S., 2000. Regional Brain Volume Abnormalities and Long-term Cognitive Outcome in Preterm Infants. JAMA 284, 1939. https://doi.org/10.1001/jama.284.15.1939

Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. Nat. Neurosci. 4, 437–441. https://doi.org/10.1038/86110

Pickles, A., Sharp, H., Hellier, J., Hill, J., 2017. Prenatal anxiety, maternal stroking in infancy, and symptoms of emotional and behavioral disorders at 3.5 years. Eur. Child Adolesc. Psychiatry 26, 325–334. https://doi.org/10.1007/s00787-016-0886-6

Posner, J., Cha, J., Roy, A.K., Peterson, B.S., Bansal, R., Gustafsson, H.C., Raffanello, E., Gingrich, J., Monk, C., 2016. Alterations in amygdala–prefrontal circuits in infants exposed to prenatal maternal depression. Transl. Psychiatry 6, e935–e935. https://doi.org/10.1038/tp.2016.146

Poussaint, T.Y., Moeller, K.K., 2002. Imaging of pediatric head trauma. Neuroimaging Clin. N. Am. 12, 271–294. https://doi.org/10.1016/S1052-5149(02)00005-9

Pujol, J., López-Sala, A., Deus, J., Cardoner, N., Sebastián-Gallés, N., Conesa, G., Capdevila, A., 2002. The Lateral Asymmetry of the Human Brain Studied by Volumetric Magnetic Resonance Imaging. Neuroimage 17, 670–679. https://doi.org/10.1006/nimg.2002.1203

Qin, S., Young, C.B., Duan, X., Chen, T., Supekar, K., Menon, V., 2014. Amygdala subregional structure and intrinsic functional connectivity predicts individual differences in anxiety during early childhood. Biol. Psychiatry 75, 892–900. https://doi.org/10.1016/j.biopsych.2013.10.006

Qiu, A., Anh, T.T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B.F.P., Kwek, K., Saw, S.-M., Chong, Y.-S., Gluckman, P.D., Fortier, M. V, Meaney, M.J., 2015. Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. Transl. Psychiatry 5, e508–e508. https://doi.org/10.1038/tp.2015.3

Qiu, A., Rifkin-Graboi, A., Chen, H., Chong, Y.-S., Kwek, K., Gluckman, P.D., Fortier, M. V, Meaney, M.J., 2013. Maternal anxiety and infants' hippocampal development: timing matters. Transl. Psychiatry 3, e306–e306. https://doi.org/10.1038/tp.2013.79

Qiu, A., Shen, M., Buss, C., Chong, Y.-S., Kwek, K., Saw, S.-M., Gluckman, P.D., Wadhwa, P.D., Entringer, S., Styner, M., Karnani, N., Heim, C.M., O'Donnell, K.J., Holbrook, J.D., Fortier, M. V, Meaney, M.J., the GUSTO study group, the G. study, 2017. Effects of Antenatal Maternal Depressive Symptoms and Socio-Economic Status on Neonatal Brain Development are Modulated by Genetic Risk. Cereb. Cortex 27, 3080–3092. https://doi.org/10.1093/cercor/bhx065

Rajagopalan, V., Scott, J., Habas, P.A., Kim, K., Corbett-Detig, J., Rousseau, F., Barkovich, A.J., Glenn, O.A., Studholme, C., 2011. Local tissue growth patterns underlying normal fetal human brain gyrification quantified in utero. J. Neurosci. 31, 2878–2887. https://doi.org/10.1523/JNEUROSCI.5458-10.2011

Rajmohan, V., Mohandas, E., 2007. The limbic system. Indian J. Psychiatry 49, 132–139. https://doi.org/10.4103/0019-5545.33264

Rakic, P., 1995. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci. 18, 383–388.

Rasmussen, J.M., Graham, A.M., Entringer, S., Gilmore, J.H., Styner, M., Fair, D.A., Wadhwa, P.D., Buss, C., 2019. Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. Neuroimage 185, 825–835. https://doi.org/10.1016/j.neuroimage.2018.04.020

Reiss, A., Abrams, M., Singer, H., Ross, J., Denckla MB, 1996. Brain Development, Gender and IQ in Children. A Volumetric Imaging Study - PubMed. Brain. 119, 1763–1774. https://doi.org/10.1093/brain/119.5.1763

Remer, J., Croteau-Chonka, E., Dean, D.C., D'Arpino, S., Dirks, H., Whiley, D., Deoni, S.C.L., 2017. Quantifying cortical development in typically developing toddlers and young children, 1–6 years of age. Neuroimage 153, 246–261. https://doi.org/10.1016/j.neuroimage.2017.04.010

Rifkin-Graboi, A., Bai, J., Chen, H., Hameed, W.B., Sim, L., Tint, M., Leutscher-Broekman, B., Chong, Y.S., Gluckman, P., Fortier, M., Meaney, M., Qiu, A., 2013. Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. Biol. Psychiatry 74, 837–844. https://doi.org/10.1016/j.biopsych.2013.06.019

Riis, J.L., Granger, D.A., Minkovitz, C.S., Bandeen-Roche, K., DiPietro, J.A., Johnson, S.B., 2016. Maternal distress and child neuroendocrine and immune regulation. Soc. Sci. Med. 151, 206–214. https://doi.org/10.1016/j.socscimed.2015.12.043

Robertson, E., Grace, S., Wallington, T., Stewart, D.E., 2004. Antenatal risk factors for postpartum depression: A synthesis of recent literature. Gen. Hosp. Psychiatry 26, 289–295. https://doi.org/10.1016/j.genhosppsych.2004.02.006

Rooks, V.J., Eaton, J.P., Ruess, L., Petermann, G.W., Keck-Wherley, J., Pedersen, R.C., 2008. Prevalence and Evolution of Intracranial Hemorrhage in Asymptomatic Term Infants. Am. J. Neuroradiol. 29, 1082–1089. https://doi.org/10.3174/ajnr.A1004

Roozenaal, B., McEwen, B.S., Chattarji, S., 2009. Stress, memory and the amygdala. Nat. Rev. 10, 423–433. https://doi.org/https://doi-org.ezproxy.utu.fi/10.1038/nrn2651

Rubertsson, C., Börjesson, K., Berglund, A., Josefsson, A., Sydsjö, G., 2011. The Swedish validation of Edinburgh Postnatal Depression Scale (EPDS) during pregnancy. Nord. J. Psychiatry 65, 414–418. https://doi.org/10.3109/08039488.2011.590606

Rubertsson, C., Hellström, J., Cross, M., Sydsjö, G., 2014. Anxiety in early pregnancy: prevalence and contributing factors. Arch. Womens. Ment. Health 17, 221–228. https://doi.org/10.1007/s00737-013-0409-0

Ruigrok, A.N.V., Salimi-Khorshidi, G., Lai, M.-C., Baron-Cohen, S., Lombardo, M. V., Tait, R.J., Suckling, J., 2014. A meta-analysis of sex differences in human brain structure. Neurosci. Biobehav. Rev. 39, 34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004

Salm, A.K., Pavelko, M., Krouse, E.M., Webster, W., Kraszpulski, M., Birkle, D.L., 2004. Lateral amygdaloid nucleus expansion in adult rats is associated with exposure to prenatal stress. Dev. Brain Res. 148, 159–167. https://doi.org/10.1016/j.devbrainres.2003.11.005

Sandberg, D.I., Lamberti-Pasculli, M., Drake, J.M., Humphreys, R.P., Rutka, J.T., 2001. Spontaneous Intraparenchymal Hemorrhage in Full-term Neonates. Neurosurgery 48, 1042–1049. https://doi.org/10.1097/00006123-200105000-00015

Sandman, C., Davis, E., Buss, C., Glynn, L., 2012. Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. Neuroendocrinology 95, 7–21. https://doi.org/10.1159/000327017

Sandman, C.A., Buss, C., Head, K., Davis, E.P., 2015. Fetal Exposure to Maternal Depressive Symptoms Is Associated With Cortical Thickness in Late Childhood. Biol. Psychiatry 77, 324–334. https://doi.org/10.1016/j.biopsych.2014.06.025

Sandman, C.A., Curran, M.M., Davis, E.P., Glynn, L.M., Head, K., Baram, T.Z., 2018. Cortical thinning and neuropsychiatric outcomes in children exposed to prenatal adversity: A role for placental CRH? Am. J. Psychiatry 175, 471–479. https://doi.org/10.1176/appi.ajp.2017.16121433

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions*. Endocr. Rev. 21, 55–89. https://doi.org/10.1210/edrv.21.1.0389

Schmitz, C., Rhodes, M.E., Bludau, M., Kaplan, S., Ong, P., Ueffing, I., Vehoff, J., Korr, H., Frye, C.A., 2002. Depression: Reduced number of granule cells in the hippocampus of female, but not male, rats due to prenatal restraint stress. Mol. Psychiatry 7, 810–813. https://doi.org/10.1038/sj.mp.4001118

Schumann, C.M., Barnes, C.C., Lord, C., Courchesne, E., 2009. Amygdala Enlargement in Toddlers with Autism Related to Severity of Social and Communication Impairments. Biol. Psychiatry 66, 942–949. https://doi.org/10.1016/j.biopsych.2009.07.007

Schumann, C.M., Bauman, M.D., Amaral, D.G., 2011. Abnormal structure or function of the amygdala is a common component of neurodevelopmental disorders. Neuropsychologia 49, 745–759. https://doi.org/10.1016/j.neuropsychologia.2010.09.028

Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., Lotspeich, L.J., Kwon, H., Buonocore, M.H., Lammers, C.R., Reiss, A.L., Amaral, D.G., 2004. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J. Neurosci. 24, 6392–6401. https://doi.org/10.1523/JNEUROSCI.1297-04.2004

Setzer, M., Ulfig, N., 1999. Differential expression of calbindin and calretinin in the human fetal amygdala. Microsc. Res. Tech. 46, 1–17. https://doi.org/10.1002/(SICI)1097-0029(19990701)46:1<1::AID-JEMT1>3.0.CO;2-P

Shaw, P., Kabani, N.J., Lerch, J.P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., Giedd, J.N., Wise, S.P., 2008. Neurodevelopmental trajectories of the human cerebral cortex. J. Neurosci. 28, 3586–3594. https://doi.org/10.1523/JNEUROSCI.5309-07.2008

Sheline, Y.I., Gado, M.H., Price, J.L., 1998. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 9, 2023–2028.

Simonson, C., Barlow, P., Dehennin, N., Sphel, M., Toppet, V., Murillo, D., Rozenberg, S., 2007. Neonatal Complications of Vacuum-Assisted Delivery. Obstet. Gynecol. 109, 626–633. https://doi.org/10.1097/01.AOG.0000255981.86303.2b

Sinesi, A., Maxwell, M., O'Carroll, R., Cheyne, H., 2019. Anxiety scales used in pregnancy: systematic review. BJPsych Open 5, e5. https://doi.org/10.1192/bjo.2018.75

Sirgiovanni, I., Avignone, S., Groppo, M., Bassi, L., Passera, S., Schiavolin, P., Lista, G., Cinnante, C., Triulzi, F., Fumagalli, M., Mosca, F., 2014. Intracranial haemorrhage: an incidental finding at magnetic resonance imaging in a cohort of late preterm and term infants. Pediatr. Radiol. 44, 289–296. https://doi.org/10.1007/s00247-013-2826-7

Sowell, E.R., Trauner, D.A., Gamst, A., Jernigan, T.L., 2007. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev. Med. Child Neurol. 44, 4–16. https://doi.org/10.1111/j.1469-8749.2002.tb00253.x

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. Manual for the State-Trait Anxiety Inventory.

Spitzer, R.L., Kroenke, K., Williams, J.B.W., 1999. Validation and utility of a self-report version of PRIME-MD: The PHQ Primary Care Study. J. Am. Med. Assoc. 282, 1737–1744. https://doi.org/10.1001/jama.282.18.1737

Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch. Intern. Med. 166, 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

Spitzer, R.L., Williams, J.B.W., Kroenke, K., Hornyak, R., McMurray, J., 2000. Validity and utility of the PRIME-MD Patient Health Questionnaire in assessment of 3000 obstetric-gynecologic patients: The PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. Am. J. Obstet. Gynecol. 183, 759–769. https://doi.org/10.1067/mob.2000.106580

Squier, W., Mack, J., 2009. The neuropathology of infant subdural haemorrhage. Forensic Sci. Int. 187, 6–13. https://doi.org/10.1016/j.forsciint.2009.02.005

Stekhoven, D.J., Buhlmann, P., 2012. MissForest--non-parametric missing value imputation for mixed-type data. Bioinformatics 28, 112–118. https://doi.org/10.1093/bioinformatics/btr597

Stephens, M.A.C., Wand, G., 2012. Stress and the HPA axis: Role of glucocorticoids in alcohol dependence. Alcohol Res. Curr. Rev. 34, 468–483.

Stiles, J., Jernigan, T.L., 2010. The Basics of Brain Development. Neuropsychol. Rev. 20, 327–348. https://doi.org/10.1007/s11065-010-9148-4

Sutter-Dallay, A.L., Cosnefroy, O., Glatigny-Dallay, E., Verdoux, H., Rascle, N., 2012. Evolution of perinatal depressive symptoms from pregnancy to two years postpartum in a low-risk sample: The MATQUID cohort. J. Affect. Disord. 139, 23–29. https://doi.org/10.1016/j.jad.2011.08.018

Swanson, L.W., 2006. The Amygdala and Its Place in the Cerebral Hemisphere. Ann. N. Y. Acad. Sci. 985, 174–184. https://doi.org/10.1111/j.1749-6632.2003.tb07081.x

Tanaka, C., Matsui, M., Uematsu, A., Noguchi, K., Miyawaki, T., 2012. Developmental Trajectories of the Fronto-Temporal Lobes from Infancy to Early Adulthood in Healthy Individuals. Dev. Neurosci. 34, 477–487. https://doi.org/10.1159/000345152

Tavani, F., Zimmerman, R. a, Clancy, R.R., Licht, D.J., Mahle, W.T., 2003. Incidental intracranial hemorrhage after uncomplicated birth: MRI before and after neonatal heart surgery. Neuroradiology 45, 253–258. https://doi.org/10.1007/s00234-003-0946-8

Teicher, M., Tomoda, A., Andersen, S., 2006. Neurobiological consequences of early stress and childhood maltreatment: are results from human and animal studies comparable? Ann. N. Y. Acad. Sci. 1071, 313–323. https://doi.org/1071/1/313 [pii]

Teixeira, C., Figueiredo, B., Conde, A., Pacheco, A., Costa, R., 2009. Anxiety and depression during pregnancy in women and men. J. Affect. Disord. 119, 142–148. https://doi.org/10.1016/j.jad.2009.03.005

Tendais, I., Costa, R., Conde, A., Figueiredo, B., 2014. Screening for Depression and Anxiety Disorders from Pregnancy to Postpartum with the EPDS and STAI. Span. J. Psychol. 17, E7. https://doi.org/10.1017/sjp.2014.7

Thompson, D.K., Wood, S.J., Doyle, L.W., Warfield, S.K., Egan, G.F., Inder, T.E., 2009. MR-determined hippocampal asymmetry in full-term and preterm neonates. Hippocampus 19, 118–123. https://doi.org/10.1002/hipo.20492

Thomson, M., 2013. The physiological roles of placental corticotropin releasing hormone in pregnancy and childbirth. J. Physiol. Biochem. 69, 559–573. https://doi.org/10.1007/s13105-012-0227-2

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W.V., Uitterlinden, A.G., White, T.J.H., Bakermans-Kranenburg, M.J., Hofman, A., Van IJzendoorn, M.H., Hudziak, J.J., Verhulst, F.C., 2012. The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. J. Am. Acad. Child Adolesc. Psychiatry 51, 1119-1135.e7. https://doi.org/10.1016/j.jaac.2012.08.021

Tollenaar, M.S., Beijers, R., Jansen, J., Riksen-Walraven, J.M.A., de Weerth, C., 2011. Maternal prenatal stress and cortisol reactivity to stressors in human infants. Stress 14, 53–65. https://doi.org/10.3109/10253890.2010.499485

Torres-Espínola, F.J., Berglund, S.K., García, S., Pérez-García, M., Catena, A., Rueda, R., Sáez, J.A., Campoy, C., 2018. Visual evoked potentials in offspring born to mothers with overweight, obesity and gestational diabetes. PLoS One 13, e0203754. https://doi.org/10.1371/journal.pone.0203754

Towner, D., Castro, M.A., Eby-Wilkens, E., Gilbert, W.M., 1999. Effect of Mode of Delivery in Nulliparous Women on Neonatal Intracranial Injury. N. Engl. J. Med. 341, 1709–1714. https://doi.org/10.1056/NEJM199912023412301

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., Nishijo, H., 2012. Developmental Trajectories of Amygdala and Hippocampus from Infancy to Early Adulthood in Healthy Individuals. PLoS One 7, e46970. https://doi.org/10.1371/journal.pone.0046970

Ulfig, N., Setzer, M., Bohl, J., 2003. Ontogeny of the human amygdala. Ann. N. Y. Acad. Sci. 985, 22–33. https://doi.org/10.1111/j.1749-6632.2003.tb07068.x

Ulfig, N., Setzer, M., Bohl, J., 1999. Distribution of GAP-43-immunoreactive structures in the human fetal amygdala. Eur. J. Histochem. 43, 19–28.

Uno, H., Eisele, S., Sakai, A., Shelton, S., Baker, E., DeJesus, O., Holden, J., 1994. Neurotoxicity of glucocorticoids in the primate brain. Horm. Behav. 28, 336–348. https://doi.org/10.1006/hbeh.1994.1030

Utsunomiya, H., Takano, K., Okazaki, M., Mitsudome, A., 1999. Development of the temporal lobe in infants and children: analysis by MR-based volumetry. AJNR AM J Neuroradiol. 20, 717–723.

Van Batenburg-Eddes, T., Brion, M.J., Henrichs, J., Jaddoe, V.W.V., Hofman, A., Verhulst, F.C., Lawlor, D.A., Davey Smith, G., Tiemeier, H., 2013. Parental depressive and anxiety symptoms during pregnancy and attention problems in children: A cross-cohort consistency study. J. Child Psychol. Psychiatry Allied Discip. 54, 591–600. https://doi.org/10.1111/jcpp.12023

Van den Bergh, B.R.H., Dahnke, R., Mennes, M., 2018. Prenatal stress and the developing brain: Risks for neurodevelopmental disorders. Dev. Psychopathol. 30, 743–762. https://doi.org/10.1017/S0954579418000342

Van den Bergh, B.R.H., Marcoen, A., 2004. High Antenatal Maternal Anxiety Is Related to ADHD Symptoms, Externalizing Problems, and Anxiety in 8- and 9-Year-Olds. Child Dev. 75, 1085–1097. https://doi.org/10.1111/j.1467-8624.2004.00727.x

Van Den Bergh, B.R.H., Van Calster, B., Smits, T., Van Huffel, S., Lagae, L., 2008. Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. Neuropsychopharmacology 33, 536–545. https://doi.org/10.1038/sj.npp.1301450

Van den Heuvel, M.I., Donkers, F.C.L., Winkler, I., Otte, R.A., Van den Bergh, B.R.H., 2014. Maternal mindfulness and anxiety during pregnancy affect infants' neural responses to sounds. Soc. Cogn. Affect. Neurosci. 453–460. https://doi.org/10.1093/scan/nsu075

van Soelen, I.L.C., Brouwer, R.M., Peper, J.S., van Beijsterveldt, T.C.E.M., van Leeuwen, M., de Vries, L.S., Kahn, R.S., Hulshoff Pol, H.E., Boomsma, D.I., 2010. Effects of Gestational Age and Birth Weight on Brain Volumes in Healthy 9 Year-Old Children. J. Pediatr. 156, 896–901. https://doi.org/10.1016/j.jpeds.2009.12.052

Vänskä, M., Punamäki, R.-L., Tolvanen, A., Lindblom, J., Flykt, M., Unkila-Kallio, L., Tiitinen, A., Repokari, L., Sinkkonen, J., Tulppala, M., 2011. Maternal pre- and postnatal mental health trajectories and child mental health and development. Int. J. Behav. Dev. 35, 517–531. https://doi.org/10.1177/0165025411417505

Vázquez, M.B., Míguez, M.C., 2019. Validation of the Edinburgh postnatal depression scale as a screening tool for depression in Spanish pregnant women. J. Affect. Disord. 246, 515–521. https://doi.org/10.1016/j.jad.2018.12.075

Velders, F.P., Dieleman, G., Cents, R.A.M., Bakermans-Kranenburg, M.J., Jaddoe, V.W.V., Hofman, A., Van Ijzendoorn, M.H., Verhulst, F.C., Tiemeier, H., 2012. Variation in the glucocorticoid receptor gene at rs41423247 moderates the effect of prenatal maternal psychological symptoms on child cortisol reactivity and behavior. Neuropsychopharmacology 37, 2541–2549. https://doi.org/10.1038/npp.2012.118

Videbech, P., 2004. Hippocampal Volume and Depression: A Meta-Analysis of MRI Studies. Am. J. Psychiatry 161, 1957–1966. https://doi.org/10.1176/appi.ajp.161.11.1957

Visser, M., Müller, D.M.J., van Duijn, R.J.M., Smits, M., Verburg, N., Hendriks, E.J., Nabuurs, R.J.A., Bot, J.C.J., Eijgelaar, R.S., Witte, M., van Herk, M.B., Barkhof, F., de Witt Hamer, P.C., de Munck, J.C., 2019. Inter-rater agreement in glioma segmentations on longitudinal MRI. NeuroImage Clin. 22, 101727. https://doi.org/10.1016/j.nicl.2019.101727

Vuori, E., Gissler, M., n.d. Perinatal statistics: parturients, deliveries and newborns 2015.

Waisbren, S.E., 2003. Effect of Expanded Newborn Screening for Biochemical Genetic Disorders on Child Outcomes and Parental Stress. JAMA 290, 2564. https://doi.org/10.1001/jama.290.19.2564

Wang, C., Shen, M., Guillaume, B., Chong, Y.S., Chen, H., Fortier, M. V., Meaney, M.J., Qiu, A., 2018. FKBP5 Moderates the Association between Antenatal Maternal Depressive Symptoms and Neonatal Brain Morphology. Neuropsychopharmacology 43, 564–570. https://doi.org/10.1038/npp.2017.232

Ward Jr, J.H., 1968. Hierarchical grouping to optimize an objective function. Journal of the American statistical association. J. Am. Stat. Assoc. 58, 236–244.

Wei, L., Hao, J., Lacher, R.K., Abbott, T., Chung, L., Colangelo, C.M., Kaffman, A., 2015. Early-Life Stress Perturbs Key Cellular Programs in the Developing Mouse Hippocampus. Dev. Neurosci. 37, 476–488. https://doi.org/10.1159/000430861

Weier, K., Fonov, V., Lavoie, K., Doyon, J., Collins, D.L., 2014. Rapid automatic segmentation of the human cerebellum and its lobules (RASCAL)-Implementation and application of the patch-based label-fusion technique with a template library to segment the human cerebellum. Hum. Brain Mapp. 35, 5026–5039. https://doi.org/10.1002/hbm.22529

Weinstock, M., 2011. Sex-dependent changes induced by prenatal stress in cortical and hippocampal morphology and behaviour in rats: An update. Stress 14, 604–613. https://doi.org/10.3109/10253890.2011.588294

Weinstock, M., 2008. The long-term behavioural consequences of prenatal stress. Neurosci. Biobehav. Rev. 32, 1073–1086. https://doi.org/10.1016/j.neubiorev.2008.03.002

Weinstock, M., 2005. The potential influence of maternal stress hormones on development and mental health of the offspring. Brain. Behav. Immun. 19, 296–308. https://doi.org/10.1016/j.bbi.2004.09.006

Welberg, L.A.M., Seckl, J.R., Holmes, M.C., 2000. Inhibition of 11β-hydroxysteroid dehydrogenase, the foetoplacental barrier to maternal glucocorticoids, permanently programs amygdala GR mRNA expression and anxiety-like behaviour in the offspring. Eur. J. Neurosci. 12, 1047–1054. https://doi.org/10.1046/j.1460-9568.2000.00958.x

Wen, D.J., Poh, J.S., Ni, S.N., Chong, Y.-S., Chen, H., Kwek, K., Shek, L.P., Gluckman, P.D., Fortier, M. V, Meaney, M.J., Qiu, A., 2017. Influences of prenatal and postnatal maternal depression on amygdala volume and microstructure in young children. Transl. Psychiatry 7, e1103–e1103. https://doi.org/10.1038/tp.2017.74

Whitby, E.H., Griffiths, P.D., Rutter, S., Smith, M.F., Sprigg, A., Ohadike, P., Davies, N.P., Rigby, A.S., Paley, P.M.N., 2004. Frequency and natural history of subdural haemorrhages in babies and relation to obstetric factors. Lancet 363, 846–851. https://doi.org/10.1016/S0140-6736(04)15730-9

Whitehead, M.T., Oh, C.C., Choudhri, A.F., 2013. Incidental pineal cysts in children who undergo 3-T MRI. Pediatr. Radiol. 43, 1577–1583. https://doi.org/10.1007/s00247-013-2742-x

Woon, F.L., Hedges, D.W., 2008. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: A meta-analysis. Hippocampus 18, 729–736. https://doi.org/10.1002/hipo.20437

Wu, Y., Lu, Y.-C., Jacobs, M., Pradhan, S., Kapse, K., Zhao, L., Niforatos-Andescavage, N., Vezina, G., du Plessis, A.J., Limperopoulos, C., 2020. Association of Prenatal Maternal Psychological Distress With Fetal Brain Growth, Metabolism, and Cortical Maturation. JAMA Netw. Open 3, e1919940. https://doi.org/10.1001/jamanetworkopen.2019.19940

Xydis, V., Drougia, A., Giapros, V., Argyropoulou, M., Andronikou, S., 2013. Brain growth in preterm infants is affected by the degree of growth restriction at birth. J. Matern. Neonatal Med. 26, 673–679. https://doi.org/10.3109/14767058.2012.746300

Yang, R., Mozhui, K., Karlsson, R.M., Cameron, H., Williams, R., Holmes, A., 2008. Variation in mouse basolateral amygdala volume is associated with differences in stress reactivity and fear learning. Neuropsychopharmacology 33, 2595–2604. https://doi.org/10.1038/sj.npp.1301665

Zagron, G., Weinstock, M., 2006. Maternal adrenal hormone secretion mediates behavioural alterations induced by prenatal stress in male and female rats. Behav. Brain Res. 175, 323–328. https://doi.org/10.1016/j.bbr.2006.09.003

Zaretsky, M. V., Alexander, J.M., Byrd, W., Bawdon, R.E., 2004. Transfer of inflammatory cytokines across the placenta. Obstet. Gynecol. 103, 546–550. https://doi.org/10.1097/01.AOG.0000114980.40445.83

Zhang, J.-M., An, J., 2007. Cytokines, Inflammation, and Pain. Int. Anesthesiol. Clin. 45, 27–37. https://doi.org/10.1097/AIA.0b013e318034194e

Zigmond, A.S., Snaith, R.P., 1983. The Hospital Anxiety and Depression Scale. Acta Psychiatr. Scand. 67, 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zohar, I., Weinstock, M., 2011. Differential Effect of Prenatal Stress on the Expression of Cortiocotrophin-Releasing Hormone and its Receptors in the Hypothalamus and Amygdala in Male and Female Rats. J. Neuroendocrinol. 23, 320–328. https://doi.org/10.1111/j.1365-2826.2011.02117.x

UNIVERSITY OF TURKU

Painosalama Oy, Turku, Finland 2020

ISBN 978-951-29-8263-9 (PRINT)
ISBN 978-951-29-8264-6 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)