

Institut für Medizinische Psychologie, Charité Universitätsmedizin
Sahand Sharifzadeh
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The influence of maternal depression during pregnancy on neonatal fiber tract integrity

Author: Sahand Sharifzadeh

Supervisor: Gustav Nilsson
Co-supervisor: Claudia Buß



**Karolinska
Institutet**

Abstract

Effekten av depression under graviditeten på neonatal nervfiberintegritet

Bakgrund: Depression hos modern är en vanlig komplikation och har korrelerats till ogynnsam utveckling av både hjärnstrukturer och beteende gällande psykologiska aspekter hos barnet. Bakomliggande mekanismer för dessa fenomen är ännu oklara. För att bidra till kunskapen om detta vore det intressant att undersöka hur depression under graviditeten påverkar neonatala hjärnstrukturer som är essentiella för optimal mental hälsa. Två sådana strukturer är fornix och fasciculus uncinatus (FU). *Syfte:* Att utforska effekten av depression under graviditeten på den mikrostrukturella integriteten av vit hjärnsubstans fibrerna fornix och FU hos nyfödda. *Material och Metoder:* 87 moder-spädbarnpar inkluderades. Inklusionskriterier var gravida kvinnor i början av första trimestern och som födde utan obstetriska komplikationer. Exklusionskriterier var bruk av psykofarmaka, kortikosteroider, tobak eller andra droger, gestationsålder <34 veckor vid födseln, samt kongenitala, genetiska eller andra större neurologiska störningar vid födseln. Depressiva symtom mättes med ett standard frågeformulär. Neonatal vitsubstansmognad mättes med diffusionstensoravbildning (DTI). Förhållandet mellan dessa parametrar undersöktes med variansanalys. *Resultat:* Prenatal moderlig depression under tredje trimestern korrelerade med högre fraktionell anisotropi i 12 konsekutiva punkter i högra fasciculus uncinatus hos pojkar ($p = 0,0428$). Inga andra signifikanta ($p < 0,05$) korrelationer upptäcktes i resterande kön, nervfibrer eller trimestrar. *Slutsatser:* Depression under graviditeten påverkar mognaden av det manliga fostrets hjärna. Innebörden av denna effekt för barnets psykiska hälsa bör undersökas i longitudinella studier.

The influence of maternal depression during pregnancy on neonatal fiber tract integrity

Introduction: Prenatal maternal depression is a common complication and has been associated with poor mental health outcomes and altered brain structure in the child. Neurobiological mechanisms mediating these outcomes remain unclear to date. To yield more knowledge surrounding this, it would be interesting to examine how prenatal maternal depression may impact neonatal brain structures that play key roles in optimal mental health. Two such structures are the fornix and the uncinate fasciculus (UF). *Aim:* To explore the influence of maternal depression during pregnancy on microstructural integrity of the white matter tracts of the fornix and uncinate fasciculus in newborns. *Materials and Methods:* 87 mother-infant pairs were included. Inclusion criteria were pregnant women in the first trimester and who after birth were deemed obstetrically free of complications. Exclusion criteria were maternal use of psychotropic medicines, corticosteroids, or tobacco or other drugs, gestational age at birth <34 weeks, congenital, genetic or other major neurological disorders at birth. Depressive symptoms were measured with a standard questionnaire. Neonatal white matter maturation was measured with diffusion tensor imaging. The relationship between these parameters was analyzed with ANOVA models. *Results:* Prenatal maternal depression during the third trimester was positively correlated with higher fractional anisotropy in 12 consecutive points along the tract of the right UF in boys ($p=0.0428$). No other significant ($p < 0.05$) associations were found with sex, tracts or trimesters. *Conclusions:* Maternal depression affects the maturation of the fetal male brain. The consequence of this for child affective problems should be examined in longitudinal studies.

Keywords: Prenatal maternal depression, developmental programming, diffusion tensor imaging, uncinate fasciculus, fornix.

Introduction

Developmental Programming of Health and Disease

In accordance with the theory of evolution, the development of any living organism is a product of its genes and environment (1). The growth of the human brain can be regarded in the same manner, meaning that circumstances during development decide the trajectory of the process (2). Although it takes many years for the brain to develop fully, several structures are formed at an early stage. An example of this is the formation of all major nuclei inside the amygdala, a brain region essential for emotion processing and regulation, at 15 weeks of gestation (3). During gestation, the brain is highly plastic. This is due to the very high rate of development, meaning that many parts are molded per time unit (4). In early gestation, genes assisting cell proliferation and neuronal differentiation are expressed more than in any other time during prenatal or postnatal life (3). Also contributing to plasticity is the continuous interaction with environmental factors. These factors, in conjunction with the limited regulation of passage that the fetal blood-brain barrier offers, make the fetal stage the time when brain development is most vulnerable to the surrounding milieu (4).

This leaves room for the environment to contribute to the developmental trajectory with increased risks for adverse health outcomes. And since the impact of environmental factors depends on the grade of plasticity (4), and plasticity declines with age (5), the intrauterine period is when they can have profound effects on the neurodevelopment of the infant. Such effects can result in long term and permanent consequences concerning the risk for neuro-psychiatric disorders (4).

Maternal Depression During Pregnancy

Prevalence

The quality of maternal care during upbringing is associated with the development of the child's overall health. Maternal depression is a condition that can interfere with maternal care. Studies show that infants of mothers who experience depression post-partum have less favorable development regarding emotion regulation (6), cognition, behavior, motor skills and general mental health (7). However, even more frequent than post-partum depression in the mother is

depression during pregnancy, which is in fact one of the most common prenatal problems with several studies reporting a prevalence of 10-51% (7-13). Furthermore, recent research suggests that this condition has a greater impact on child behavioral outcomes than other psychiatric complications around pregnancy, such as prenatal anxiety or post-partum depression (14).

Effects of Prenatal Maternal Depression on Offspring Mental Health and Cognition

Looking at depression during pregnancy, there are a vast amount of studies revealing various behavioral and health outcomes in the offspring. The condition has been shown to have negative effects on the development of the child in terms of behavior, emotions and cognition (14). Available evidence shows increased risks of both internalizing and externalizing disorders, psychopathology, attention and behavior problems (5). It has also been linked to decreased IQ in a study sample of $n = 5029$ (7) and decreased verbal IQ in a study of $n = 3298$ mother-infant pairs. The latter study also showed a strong link to increased internalizing difficulties (14). Emotional states observed as early as infancy have been associated with maternal prenatal depression, such as difficult temperament (15) and heightened irritability (16). A recent study containing a large sample, $n = 3925$, established a strong link between prenatal depression in the mother and depression in the offspring in adolescent years (17). Another study showed that 52% of children to mothers with prenatal depression were diagnosed with depressive or conduct disorders at ages 11 and 16 (18).

Effects of Prenatal Maternal Depression on Offspring Brain Structures

Examining possible mechanisms by which maternal depression influences offspring development, researchers have focused on structural alterations in the brain. Sandman and colleagues reported an association between depressive symptoms in a pregnant population and thinning of the cortex in the children, $n = 81$, at age 6-9 (7). Maternal depression at 25 weeks of gestation was most strongly linked, with cortical thinning was observed in 19% of the entire brain and 24% of the frontal cortex. The cortical thickness measured in these children study was further shown to correlate, in terms of levels and regions, with such represented by individuals with for example previous history of depression, current symptom severity, exposure to maternal depression during upbringing, and familial risk for depression in currently healthy persons.

Additionally, mediation analyses showed that cortical thinning was a viable mediator between maternal prenatal depression and offspring externalizing problems (7).

In a study from 2013, Rifkin-Graboi and colleagues argued that for the sake of avoiding post-natal confounding elements, including all aspects of parental care, it is essential to acquire neuroimaging data in the earliest possible neonatal stage (15). This is favorable as it helps to correctly determine the timing of any relevant changes, to establish when preventive interventions are to be optimally applied (14). The study, $n = 157$, found a relationship between prenatal maternal depression and less microstructural development of the right amygdala in the children. This is a structure that is strongly involved in vulnerability for depression, and stress regulation (15).

Prenatal Maternal Depression and Alterations in the Intrauterine Environment

To further examine the underlying mechanism through which prenatal maternal depression contributes to affective disorders in the offspring, researchers have hypothesized that the condition exerts certain physiological changes in the intrauterine environment, and that such changes in turn may have an impact on fetal affective development (3).

A common model suggests prolonged or elevated cortisol production above what is considered normal during pregnancy as a mediator of the effects of prenatal maternal depression related to offspring development of affective disorders (3, 7, 14, 15). Such heightened levels of cortisol have been recorded in mothers with prenatal depression (13). High prenatal maternal cortisol levels have been associated with worse mental and motor development, social anxiety, internalizing behavior, and neuroendocrine dysregulation in the child (4). Prenatal maternal cortisol has also been established as a significant predictor for preterm delivery and low birth weight (19), which are conditions that leave the offspring highly vulnerable for various health issues that can have long-term or permanent effects (20).

Other studies have examined the possible role of placental CRH as a mediator for the effects of maternal depression during pregnancy on child mental health. In a study sample of 800 pregnant women, Rich-Edwards and colleagues found higher than normal CRH levels in mothers who

reported depression symptoms (21). Elevated levels of placental CRH, for instance caused by maternal stress or infection, have been associated with preterm child birth and subsequent low birth weight (20). Evidence also supports that high levels of CRH contribute to delayed habituation by the fetus, and is associated with having harming effects on infant temperament (22).

Other biological mediators that have been found to be altered in the context of prenatal depression are inflammatory agents (13, 23). States of inflammation are known to be strongly correlated with depression (13, 24). The inflammation related to depression is most frequently characterized by increased levels of pro-inflammatory cytokines and inflammatory markers, including interleukin-6 (IL-6) and C-reactive protein respectively (25). Evidence has shown that excess circulating levels of maternal IL-6 and CRP can impact the fetal brain development negatively (4, 23).

White Matter Tracts and Affective Disorders

White Matter Myelination

The brain consists of two types of tissue, gray matter (GM) and white matter (WM). Brain development relies on a coordinated maturation of GM regions such as the cerebral cortex and central nuclei as well as the growth and myelination of WM connections between different brain regions (26, 27). The development of such connections is an intricate process, starting in early gestation and ending in adulthood (28-31). A critical component of WM maturation is myelination. Starting in the late fetal period and continuing postnatally, myelination is the process by which parts of neuronal axons are encapsulated with myelin. Myelin is a lipid-layered type of tissue that permits rapid, synchronized (28, 29) and optimized communication between functional brain systems (27). Possessing such a role, studies have associated WM myelination with the development of high-order cognitive functions (26, 28, 29). Thus, abnormalities in WM myelination is a key factor in neurodevelopmental deficiencies, including a variety of affective disorders (27, 32).

The Fornix and Uncinate Fasciculus

As WM fibers make out paths of communication between different brain regions (26, 27), healthy maturation of such tracts is essential to adequate operation of the brain functions they are associated with (26-29). Two specific WM tracts that are reported to be altered in affective disorders are the fornix and uncinata fasciculus (UF) (30, 33-36). To date, neither of which have been researched as structures in the offspring affected by prenatal maternal depression.

The fornix is a connective structure in Papez circuit of the limbic system and consists of a right and left part residing in each hemisphere of the brain. The circuit is the largest efferent neuropathway from the hippocampus, and is essential for the ability of the limbic system to manage factual details of a memory. As another part of the limbic system adds emotional value to the memory, the integrated output from these structures affects psychological behavior (36). In accordance with being involved in behavior regulating structures, the fornix has been shown to be altered in affective disorders such as trait anxiety (33), Alzheimer's disease, multiple sclerosis, schizophrenia, and other psychiatric or neurodegenerative disorders (31). The fornix is also implicated in top-down emotion regulation carried out by higher cortical structures on lower level systems such as the limbic system (33). This is defined as the process of higher order cognitive structures such as the prefrontal cortex (PFC) exerting inhibitory regulation on lower structures such as those of the limbic system, and is a critical part of human emotion regulation (37).

As top-down control enables an individual to refuse tempting behaviors or automatic responses of lower structures, a lack or deficiency of it may lead to detrimental character traits including strong impulsivity, vulnerability for addiction, high risk behaviors, affective problems, and conduct issues. Defects in such functions have also been associated with numerous neuropsychiatric disorders (37), including internalizing disorders (34).

The specific function of the UF is yet largely unclear and mostly related to the functions of the brain areas that it connects to. The UF connects the perirhinal cortex, parts of the anterior parahippocampal gyrus and the amygdala to the lateral orbitofrontal cortex and the anterior

prefrontal cortex (30). Like the fornix, the UF is also a part of top-down control (34). It plays a key role in this by connecting structures of the limbic system, such as the right and left amygdala, with sub-regions in both sides of the PFC, such as the ventromedial PFC. These are namely regions that participate in top-down regulation (34). Disturbances in the UF are linked with disorders that indicate deficiencies in the limbic system as they affect character, emotion and episodic memory (30). It is further considered as one of the most important WM tracts in the neurological circuitry that forms the basis of emotional empathy in humans. In this aspect, Oishi and colleagues associated lesions in the right UF with reduced performance in an emotional empathy task (35).

Characterization of White Matter Maturation with Diffusion Tensor Imaging

Magnetic resonance imaging (MRI) is a non-invasive technique that produces pictures by detecting signals from protons. In the human body, 90% of protons reside within water molecules (29). As an inherent trait, these water molecules may diffuse freely, but certain patterns arise due to properties of the local surroundings (32). It is especially so when they are located within WM where diffusion occurs in a restricted environment. Structures such as axonal fibers, of which the WM mainly consists, inhibit or allow diffusion in certain directions due to the confines of their cell membranes and the myelin around them. Measuring the direction of water molecule diffusion can thus help reflect an image of WM microstructure. This type of diffusion can be depicted as the movement of ink when added to a tubular structure containing water, in which the diffusion of the ink will be restricted in directions perpendicular to the length of the tube and allowed in longitudinal directions. This allows for an ellipsoid or anisotropic shape of diffusion. This is in contrast to isotropic where movement is equally likely in all directions in a spherical fashion (29, 38). Diffusion tensor imaging (DTI) is an MRI-based imaging technique that uses this phenomenon. Diffusion anisotropy can be measured with DTI. The technique measures values of diffusion from one point, or voxel, in the 3D structure of a WM tract to another. A voxel is a 3D coordinate within the tract, from which parameters of diffusion can be measured. It is analogous to a pixel in a 2D grid, and its size likewise dependent on the resolution of the image. In this way, DTI can be used to reflect geometrical data on WM fibers' properties, such as degree of myelination and organization (32). Parameters measured with DTI, producing such data are fractional anisotropy (FA), radial diffusion (RD), axial

diffusion (AD), and mean diffusivity (MD). FA is a measure of anisotropy, in which a high value indicates the diffusion being confined to mainly one direction. RD and AD measure the rate of diffusion perpendicular to and along the fiber length, respectively; thus, reflecting factors inhibiting motion versus allowing it. MD corresponds to the presence of barriers inhibiting free diffusion, giving a sense of the magnitude of motion, however, not depicting any certain direction (29, 32).

To summarize, it is well known that neural plasticity plays a key role in the development of the brain. Studies have found that the intrauterine time is of high importance and relevance in terms of environmental effects (39). Being one of the most common prenatal complications, maternal depression has been linked to potential negative effects on the offspring health, such as detrimental infant affective development (7). It has been shown that such effects of maternal depression on the offspring health outcomes might be modulated by alterations in certain brain regions related to affective functioning, e.g. the cortex (7) and amygdala (15). These alterations in brain morphology might then, in turn, have implications for subsequent risk of developing neuropsychiatric disorders (3, 4, 40). Recent studies have suggested that early intervention towards lessening the depression of the mother (15) and optimizing the post-natal milieu of the child (4) can help buffer this direction of development.

With these elements in mind, the flexible nature of the fetal brain becomes clear, and that it leaves room for therapy to be designed for positively altering the course of brain maturation. However, no research has so far concluded the precise mechanics through which prenatal depression exerts its influence on infant affective health. This limited knowledge concerning underlying mechanism complicates creating concepts of risk. It can furthermore be viewed as an important gap of knowledge to be filled for the sake of reasoning optimal design and timing of preventive measures. For this matter, it is important to know through which pathways these functional and morphological changes are mediated.

Natural points of foci are then fiber tracts that carry the communication between brain regions involved in emotion regulation. Especially since this connectivity forms a structural basis for affective aspects of human behavior such as defense, motivation, pain (41), and processing of

emotional stimuli (33). The focus ought to be placed on the white matter development of such fiber tracts, since it is essential for their purpose of mediating communication between functional brain areas (26). Outlying the connectivity between brain structures that are essential to emotion regulation, and reported to be altered in affective disorders are fibers of the uncinate fasciculus and the fornix (33). This project will specifically research the influence of maternal depression during pregnancy on the white matter development of the fornix and uncinate fasciculus.

Aims

This study aimed to explore the influence of maternal depression during pregnancy on the development and microstructural integrity of the white matter tracts of the fornix and uncinate fasciculus in newborns.

The study hypothesized that higher values of maternal depression are correlated with less white matter maturity in the fornix and uncinate fasciculus in newborns.

Material and Methods

Design

This project is a part of a prospective, longitudinal, follow-up cohort study that measures and assesses multiple variables pertaining to stress and overall mental health in both mothers and their infants. The aim of it is to test the effects of intrauterine biological stress exposure on brain development in terms of morphology and white matter integrity in neonates and over the first 12 months of life.

Participants

The study population consists of mother-infant pairs. The mothers were recruited during the first trimester of pregnancy through leaflets at the doctors' offices. Included in the study were pregnant women that were deemed as obstetrically free of complications and healthy neonates. Exclusion criteria were birth age less than 34 weeks of completed gestation, unhealthy preterm (<37 weeks) neonates, maternal use of psychotropic medicine, corticosteroids, and or tobacco

and or other drugs, neonates having congenital, genetic and or major neurological disorders at birth.

Maternal Depression During Pregnancy

Maternal mental health was evaluated consecutively with questionnaires of the Center for Epidemiological Studies-Depression scale (CES-D) (42) over the course of gestation. The scale is internationally known as a screening measure for depression and is one of the most frequently used of such tools for adults (43). It is a 20-item self-report questionnaire that asks about symptoms related to depression. The responses are based on frequency, including four numeric alternatives ranging from 0 or “rarely/none of the time” to 3 or “most/all of the time.” The score scale is continuous and ranges between 0 and 60, a higher score implies worse depressive symptomatology (42). Studies have validated internal consistency and test-retest reliability of the CES-D (43). In the current study, surveying occurred sequentially in the first (10-12 weeks of gestation), second (20-22 weeks), and third trimester (30-32 weeks). To account for singular missing items the mean responses were calculated for each time point. Participants with 3 or more missing items were excluded from the analyses. The mean item scores of each mother, ranging from 0 to 3, at each different measure points are used as predictors in this study.

Data Acquisition in Neonates

Magnetic resonance imaging (MRI) data of neonates’ brains was collected during natural sleep on a TIM Trio, Siemens Medical System 3.0T scanner. The technique is commonly used to study white matter development in different stages of brain formation (29, 38). For analyzing the DTI raw data, through which the fiber tract properties are measured, the UNC-Utah NA-MIC DTI framework was applied as described Figure 1. The framework has been designed and quality tested by Verde and colleagues (38). FA values of right and left uncinate fasciculus and fornix of the newborns were used as outcome measures in the current study.

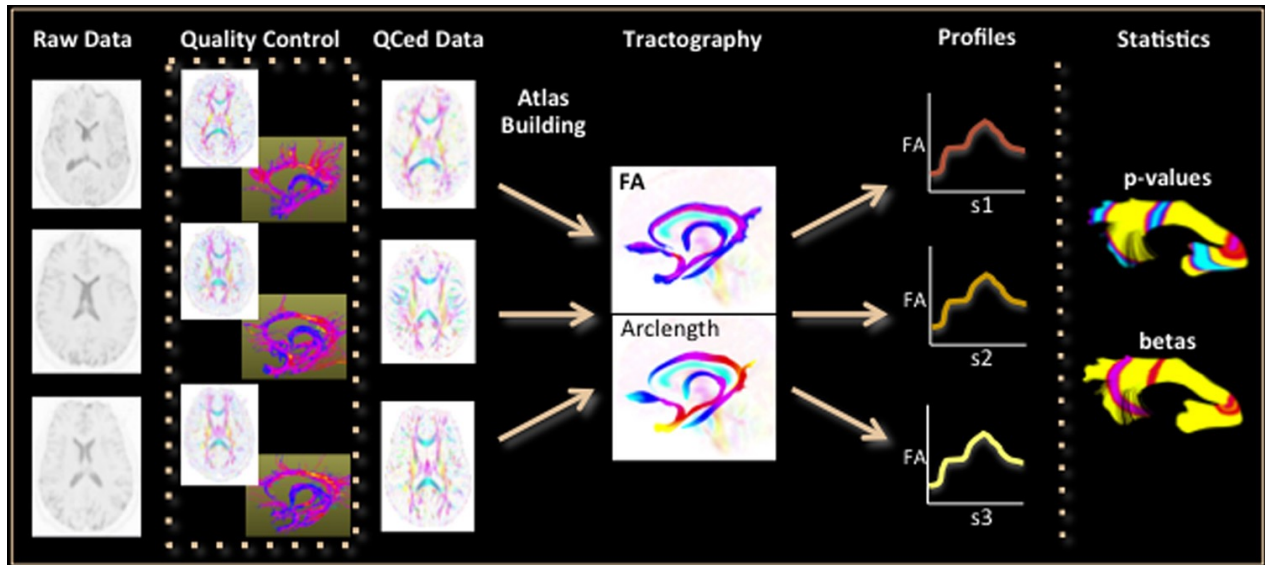


Figure 1 – The UNC-Utah NA-MIC DTI Framework. After rigorous quality control, specific fiber tracts were visualized by tractography. Tracts were analyzed to derive fiber profiles containing values of FA, RD, AD, and MD (38), with FA being the outcome measure in this study. Courtesy of Verde and colleagues (38).

To specifically examine the effect of the prenatal condition on white matter development and to rule out any postnatal influences on brain development, imaging was conducted shortly after birth. Neonates were fed, swaddled and fitted with ear protection to reduce scanner noise. The infants’ heads were fixed with a Vac-Fix immobilization device. Waking and respiration were monitored throughout the scan to ensure the safety and comfort of the neonates.

Other Measures

Information regarding offspring gender, gestational age at birth, age at scan date, household annual income, maternal education and body mass index (BMI) pre-pregnancy were recorded and calculated respectively. Information was gathered from doctor examinations during the pregnancy regarding the eventual existence of obstetrical risk. From data on income and education a continuous variable of socio-economic status (SES) was calculated based on the mean scores of the two variables.

Statistical Analysis

This project used continuous predictor variables consisting of CES-D questionnaire scores as measurement of maternal depression during gestation. Maternal depressive symptom score during each trimester separately as well as the average across pregnancy, were derived using IBM SPSS Statistics version 23. SPSS was also used to calculate means and standard deviations of the study population and β -values of the ANOVA analysis. Outcome measures included neonatal FA of the right and left fornix and uncinate fasciculus based on fiber tracking frameworks.

To test the association between maternal depression during pregnancy and fiber tract integrity in newborns, ANOVA modules were performed using MatLab version R2014a. ANOVA modules were run using CES-D mean scores from each trimester separately and a mean score encompassing all three periods as predicting variables. Each analysis was run three times, while including the full sample, only boys and only girls. All analyses controlled for the continuous variables offspring gestational age at birth, age at scan date, maternal BMI pre-pregnancy and SES, as well as offspring gender and existence of obstetric risk as binary variables. This was done in an attempt to isolate the influence of maternal depression, as the aforementioned factors have all been reported to independently have significant impacts on offspring brain development, including WM maturation, and or maternal mental health (3, 4, 26, 44). Analyses on the full sample also controlled for sex, as the brain has been reported to mature differently between genders. Sex stratification was done to see if the influence of maternal depression was equal in males and females, as there is evidence supporting a difference between how these two groups are affected by prenatal conditions (3).

The ANOVA analysis was performed on each voxel, or each 3D coordinate within the fiber tract from which values of diffusion were derived. This implies that the hypothesis was tested for each voxel, to see how strongly (p-value) and in which direction (β -value) the predictor affected the outcome. When conducting such voxel wise statistical analyses one major concern is the total amount of tests run, as type I error inflation is a common issue. To amend for this it is important to run multiple comparison tests correction (45). For multiple comparison correction, this study implemented the use of Monte Carlo simulation to extract a corrected p-value (p_c) for each

analysis. The simulation used a created random variable to interrogate the chosen predictor for statistical inference, meaning that it examined to which extent a random variable could produce the same effect on the outcome as seen by the chosen predictor. This study used 10 000 Monte Carlo iterations on each analysis.

Ethical Considerations

All participating subjects were volunteers and gave their informed consent for the procedures and tests performed in this study. The safety and comfort of the newborn children were well taken care of during neuroimaging, where they were studied under their natural sleep. Regarding the data that was collected, all personal identification parameters were replaced with ID-numbers. In cases of incidental findings on the MRI-images of the newborns, they were considered respectfully and necessary measures were taken.

The current project was approved by the head of the institution where it was carried out. I, the author of this project, also promise to manage all data with respect to confidentiality and perform necessary analyses with regards to the limits of my research and following the institution's rule of practice. All procedures were approved by the Institutional Review Board of University of California, Irvine (reference number #2009-7251).

Results

The study population included 87 mother-infant pairs, as displayed in Table 1. There were almost an equal number of boys and girls examined. Calculations of means and standard deviations give a sense of individual differences within the group of neonates and the group of mothers in terms of age at different time points.

Table 1 – Demographic Characteristics of the Study Sample (*n* = 87).

	Entire Sample (<i>n</i> = 87)
Gestational Age (weeks), mean (SD)	39.4 (1.35)
Age on Scan Day (days), mean (SD)	26.0 (12.26)
Child Gender, %	
Male	54.0 (<i>n</i> = 47)
Female	46.0 (<i>n</i> = 40)
Maternal Age at Baseline (years), mean (SD)	28 (5.5)
Maternal Ethnicity, %	
Hispanic	40.0
Non-Hispanic	60.0
Paternal Ethnicity, %	
Hispanic	40.0
Non-Hispanic	60.0
Household income past year (USD), %	
<15 000	11.1
15-29 999	17.3
30-49 999	22.2
50-100 000	42
>100 000	7.4
Highest Level of Formal Education, %	
Primary, Elementary, or Middle School	5.9
High School or GED ¹	16.5
Technical or Vocational School	10.6
Some College, but no Degree	35.3
Associates Degree	3.5
Bachelors Degree	16.5
Graduate Degree	9.4
Certificate	2.4
SES ² , mean (SD)	3.13 (0.96)

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General Education Development

² Socio-Economic Status, a continuous variable calculated upon mean scores of education and income.

The CES-D scores of the mothers showed little variance between different periods of gestation, illustrated by Table 2.

Table 2 – CES-D Scores of Maternal Depressive Symptoms during Gestation. Each bar reflects the mean score of all mothers on a CES-D question item during the different measure points. The questionnaire allows scores ranging from 0 to 3 on each item, where a higher number depicts greater depressive symptomatology (42). Confidence interval (CI) is set to 95 %.

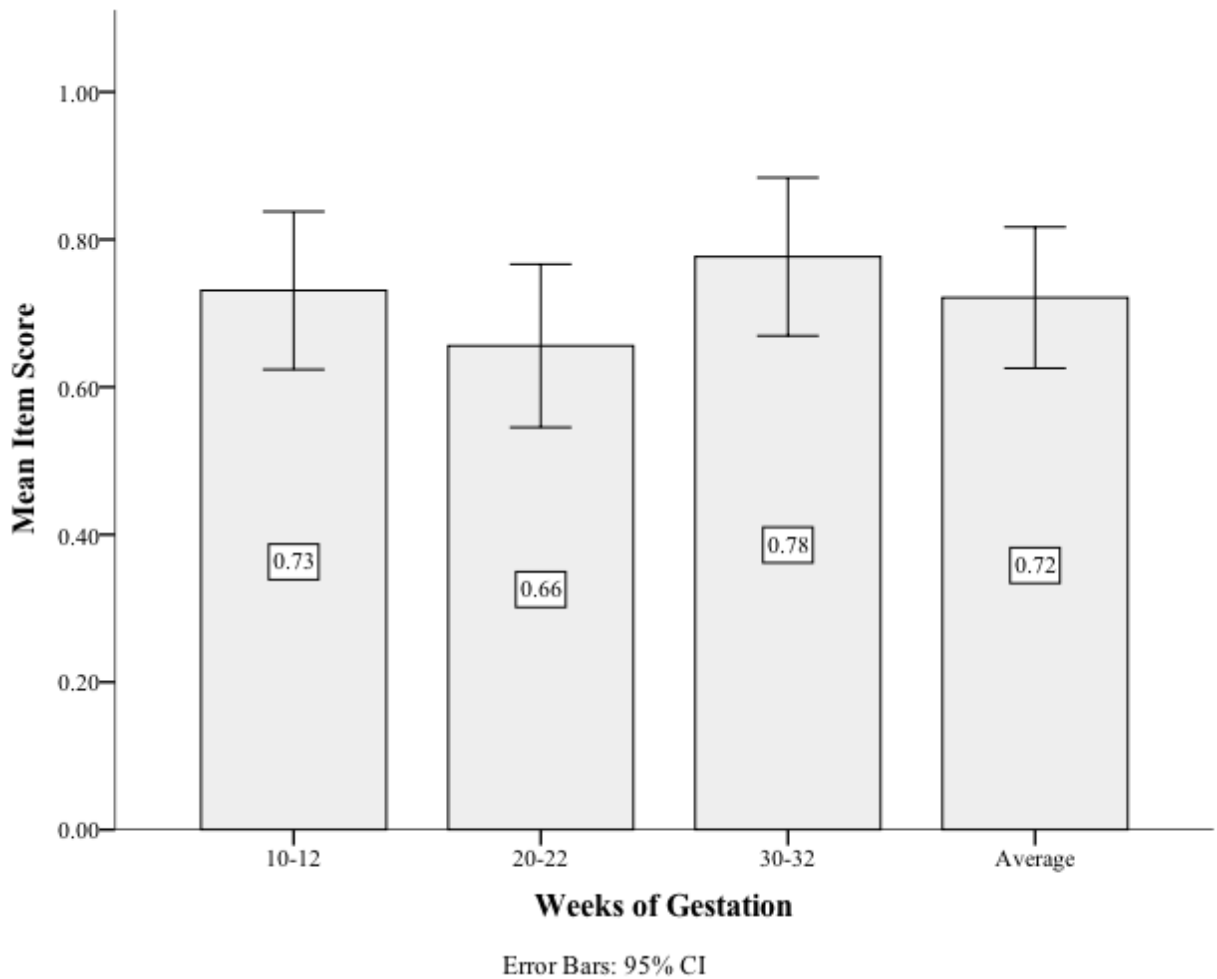


Table 3 and Table 4 show the correlation between increased maternal depressive symptoms during the different time periods and alterations in FA of the UF and fornix. Significant ($p_c < 0.05$) associations between maternal depressive symptoms and offspring fiber tract FA were only

discovered in the third trimester in boys. The association was present as a cluster of 12 consecutive voxels ($p_c = 0.0428$) along the right uncinate fasciculus in male neonates, $n = 47$. The mean unstandardized β -value for the points in the cluster was 0.00123 (SD = 0.00041). The cluster represents a contiguous area making up 14 % of the tract, based on the chosen voxel density, or image resolution, by the DTI framework. No significant associations were discovered between maternal depression and offspring fiber tract FA in either remaining fiber tracts or trimesters. This was true in analyses examining the complete sample as well as stratifying by sex.

Table 3 – Results of ANOVA between Maternal Depressive Symptoms and the UF. Amount of contiguous voxels along the left and right uncinate fasciculus where FA was associated ($p_c < 0,05$) with increase in maternal depressive symptoms during different time periods. A + or – symbol signifies the corresponding β -values along the cluster being >0 or <0 respectively. Zeros indicate no significant associations between maternal depressive symptoms and fiber tract FA in any voxel.

Fiber Hemisphere	1 st Trimester 10-12 weeks		2 nd Trimester 20-22 weeks		3 rd Trimester 30-32 weeks		Pregnancy Average	
	Left	Right	Left	Right	Left	Right	Left	Right
Complete Sample	0	0	0	0	0	0	0	0
Boys	0	0	0	0	0	12 ⁺	0	0
Girls	0	0	0	0	0	0	0	0

Table 4 – Results of ANOVA between Maternal Depressive Symptoms and the Fornix. Amount of contiguous voxels along the left and right fornix where FA was associated ($p_c < 0,05$) with increase in maternal depressive symptoms during different time periods. A + or – symbol signifies the corresponding β -values along the cluster being >0 or <0 respectively. Zeros indicate no significant associations between maternal depressive symptoms and fiber tract FA in any voxel.

Fiber Hemisphere	1 st Trimester 10-12 weeks		2 nd Trimester 20-22 weeks		3 rd Trimester 30-32 weeks		Pregnancy Average	
	Left	Right	Left	Right	Left	Right	Left	Right
Complete Sample	0	0	0	0	0	0	0	0
Boys	0	0	0	0	0	0	0	0
Girls	0	0	0	0	0	0	0	0

Discussion

Discussion of Results

The current study aimed to examine the effects of maternal depression during pregnancy on the development and microstructural integrity of the white matter tracts of the fornix and uncinate fasciculus in newborns. The hypothesis was that maternal depression during pregnancy would be correlated with lesser developed white matter integrity of the fornix and uncinate fasciculus in newborns. Using depression questionnaire scores of 87 pregnant mothers and fiber tract profiles based on DTI scans of the newborns, the study successfully examined with ANOVA models the relationship between the two variables and thus fulfilled its aim. One significant association between the two parameters was discovered. Maternal depression during the third trimester was associated with higher FA in the right UF in male newborns.

Higher FA values are reported to be related to increased levels of myelination and axonal organization and maturation in a fiber tract (29). Studies show that such properties reflected by higher FA, contribute to healthy functioning of the structures connected by the associated WM tracts (27-29). As the UF and fornix connect brain areas that are essential to psychological health (30, 33-35), and have been measured with lower FA in a variety of affective disorders (30, 33, 34); it may, at first glance, seem like the findings of this study suggest that prenatal maternal depression has beneficial influence on the mental health of neonatal boys. This would then stand in contrast with reports from several other studies, which have concluded that prenatal maternal depression is associated with affective disorders in the child (5, 7, 14-18).

Increased Cortisol and Brain Maturation

Current research has discovered that WM microstructure of the UF is measured as less mature in affective disorders (30, 33, 34). Studies have also shown that higher values of maternal depressive symptoms are correlated with developing affective disorders (5, 7, 15-18). By looking at how the two variables independently have been related to affective disorders, the results of this study may at first seem to contradict previous evidence. A closer look at how maternal depression physiologically affects the intrauterine environment may however shed some light on the findings. Depression during pregnancy is known to be correlated with higher levels of maternal cortisol (7, 13-15). Cortisol is known to be able to pass the placental blood barrier. The

passage is regulated by the placental enzyme 11 β -HSD2, however it serves only as a partial barrier and the function of it is in fact downregulated by excessive maternal cortisol (4, 15, 40), as seen in prenatal depression. Moreover, fetal exposure to cortisol during the end of pregnancy is known to be critical for nervous system maturation (40). Hence, this may be what is reflected by the positive association between prenatal depression and higher neural fiber maturation found by this study.

Meaning of Increased Fractional Anisotropy

The mean β -value of the significant cluster being 0.00123 (SD = 0.00041) shows that for one increased mean score of CES-D in the third trimester, FA in the right UF of the average boy is increased with 0.00123 points \pm 0.00041. Discovering here that maternal depressive symptoms were positively correlated with fiber tract integrity raises the important question about whether or not higher grade of maturation is beneficial. Research has found that increased FA in some populations is due to mechanisms compensating for unaccounted alterations. And that higher FA very early in life may indicate a deficit in cognitive flexibility, which in turn can have unfavorable results for neural network organization needed in active learning (32). Several studies have discussed pathological brain over-maturation in the context of neurodevelopmental disorders. In a prospective longitudinal study of infants with familial risk of autism spectrum disorder (ASD), Wolff and colleagues examined microstructural properties of 15 white matter tracts. At 6 months age, they found infants who would go on developing ASD presenting higher FA in 12 of the 15 fiber tracts including the UF (46). As with ASD, anxiety disorders such as obsessive compulsive disorder (OCD) can be present at an early age. FA in several fiber tracts has been discovered to be increased in populations with OCD (32). The UF is an essential structure to healthy functioning of top-down control (33, 34), the deficiency of which is a key factor in attention deficit hyperactivity disorder (ADHD). In a younger population with ADHD, higher FA has been observed in white matter tracts connecting to frontal parts of the cortex (32), as does the UF (30). Conduct disorder has been reported to be prevalent among 16% of preadolescents, and is displayed as a series of socio-empathic misbehaviors, such as severe aggression and harming others. Zhang and colleagues found young males with conduct disorder to have significantly higher FA in the UF compared to healthy males (47). Researchers have suggested that this increase in FA in a young population with conduct disorder, could be a sign

of disruptions in the maturation clock. They have further suggested that such early maturation of the UF successively converts to degradation with age, and might bring about traits of psychopathology associated with underdevelopment (30). Thus, researchers agree that higher FA, although in many cases signifying healthy or abundant white matter tracts, cannot be regarded as necessarily beneficial. The extent and direction of white matter alterations should rather be related to each specific disorder's developmental stages, where the place and time for higher FA to be present might not be favorable to behavioral outcomes (32).

Developmental Differences Along the Fiber Tract

According to the applied DTI framework, the value displayed in each voxel along the fiber profile reflects the diffusivity from a corresponding anatomical point along the tract (38). The findings of this study indicate that prenatal maternal depression may influence the FA in one cluster of 12 voxels along the right UF. This corresponded to 14 % of the measured amount of voxels along the whole tract. The finding that the whole tract is not affected symmetrically concurs with recent DTI research that, for instance, have described FA alterations limited to one anatomical part, the crus, of the fornix in participants with juvenile myoclonic epilepsy. Further explained is that, in adolescence, the influence of age on FA is significant in the crus of the fornix and not in the body, or column, of the fornix (31). The occurrence of such phenomena can be explained by the nature of WM maturation, which progresses at different times and velocities between separate spatial locations within any certain fiber tract (26).

Timing of Prenatal Maternal Depression

The discovered link between maternal depression and offspring fiber tract integrity was confined to depressive symptoms during 30-32 weeks of the third trimester. These findings agree with the current state of research, since a variety studies report differently as to during which period of gestation prenatal conditions exert their influence on the offspring. Betts and colleagues reported higher maternal depression, stress and anxiety during 18 weeks of pregnancy to be correlated with increased internalizing problems in the children (17). Rifkin-Graboi and colleagues found their link between maternal depression and lower microstructural integrity in the right amygdala of the offspring to be true for maternal depressive symptoms during 26 weeks of gestation (15). Barker and colleagues reported both maternal depression and anxiety during 32 weeks of

gestation to be associated with child externalizing behavior and lower verbal IQ (14). Sandman and colleagues reported several time points spread throughout the trimesters, namely 19, 25 and 31 weeks of gestation, during which they found maternal depression associated with offspring cortical thinning (7).

Hemisphere Specific Influence

The association between prenatal maternal depression and neonatal fiber tract integrity was confined to the right uncinate fasciculus. This is in agreement with recent research supporting that there are functional differences between hemispherical correspondents of a brain structure (3, 7, 15, 30). For example, professor Buss and colleagues reported an association between maternal cortisol during pregnancy and increased right amygdala volume and activity in the child. The study refers to models that suggest negative emotions mainly being processed in the right amygdala (3). Studies have reported similar exclusivity in the UF and fornix (30, 31, 35). For instance, disorders affecting the ability to empathize have been correlated with FA changes in the right UF and not the left (35). In another study on children, Elison and colleagues found that FA in the right UF explicitly predicted non-verbal social communication of joint interest, which is an essential part of healthy socio-emotional behavior (48). Similarly, evidence supports trends of age-related increase in FA confined to the right fornix in girls, and the left in boys. In other cases, associations between schizophrenia and higher grade of myelination of the left fornix have been found in men, but not in women (31).

Sexual Dimorphism

The discovery that prenatal maternal depression influences offspring fiber tract integrity was in turn present in the male offspring exclusively. Thus, suggesting that prenatal conditions may affect the sexes differently. This agrees with several examples from available literature. Professor Buss and colleagues found, for instance, that maternal cortisol during pregnancy predicted larger amygdala volume and increased affective problems in girls but not in boys (3). Sexually dimorphic susceptibility to developmental programming influences has also been reported in cases where higher prenatal anxiety predicted lower ability of top-down control in girls only (49). Similar gender differences have been discovered regarding myelination of the fornix, as mentioned in the previous paragraph (31). Regarding the UF, Zhang and colleagues

found significantly higher FA in males with conduct disorder in comparison with females (47). Moreover, this can be explained partly by the phenomenon of white matter microstructure maturing at different rates between the sexes, as seen in the UF (30) .

Strengths and Limitations

Strengths

One of the strengths of this study is that it provides an illustration of the potential impact of prenatal environment on fetal brain development. Very little room was left for influence from the postnatal environment as the infants were scanned at a mean of almost 4 weeks (SD = 1.7 weeks) after birth. The CES-D questionnaire used for measuring levels of maternal depressive symptoms has been determined with good test-retest reliability and internal consistency (43). Other strengths include the control for confounders including offspring gestational age at birth, age at scan, maternal BMI, sex, and existence of obstetric risk. Evidence has shown that these factors independently have significant impact on either offspring brain development or maternal psychological state (3, 4, 26, 44). Hence, this study has to a certain degree isolated the analysis to be confined to examining the influence of prenatal maternal depression on offspring fiber tract microstructure. Inclusion criteria of risk free births and healthy newborns not born too early, together with exclusion criteria of maternal use of tobacco or other drugs, psychotropic medicine, corticosteroids; also contributed to rule out significant interactions with both predictor and outcome variables (3). A statistical strength added to the study was the application of multiple comparison correction on each analysis with Monte Carlo simulation and a number of executed tests of 10 000. There were also notable strengths concerning the DTI data used in this study. One strength was the availability of the technique itself, which allowed measurements of diffusion parameters within the fiber tracts of interest. Another strength was due to the applied framework the processing of the data, which implied a series of quality checks of the raw images, including controlling for artifacts, subject motion, and anatomical accuracy pertaining fiber quantity, length and localization (38).

Limitations

The total sample size of $n = 87$, and $n = 40$ girls versus $n = 47$ boys in the stratified analyses, can be argued as relatively small in terms of statistical power. The size can, however, at the same

time be deemed as ample in relation to what is common in fields of neuroscience. Further, due to the limitations of the analyses, conclusions about the implications of the findings on child affective behavior can only be speculated by the current results. The predictor variable maternal depressive symptoms was measured with CES-D, which is a self-report questionnaire (42), and was subsequently liable to the limitations of first-person subjectivity. The outcome variable neonatal fiber tract fractional anisotropy has its own limitations as well. First, this variable could have been influenced by postnatal conditions as the infants were not scanned immediately after birth, hence not exclusively reflecting impacts of the prenatal environment. Second, although it is tempting to relate this parameter with degree of fiber tract myelination as well as axonal organization and maturation alone, it has been shown to also be influenced by a variety of other factors including but not limited to axon membrane density, spacing among axons and axonal diameter (29, 37). This makes it difficult to ascribe alterations in FA to changes in fiber tract integrity. The interpretation of FA is further complicated by certain inherent properties of the neuroimaging technique of DTI. A specific concern for DTI imaging of the fornixes are their proximity to the ventricles, which makes them susceptible to decrease in volume due to suppression by the cerebrospinal fluid. This in turn can result in false measures of diffusivity with DTI (31).

Significance

The above-mentioned limitations notwithstanding, this is the first study to examine the impact of maternal depression during pregnancy on fiber tract integrity of the fetal fornix and uncinate fasciculus. Measuring early variances in brain development is important from a clinical aspect. The integrity of white matter tracts is essential for mediating neurological functions. Disturbances in such pathways of brain connectivity can predict deficiencies pertaining to cognition and mental health (29). Showing that prenatal maternal depression affects offspring fiber tract integrity in a way that have detrimental outcomes may help understanding the origins of individual mental health disorders. Understanding the timing and mechanism behind any disorder is important for choosing adequate clinical approaches in terms of both prophylactic and intervening therapy. These findings may therefore provide essential knowledge for designing future clinical treatments of affective disorders.

Future Studies

Whether or not higher FA in neonatal right uncinate fasciculus of males predict later affective outcomes will have to be determined in the longitudinal follow-up of these infants. Other future research should attempt to correct for the limitations of this study in order to achieve refined scientific results. Methods for carrying out such a task include a higher number of participants, measuring maternal depressive symptoms objectively with the aid of third party experts, surveying for maternal depression at a more frequent rate during each trimester, controlling for additional essential confounders, using more accurate imaging techniques for visualizing white matter integrity and scanning the neonates closer to their date of birth, as well as performing a longitudinal follow-up of the children. Conducting a longitudinal study is also beneficial since it would have higher inferential value, as they control for inter-subject variation (30).

Conclusions

The conclusion of this study is, thus, that maternal depression during the third trimester may contribute to higher degree of maturation of the right uncinate fasciculus in male neonates. And that maternal depression during neither trimester independently nor over the whole course of pregnancy influences the white matter integrity of either the uncinate fasciculus or fornix in female newborns. As this was the first study to examine the effects of maternal depression on neonatal white matter integrity of the uncinate fasciculus and fornix, it is important to examine future similar studies for determination of accuracy of these results. Whether or not the associations found by this study are further linked to detrimental mental health conditions in the children later in life needs to be examined with a follow-up study or new studies that are of longitudinal design.

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