Faculty of Science and Engineering

Postpartum maternal depression increases the chance of autistic offspring

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Foreword

This research strives to investigate the potential influence of postpartum maternal depression, irrespective of antidepressant usage, on developmental changes in offspring, thereby contributing to the ongoing debate in this field. The central focus of this study revolves around autism, primarily due to its high prevalence and the current limited understanding of the developmental impact of environmental factors. This thesis was conducted as a final component of the Bachelor Biology, under the expert supervision of Jocelien Olivier.

Abstract

Maternal depression is a widespread issue, with approximately one in three women experiencing symptoms of depression during the four years following childbirth. Evidence suggests that maternal depression increases the risk of altered neurodevelopmental outcomes in children, including problems in emotion, behavior, and cognition. While the hereditary nature of ASD is acknowledged, the potential influence of maternal depression during pregnancy in augmenting the risk of ASD remains uncertain. The impact of depression during pregnancy on offspring neurodevelopment is not well understood. This thesis explores whether postpartum maternal depression is associated with the development of autism disorder in offspring.

In this thesis, different animal models, specifically rats and mice, were reviewed to answer the question whether postpartum maternal depression induces autistic-like behaviors in the offspring. The literature search included behavior of depressed dams and their impact on maternal care, and it explored the consequences of low maternal care on offspring behavior. In addition, autistic-like features in mice models were included, particularly focusing on social behavior. Finally, the social behavior of offspring exposed to postpartum maternal depression was compared to that of autistic mice models to evaluate potential similarities or differences.

Findings exhibit that postpartum maternal depression leads to altered maternal care and reduced social behaviors in the offspring. Maternal depression negatively affects the offspring's neurodevelopment, including social play behavior, through the disruption of maternal care. Similar observations are evident in mouse models of autism, demonstrating a potential association between postpartum maternal depression and the emergence of autistic traits in offspring.. In the thesis, the importance of emotional care for pregnant women and the potential long-term consequences for the child's development was highlighted. The findings contribute to understanding the association between postpartum maternal depression and the risk of autism spectrum disorder in offspring and may change the angle for future investigations in this field of research, for example the underlying mechanisms of autism development.

Introduction

Physical care for mothers has been improved in developed countries, but emotional care has not received the same level of attention. For the mothers themselves, but also for the future child, the well-being of the women is important (Van Den Bergh et al., 2005).

Evidence from different studies shows that when women suffer from depression after pregnancy, the child has a higher chance of altered neurodevelopmental outcomes compared to other mothers. The altered outcomes can be problems in emotion, behavior and cognition. These outcomes were also seen in mice and rats (Glover, 2014).

The effects of antidepressant usage during pregnancy on offspring have been extensively studied, while the impact of depression during/after pregnancy on offspring neurodevelopment is not as well understood. It is still under debate if the anti-depressant causes the altered offspring or the depression itself (Olivier et al., 2015).

According to Juszczyk et al. (2021), the HPA axis plays a crucial role in maintaining the body's balance and response to stress. Figure 1 illustrates that stress triggers the release of corticoliberin-releasing hormone (CRH) from the hypothalamus. This information is then transmitted to the anterior lobe of the pituitary gland, leading to the secretion of adrenocorticotropic hormone (ACTH). Subsequently, cortisol, a glucocorticoid, is released into the bloodstream from the adrenal cortex. Increased cortisol levels result in the inhibition of CRH and ACTH secretion through a negative feedback loop, accomplished by binding the glucocorticoid receptor (GR) in the hypothalamus and hippocampus. In depression, hyperactivity of the HPA axis occurs due to impaired negative feedback mediated by the GR ((Juszczyk et al., 2021)

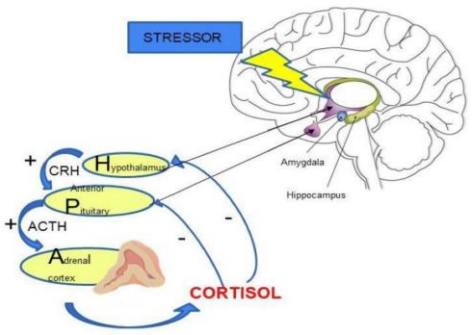

Figure 1: Regulation of hypothalamic-pituitary-adrenal (HPA) axis activity: stress as a factor activating the HPA axis.

Additionally, serotonin (5HT) hormone plays a role in regulating the release of CRH, ACTH, and cortisol in the HPA axis. The influence of serotonin on the release of CRH from the hypothalamus is now widely recognized (Dinan, 1996). In individuals with depression, changes in serotonin and cortisol levels are observed, which could disrupt the HPA axis and potentially contribute to the development of depression (Dinan, 1996).

The precise understanding of the neurobiological mechanisms underlying depression is limited by various challenges, including its complex nature, heterogeneity, and its frequent co-occurrence with other psychiatric disorders (Krishnan and Nestler, 2008). To address these limitations, animal models have emerged as a valuable tool for investigating the neural

circuits, molecular pathways, and cellular processes that may contribute to the development of depression. Initially, there were concerns about the use of animal models due to differences in cognitive and emotional capacities compared to humans. However, significant progress has been made in improving these models to include various aspects of depression-like behavior and cognitive functions that are similar to human depression (Wang et al., 2017). Animal models give several advantages, including avoiding ethical concerns associated with studying depression in humans and overcoming challenges related to obtaining sufficient sample sizes (Pryce et al., 2005).

In most cases, autism spectrum disorder (ASD) is inherited but as stated earlier depression in women during pregnancy can cause neurodevelopmental disorders. One example of a neurodevelopmental disorder is ASD. Over the years there is a much more understanding of the characteristics of ASD. Core features of ASD are social communication deficits and repetitive and unusual motor behaviors. Nevertheless, autism is a spectrum that can go from mild to severe. There are also different kinds of autism with different features. In this thesis, the focus will be on general autism features like social deficits as a result of exposure to maternal depression. ASD involves altered brain development and neuronal organization (Lord et al., 2018).

There has been a growing focus on investigating the adverse impact of parental depression, particularly postpartum maternal depression, on the neurodevelopment of children, including autism spectrum disorder (ASD). A fundamental finding in the field of research is the identification of a robust association between human maternal depression and autism spectrum disorder (ASD) in children, irrespective of antidepressant usage during the perinatal period (Hagberg et al., 2018). In a comprehensive meta-analysis, it was observed that human maternal depression, but not paternal depression, increased the risk of ASD in children (Ayano et al., 2019). However, another study revealed that in humans both maternal and paternal depression elevates to an increased risk of ASD in children, with maternal depression showing a higher likelihood (Chen et al., 2020). This raises a question into the potential association between postpartum maternal depression and the occurrence of autism in children, regardless of the use of antidepressants.

The inheritance of ASD is well established, but the potential role of postpartum maternal depression during pregnancy in increasing the risk of ASD is less clear. Given the high prevalence of depression in pregnant women, investigating the mechanisms underlying the association between postpartum maternal depression and ASD in offspring is of critical importance. Therefore, the research question of this paper is: How does postpartum maternal depression contribute to autistic behavior in the offspring?

Animal model for maternal depression

Depression is a complicated disease that significantly impacts the well-being of individuals. Due to the different range of clinical symptoms observed in affected individuals, the exact mechanisms involved in the development of depression are still not fully understood. While it is not feasible to replicate every aspect of human depression in rodents, the field of preclinical research has made significant progress in replicating certain fundamental

affective and physiological changes of depression. These include social withdrawal, anhedonia (loss of pleasure), and weight loss (Deussing, 2006).

One such rat model that has been suggested as a viable model for depression is the Flinders Sensitive Line (FSL). This is a selectively bred rat line with increased sensitivity to , diisopropyl fluorophosphate (DFP), a cholinesterase inhibitor. This increased sensitivity to cholinergic agonists is comparable to the increased sensitivity to cholinergic agonists observed in depressed humans (Overstreet, 1993). When studying FSL rats, Flinders Resistant Line (FRL) rats serve as a control group. This selectively bred rat line demonstrates greater sensitivity to stressful stimuli compared to the SD rats (Overstreet, 2002). The FSL rats display more prominent behaviors analogs with human depression when exposed to stress, particularly anhedonia (Overstreet, 1993). In comparison to the FRL rat control group, the FSL rats exhibit more pronounced anhedonia when exposed to stress (Overstreet, 1993).

Met opmerkingen [1]: Full name

The FSL rats exhibit characteristics similar to those observed in depressed humans, such as reduced body weight, decreased physical activity, increased REM sleep, and impaired learning abilities when under stress. These similarities make the FSL rats a suitable model that meets the criteria of face validity (Overstreet, 1993). One prominent behavioral symptom shown by the FSL rats is an exaggerated immobility response when exposed to stressors like foot shock and forced swimming. This abnormal behavior has been inverted by several well-known antidepressant drugs such as imipramine and desipramine (Overstreet, 1993). Additionally, the FSL rats demonstrate changes in factors associated with the activity of the catecholaminergic system, including increased levels of dopamine, serotonin, and norepinephrine in multiple regions of the brain (Wörtwein et al., 2006).

Due to the depressive-like behavior exhibited by the FSL rats, they fulfill all significant criteria necessary for an animal model of depression. Consequently, FSL rats hold promise as a potential model for studying postpartum maternal depression and its impact on the development of autism in their offspring.

The behavior of maternal depressed dams

To investigate the effect of postpartum maternal depression on offspring, it is crucial to observe the behavior of the depressed female dams. Most research on FSL rats was performed with males but according to one study, postpartum FSL females meet the criteria for depressive-like behavior in rats, as they demonstrate longer periods of immobility in multiple versions of forced swim tests, in contrast to postpartum Sprague-Dawley (SD) dams. (Hawkins et al., 1978).

Met opmerkingen [2]: Would be nice to explain why they said that. Can you explain?

In a study of Lavi-Avnon, they further evoked depressive-like behavior in the postpartum FSL dams by stressing them in a 15 minute acute swim test during the first postpartum week. In this research, the authors investigated the behavior of these dams and compared their maternal care to that of the SD dams in the first to third postpartum weeks. Maternal care included various behaviors, including carrying, grouping, non-nutritive contact, licking, nest-

building, self-grooming, eating, resting, rearing, and horizontal activity. All behaviors were categorized into 4 groups: 1. Organized of pups behavior: Carrying, grouping, and beginning of the nutritive episode. 2. Maternal behavior: nutritive contact, non-nutritive contact licking, and nest-building. 3. Non-maternal behavior/ self-directed behavior: resting, self-grooming, and eating, and 4. Motor activities: horizontal activities and rearing (Fig. 2) (Lavi-Avnon et al., 2005).

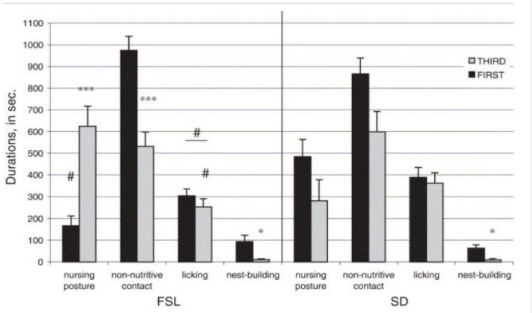

Figure 2. Maternal care towards pups. The average durations (in seconds) with standard error (SE) of nursing postures, non-nutritive contact, licking, and nest building were compared between the first and third week postpartum of FSL and SD dams during interactions with their respective litters. *Significantly different from first week postpartum within line (*$p < 0.05$, ***$p <= 0.001$). #Significantly different from SD dams (#$p < 0.05$).

Results showed different maternal behaviors in FSL dams compared to the control dams when interacting with their offspring during the first to third postpartum weeks. FSL dams spent significantly less time on maternal behaviors, especially nutritive contact and licking, after swim stress exposure compared to the SD dams (Fig. 1). In addition, in the first postpartum week, the duration of nursing behavior was shorter in the FSL dams compared to the SD dams. During the third week postpartum this difference in nursing behavior between the dams was significantly increased. Additionally, the frequency of self-grooming (non-maternal behavior) was higher in the FSL rats than in the SD dams (Lavi-Avnon et al., 2005). These differences were only evident after stress exposure but not at baseline conditions. The control dams exhibited increased maternal motivation after stress, whereas the FSL dams failed to show an increase in maternal care after stress exposure (Lavi-Avnon et al., 2005).

As previously stated, the FSL dam model can serve as a model for postpartum maternal depression due to the reduced maternal care, which is also seen in human depressed behavior (Overstreet, 1993). The FSL model shows clear alterations in maternal care. Therefore, this genetic rat model can be used to study the impact of maternal care on offspring development. Taken together, the FSL rat model shows decreased maternal care towards their offspring. Therefore, it can be stated that postpartum maternal depression has a negative effect on maternal care toward the offspring.

The effect of low maternal care on the behavior of the offspring

Maternal care plays a crucial role in the emotional and cognitive development of offspring, as evidenced by the increased risk of psychopathologies in children who have been abused or neglected (Kaffman & Meaney, 2007). These effects are observed not only in humans but also in rodents. Therefore, maternal care's impact on the neurodevelopment of infants is shared among all mammals. Animal models, such as rats, can therefore be used to study the consequences of altered maternal care on offspring and understand the underlying mechanisms (Kaffman & Meaney, 2007).

In the previous chapter, it was shown that postpartum depressed dams exhibit less maternal care towards their offspring (Lavi-Avnon et al., 2005). The maternal changes in human maternal depression have been linked with negative effects on the neurodevelopment of children. Similarly, the abnormal maternal care seen in postpartum depressed FSL rats, in

particular the low amount of licking and non-nutritive contact, can have a significant impact on the neural, social, emotional and cognitive development of the offspring. The reason for this impact is that maternal care, including licking and non-nutritive contact, plays a role in activating or suppressing behavioral and endocrine responses to stress, such as CRF, by influencing the noradrenergic systems in the forebrain (Caldji et al., 2000).

Met opmerkingen [3]: How?

Maternal care is essential during the first postnatal weeks in rodents. It has lasting consequences on the neuronal structure, brain function, and behavior of rats later in life, including social functions, social play behavior is an important form of social interaction in rodents, also in adolescence (Van Hasselt et al., 2012). In rodents, social play behavior is the earliest form of social behavior not directed toward the mother (Vanderschuren et al., 1997). The effect of maternal care on social play behavior in adult rats was investigated by studying the correlation between the amount of licking and grooming of the mother and the amount of social play behavior, such as pinning and pouncing, in the offspring. The study observed that an increased amount of licking and grooming, and therefore maternal care, in the early life of the offspring correlated positively with an increased amount of social play behavior later in life, particularly in male rats. Conversely, a decrease in maternal care, as indicated in the study by less licking and grooming, resulted in a decrease in the level of social play behavior in adult rats (Fig.3 A-D) (Van Hasselt et al., 2012). This indicates that low maternal care provided by the mother results in reduced social play behavior in the offspring.

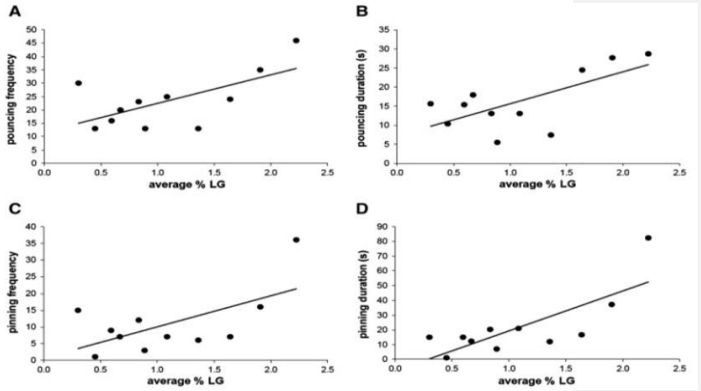

Figure 3. Social play behavior in male adolescent mice. The amount of social play behavior in adolescent male mice receiving high licking and grooming compared to low licking and grooming when juvenile. The correlation between %LG (x-axis) and the frequency (A; number of times during the 15 minute observation period) and duration (B; cumulative time in seconds during the 15 minute observation period) of pouncing, as well as the frequency (C) and duration (D) of pinning.

Another study found that offspring who received a high licking and grooming from their mother spent more time in social contact with unfamiliar individuals compared to offspring of dams that provided low licking and grooming. This finding shows that social play behavior is lower in offspring who received lower maternal care compared to those who received a high level of maternal care (Starr-Phillips & Beery, 2014).

In conclusion, maternal care seems to play a crucial role in the behavior development of the offspring. Low maternal care postnatally affects the offspring negatively by reducing the amount of social behavior later in life (Van Hasselt et al., 2012; Starr-Phillips & Beery, 2014). Maternal depressed rats tend to give less maternal care towards their offspring (Lavi-Avnon

et al., 2005). Offspring of maternally depressed rats therefore have a higher risk for altered social behavior later in life.

Autistic disorder in offspring: characteristics

Autism is a developmental disorder that affects around 6-11 persons in 1000 people, with a higher prevalence in males compared to females (ratio of 4:1). The disorder is primarily characterized by impairments in social behavior, although the cause of autism remains largely unknown. While environmental factors may play a significant role in the development of the disorder, genetics appears to be the most prominent factor (Ronald & Hoekstra, 2011b). The criteria for human autism include atypical social behaviors, altered communication, and repetitive behaviors with limited interests (Moy et al., 2009). However, the complexity of autism disorder has encouraged the use of animal models to investigate the role of environmental factors in its causation (Ronald & Hoekstra, 2011b).

Autism disease is a difficult disease to model in rodents. Characteristics of autism, like the disability to emphasize the feelings and intentions of other people, can be very hard to remodel in mice. Fortunately, the mouse species, Mus musculus, is used in research to investigate molecular and behavior genetics, and is seen as a social species that shows a high level of social interactions and communications (Gheusi et al., 1994). The need for a specified amount of behavioral tasks that are relevant for the characteristics of autism are increasing. Social, communication and repetitive behaviors that are seen in autism are the most needed and can be applied on mouse models (Crawley, 2007). Despite the challenges in modeling autism in rodents, several mouse models have been put forward, including the Ehmt1+/- and En2-/- mice.

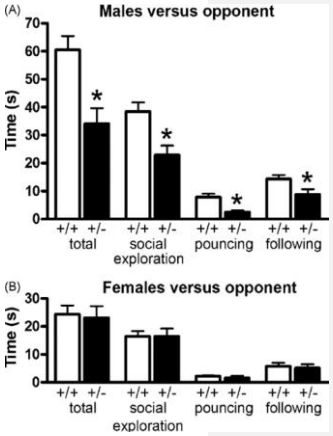

Figure 4. Social play in Ehmt+/- mice. The amount of time spent on of social play behavior in Ehmt+/- mice compared to juvenile wildtype (Ehmt+/+). (A) Duration of total social play, social exploration, pouncing, and following in male juveniles. (B) Duration of total social play, social exploration, pouncing, and following in female juveniles. *Significantly different from wildtype.

Ehmt1+/- mice model is characterized by haploinsufficiency of euchromatin histone methyltransferase 1 (EHMT1), which causes the Kleefstra syndrome, a syndrome that is defined by autism spectrum disorder (ASD) (Koemans et al., 2017). In the research from Balemans and colleagues, the amount of social behavior in the Ehmt1+/- mice was investigated using two behavioral tests, a social play test for the juvenile mice and for the adults a social approach test. The results indicated that the social play of the Ehmt1+/- juvenile male mice was two-fold decreased in comparison with the wild type group, indicating that the Ehmt1+/- mice model exhibits autistic like features (Fig. 4 A/B). Nonetheless, the impact of the hypoactive phenotype of the Ehmt1+/- on their social behavior cannot be lessened. In the female juvenile Ehmt1+/- mice there was no significant decrease in the amount of social play. Possibly because all the female mice, wildtype included, played for a small amount of time (Balemans et al., 2010). In another study they found that female juveniles played less than males in rats, which could verify the difference

in female and male mice play behavior in the study from Balemans (Vanderschuren et al., 1997b).

In addition to social play, the Ehmt1 +/- mice underwent a sociability and social approach test. The test involved placing the mice in a rectangular three-compartment box, with replaceable doorways dividing the center compartment from the two side compartments. Each side compartment contained a small round cage where stranger mice were placed during the test. At the start of the test session, the test mice were given ten minutes to familiarize themselves with all three compartments. Subsequently, the test mouse was briefly confined to the center compartment while a new mouse (stranger 1) was placed under one of the small cages. Then, both side doors were simultaneously lifted, granting the test mouse access to all three compartments for 10 minutes (sociability). Following the initial 10-minute session, the test mouse was returned to the center compartment with the doors closed. Another stranger mouse (stranger 2), sourced from a different home cage and having had no previous physical contact with the test mice or each other, was placed in the other cage. To test social novelty, the test mouse was once again allowed to explore all three compartments for a second 10-minute session (Balemans et al., 2010).

The social approach test on adult Ehmt1+/- mice revealed that these mice show a prolonged sociability response towards stranger 1, while their response to social novelty towards stranger 2 was either delayed or absent. This prolonged sociability response in Ehmt1+/− mice could potentially indicate another autistic-like characteristic. Notably, both groups of Ehmt1+/− mice exhibited a persistent preference for the stranger 1 mouse, suggesting a preference for a familiar conspecific over an unexplored area (Balemans et al., 2010). Interestingly, when stranger 2 was introduced into the cage, the Ehmt1+/− mice did not demonstrate a preference for spending more time with this second new stranger. Both the male and female Ehmt1+/− groups displayed an abnormal pattern in terms of time spent in the different compartments compared to both wildtype groups. These findings lead to the conclusion that social approach behavior is disrupted in Ehmt1+/− mice (Balemans et al., 2010).

Another mice model that has been proposed as a model for autism is the En2-/- mice. In human ASD individuals the two allelic variants of the En2 gene are more frequently inherited by the parents than the siblings who do not have ASD. The En2-/- mice show similar phenotypes to ASD in their behavior and neurochemistry as described below. Therefore, the En2-/- can be relevant for investigating the etiology of autism (Gharani et al., 2004).

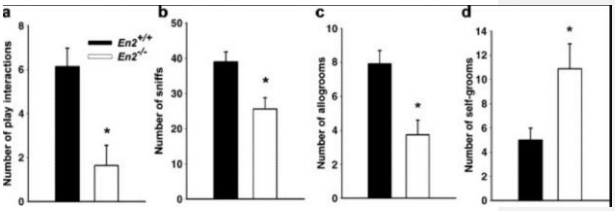

Figure 5. Social behavior in juvenile En2-/- mice. The amount in social behavior in juvenile En2-/- mice compared to control (En+/+). (A) The number of play interactions, (b) social sniffs, (c) number of allogrooms, and (d) the number of self-grooms. *Significantly different from En2+/+.

In the research by Cheh, the social behavior of the juvenile En2-/- mice was studied by doing multiple social tests on social play, sniffing, allogrooming and self-grooming. The results showed that the juvenile En2-/- mice exhibited a decreased level of social play, social sniffing and allogrooming when compared to

the control mice (Figure 5 A-D) (Cheh et al., 2006). This decline in social and play behavior in En2-/- was observed at a time when increased social play become frequent behavior in mice (Terranova et al., 1993).

Additionally, in adult social measurements, the En2-/- mice displayed disturbed aggressive behavior. The attack behavior in the knockout mice was reduced in the neutral cage and in the residents home cage. However, when the mice were put into the resident-intruder approach, to test their aggressive behavior, a significantly lower amount of attacks towards the intruder were measured in the En2-/- mice in contrast to the control (Cheh et al., 2006). The decreased attack behavior in En2 -/- adult mice indicate significant disturbance in territorial aggression, an important aspect of social behavior among adult males (Cheh et al., 2006). It is worth noting that juvenile play behavior is known to serve as a way to learn species-specific adult behavior, such as fighting (Panksepp, 1981). Therefore, the decrease in social play behavior shown by juvenile *En2-/-* mice could have impacted their behavioral development, leading to a decrease in aggression during adulthood.

Mouse models such as Ehmt1 +/- and En2-/- have been proposed as models for investigating the etiology of autism, and their social behaviors have been observed to exhibit characteristics similar to those seen in human autism (Ronald & Hoekstra, 2011b). In both the Ehmt1+/- and the En2-/- mice models, there was a decrease seen in social play behavior, but as well as other social behaviors such as sniffing, social approach, allogrooming, and aggressive behavior. Therefore, mice that model ASD in humans exhibit a reduced level of all sorts of social behavior, particularly social play behavior.

In the previous chapter, it was demonstrated that mice receiving reduced maternal care due to their mothers maternal depression exhibited decreased social behavior later in life. This is also seen in the mouse models for ASD, such as En2-/- and Ehmt 1+/-. This suggests a potential link between maternal depression and the development of autism disorder in offspring.

Animal studies versus Human studies

According to the World Health Organization (WHO), 10-12% of the world's population suffers from major depressive disorder (MDD), making it the leading cause of disease worldwide (Greenberg et al., 2003). Women have a twofold higher risk of developing MMD and often experience more critical symptoms compared to men, particularly during their reproductive years. Hormonal fluctuations and reproductive circumstances may therefore play important roles in the onset of depression (Sloan and Kornstein, 2003). Additionally, women can experience postpartum depression (PDD) following childbirth, which represents a specific form of depressive disorder.

Postpartum depression (PPD) has been associated with decreased levels of mother-child interactions and maternal care. Research indicates that compared to non-depressed mothers, women experiencing PDD exhibit higher levels of negative and neglectful behavior towards their children of all ages (Lovejoy et al., 2000). These findings are supported by studies such as Ferber, which found that maternally depressed mothers displayed reduced affection and physical contact with their children (Ferber et al., 2008). Additionally,

depressed mothers demonstrated lower levels of smiling, face-to-face contact, and engaging in child directed speech or storytelling, which are important forms of vocal and visual communication towards the child (Herrera et al., 2004).

Mother-child attachment, defined as the infant relying on the mother for safety, security and protection, is highly affected in cases of maternal depression (Benoit, 2004). Meta-analysis indicates that depressed mothers and their children have reduced levels of mother-child attachment (Martins and Gaffan, 2000). The duration of maternal depression also plays a role in the correlation between maternal depression and mother-child attachment, with longer periods of depression having a greater impact (Wan and Green, 2009)

Animal studies have further highlighted similarities between human and animal maternal care behaviors. Maternally depressed animals models, like their human counterparts, demonstrate decreased maternal care behaviors, albeit in different behavioral forms such as licking and grooming (Lavi-Avnon et al., 2005).

Postpartum maternal depression has significant negative consequences not only for the mother itself but also for their children. Infants born to mothers suffering from postpartum depressive disorder (PDD) face heightened vulnerability to various developmental and psychological issues, lasting early infancy. These challenges encompass emotional, behavioral and psychological problems, as well as cognitive and language developmental delays (Murray et al., 2010b).

Moreover, a higher incidence of antisocial disorders and altered cognitive and emotional development is observed in boys rather than girls born to mothers with PDD, both in human studies (Deave et al., 2008), and in animal studies (Van Hasselt et al., 2012). Due to the compromised maternal care provided by depressed mothers, children are at a higher risk of developing behavior issues, including antisocial behavior. Consequently, a correlation exists between the nurturing environment affected by postpartum maternal depression and the development of antisocial behavior in the children (Kim-Cohen et al., 2005).

Similarly to humans, various animal studies have revealed altered social play behavior resulting from changed maternal care, further emphasizing the impact of postpartum maternal depression on offspring (Van Hasselt et al., 2012, Starr-Phillips & Beery, 2014).

Discussion

The high prevalence of maternal depression and its consequential impact on the well-being of both the mother and child are significant concerns. Offspring born to mothers experiencing maternal depression are at a heightened risk for developmental behavior disorders (Van Den Bergh et al., 2005). Autism Spectrum Disorder (ASD) represents a well-known neurodevelopmental disorder (Lord et al., 2018). While the genetic role in autism are relatively well understood, the mechanisms through which maternal depression leads to ASD in offspring, despite being another neurodevelopmental disorder, remain less explored.

Conversely, extensive research has been conducted on the influence of antidepressant usage during pregnancy on offspring, but less attention has been given to the direct influence of maternal depression itself on the neurodevelopment of offspring (Olivier et al., 2015). Consequently, the present study aims to investigate by which postpartum maternal depression may contribute to the occurrence of autism in offspring, specifically focusing on animal models such as rats and mice.

Maternal depression has been extensively investigated through the use of animal models, which have proven to be valuable tools for replicating postpartum maternal depression in humans. One of these models is the FSL rats, which exhibit symptoms of anhedonia and heightened sensitivity to stress stimuli (Overstreet, 1993 ; Overstreet, 2002). These rats serve as a valuable model for studying the effects of postpartum maternal depression on mood-related behaviors and the response to stressors.

When investigating the impact of postpartum maternal depression on offspring, it is essential to observe the behavior of depressed female rats. Postpartum FSL dams exhibit depressive-like behavior, which can be further intensified by exposure to stress. These depressed dams display reduced maternal care towards their offspring, as evidenced by decreased nutritive contact and licking behavior compared to control dams. Additionally, FSL dams exhibit a decrease in the duration of maternal care and an increase in self-grooming compared to control dams. These differences in maternal behavior become particularly evident following stress exposure. In contrast, control dams demonstrate an increase in maternal motivation after stress, while FSL dams did not. The altered maternal environment resulting from depression in FSL dams negatively impacts maternal care provided to their offspring (Lavi-Avnon et al., 2005). In the next paragraph it becomes clear how this may affect social behavior in the offspring, an important behavior in ASD.

Both in humans and rodents, disrupted maternal care has been associated with negative neurodevelopmental outcomes (Field, 1998). In rats, diminished maternal care, characterized by reduced licking and grooming behaviors, has been shown to impact social behavior in the adult offspring (Caldji et al., 2000). Offspring that receive high levels of maternal care showed increased engagement in social play, whereas those exposed to low maternal care display decreased social play behavior (Van Hasselt et al., 2012). Furthermore, it was demonstrated that rats receiving minimal or no licking and grooming, indicating limited maternal care, exhibited prolonged latency in interacting with unfamiliar subjects. Maternal depression models, such as the FSL rats, have shown that depressed mothers exhibit reduced maternal care, establishing a link between decreased maternal care and altered social play behavior in the offspring (Starr-Phillips & Beery, 2014). These findings reveal the impact of postpartum maternal depression in rats, leading to low maternal care and as a consequence altered social behavior of the offspring

Researchers have employed animal models to gain insights into the impact of environmental factors on autism disorder development. Two mouse models, namely Ehmt1+/- and En2-/- mice, have been proposed for studying autism. In a study conducted by Balemans et al. (2010), it was observed that juvenile male Ehmt1+/- mice exhibited a significant reduction in

social play behavior compared to the wild type group, indicating the presence of autistic-like characteristics.

The En2-/- mice exhibit phenotypes similar to ASD in terms of behavior and neurochemistry. Cheh et al. (2006) investigated the social behavior of En2-/- mice and found a decrease in social play, social sniffing, and allogrooming compared to control mice. Moreover, En2-/- mice displayed reduced aggression towards intruders in a resident-intruder test.

In both the Ehmt1+/- and En2-/- mouse models, there is a common observation of reduced social play behavior, indicating a disruption in social interactions. However, other social behaviors such as sniffing, social approach, allogrooming, and aggression are also affected to varying degrees in these models (Balemans et al. 2010; Cheh et al., 2006). These findings suggest that autistic mice models exhibit a reduced level of multiple forms of social behavior.

When comparing animal studies to human studies, it is evident that postpartum depressed mothers in humans exhibit altered maternal care, including reduced affection, physical contact and increased neglect towards their children (Lovejoy et al., 2000; Ferber et al., 2008). Additionally, a meta-analysis has demonstrated that mothers experiencing depression tend to exhibit diminished levels of mother-child attachment, which is defined as the infant's reliance on the mother for safety, security, and protection (Benoit, 2004; Martins and Gaffan, 2000). The children of these mothers are at higher risk to develop disorders, such as antisocial disorders (Murray et al., 2010b). A significant finding is that the children of postpartum depressed mothers have an elevated risk of ASD, even in the absence of maternal antidepressant usage (Hagberg et al., 2018; Ayano et al., 2019).

The observation of reduced social behavior in mouse models of autism is also evident in the offspring of postpartum depressed dams displaying low maternal care. This suggests a potential link between postpartum maternal depression in mice and the development of autism spectrum disorder in the offspring. For instance, both the autistic mouse model and the offspring of maternally depressed dams, showing reduced maternal care, exhibit a decrease in social play behavior. Additionally, the offspring of maternally depressed rats exhibit an increased latency in approaching unfamiliar subjects, similar to the reduced social approach observed in the mouse model for autism. Looking at the similarity in behavior it can be said that there could be a potential link between maternal depression and the development of autism disorder in the offspring. These findings suggest that there may be similarities in the underlying mechanisms of autism between the offspring from postpartum maternal depressed mothers and the ASD mouse models.

Met opmerkingen [4]: Just that they show the same behavior doesn't make that there is a link between the two. See my comment above. So here you could describe that the next step would be to find this link and look for overlapping mechanisms in the two (asd and offspring exposed to maternal depression)

Brain-derived neurotrophic factor (BDNF) plays an important role in the postnatal development of GABAergic neurons in the forebrain, and it has been suggested that disrupted GABA signaling may contribute to the symptoms of ASD (Zunino et al., 2016). In another study, it was observed that those exposed to low maternal care exhibited higher levels of DNA methylation on the BDNF gene compared to those receiving high maternal care (Unternaehrer et al., 2015). Similarly, En2-/- mice showed a decrease in the expression

of several BDNF mRNA molecules, indicating a potential overlap in the dysfunctional mechanisms involving BDNF genes in both mouse models (Zunino et al., 2016).

Additionally, studies on Ehmt1+/- mice have revealed an upregulation of Tdo2, a gene indirectly associated with serotonin metabolism, indicating disrupted serotonin regulation in the Ehmt1+/- mouse model (Lo Iacono et al., 2018). Similarly, dysregulation of serotonin receptor gene expression has been observed in offspring from dams experiencing maternal depression (Scarborough et al., 2021). These findings suggest a potential overlap in the dysregulation of the serotonin system, which is also observed in individuals with ASD (Muller et al., 2016). Overall, both the altered BDNF gene expression and the serotonin dysregulation show that there could be a potential overlap in autism related underlying mechanisms between the ASD mouse model and the offspring from postpartum maternal depressed mothers.

It is important to note that there is currently limited research investigating the specific effects of postpartum maternal depression on autism in offspring. Consequently, the findings of this study serve as a suggestion for further research in this area. Another limitation of this study is the reliance on mouse models for autism despite the use of rat models for maternally depressed dams. Mice and rats are social rodents with distinct social behaviors. However, due to the challenges associated with genetically targeting genes in rats, mouse models have been commonly used to study autism (Netser et al., 2020). Nevertheless, it is plausible that postpartum maternal depression may increase the risk of autism development in offspring.

Due to the limited number of studies available, further research is justified to explore the mechanisms through which postpartum maternal depression may lead to the development of autism in offspring, specifically using rat models. Rats are preferred for studying this phenomenon due to their more observable social behavior compared to mice (Netser et al., 2020). A proposed research plan involves using FSL rats as a model for postpartum maternal depression and investigating whether their offspring exhibit autistic features, such as repetitive behavior, but also to look if underlying mechanisms regarding to autism are altered in these offspring. There are various underlying mechanisms that could be explored as potential factors associated with ASD. These mechanisms include genetic mutations, neuroinflammation, neural abnormalities in the GABAergic inhibitory system, decreased synthesis of glutamate, deficiencies in vitamins and minerals, and a condition known as leaky gut (Dera, 2022).

Furthermore, additional research is needed in humans to investigate the link between postpartum maternal depression and the development of autistic offspring. This research is particularly important to address the ongoing debate regarding the potential role of antidepressants in neurodevelopmental disorders in children. This is of significance considering the rising prevalence of postpartum depressive disorder and its potential association with an increased risk of ASD. Moreover, further studies are required to understand the underlying mechanisms by which postpartum maternal depression contributes to the development of autism in offspring.

Afterword

My experience of writing a thesis proved to be highly educational and captivating, particularly due to my biomedical background which had limited exposure to neurobiological literature research. Through this thesis, I gained extensive knowledge on the methodologies used in neurobiological research. Initially, my intention was to explore the potential link between depression during pregnancy and the development of autism in offspring. However, due to insufficient animal models and studies in this area, I shifted my focus to postpartum maternal depression.

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