Maternal Serotonin System, Maternal Care, and Offspring Risk for Neuropsychiatric Disorders

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Abstract
Despite extensive research, no effective treatments have been developed for the highly comorbid neuropsychiatric disorders depression, anxiety, ADHD, and ASD. A potential denominator in their etiology is the serotonergic system, as serotonin (5-HT) plays an essential role in neurodevelopment and the maturation of circuitries related to these disorders. Maternal-fetal interactions may influence 5-HT levels in the early fetal brain. Moreover, the maternal 5-HTergic system may affect downstream effects of brain development and potentially affect behavior in offspring. Serotonin also plays a role in maternal care which affects offspring's behavior. Therefore, this essay aimed to examine how the maternal 5-HTergic system influences maternal care and the development of neuropsychiatric disorders in offspring. In rodents, the maternal serotonergic system is able to influence maternal care. In addition, offspring receiving low maternal care showed increased anxiety- and depressive-like behavior. Yet, in humans, association studies between maternal care and the serotonin transporter linked polymorphic region (5-HTTLPR) gene variance are inconsistent, and links between the maternal serotonergic system and neuropsychiatric disorders in offspring are not robust. However, parenting in humans is more complex than in rodents, so future studies could focus on different types of parenting to further explore the relationship between maternal care and neuropsychiatric disorders in offspring. Also, as many receptors are involved in serotonin signaling and the development of neuropsychiatric disorders, future research should further explore possible receptors and mechanisms involved in parental care to provide more information for potential treatments and minimize the risk of neuropsychiatric disorders in offspring.

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Introduction

Mental/psychiatric disorders affect men and women of all ages and are becoming more prevalent. All psychiatric disorders combined have a prevalence of about 13% worldwide (Global Burden of Disease Collaborative Network, 2021). This essay will focus on four psychiatric disorders, including depression, anxiety, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD).

Major depressive disorder (MDD), also known as depression, is one of the most common psychiatric disorders globally (Li et al., 2021). In 2019, the Global Burden of Disease Study showed that over 279 million people of all ages suffer from depression, which is 3.76% of all people globally (Global Burden of Disease Collaborative Network, 2021). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), at least five symptoms for a minimum of 2 weeks are required for the diagnosis of depression. At least one of the symptoms must either be a depressed mood or a loss of interest in almost all activities (anhedonia) (Kennedy, 2008). The other symptoms are described in the DSM-V (American Psychiatric Association (APA), 2013). Family and twin studies have demonstrated compelling evidence that genetic factors contribute to the risk of depression (Shadrina et al., 2018). For example, a meta-analysis study on twin data revealed that depression had a heritability rate of 37% (Sullivan et al., 2000). The onset of depression can emerge throughout life and often co-occurs with anxiety and ADHD (Avenevoli et al., 2015; Kessler et al., 2007).

Anxiety is a normal stress response that can be helpful in some situations as it can notify danger and help pay attention. However, when there is an overreaction to situations when something triggers the emotion, or anxiety interferes with the ability to function normally and the responses to situations are out of control, it may be considered an anxiety disorder. Generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder are five major types of anxiety disorders (Torpy et al., 2011). The prevalence of anxiety disorders is more than 4% as more than 300 million people are suffering from this disorder worldwide in 2019 (Global Burden of Disease Collaborative Network, 2021). Common anxiety symptoms include feeling nervous or restless, having excessive anxiety, worry and fear, having an increased heart rate, sweating, breathing rapidly, feeling weak or tired, and easily irritated (American Psychiatric Association (APA), 2013). The onset of anxiety disorders, like depression, can take place throughout life.

Another heritable neuropsychiatric disorder is ADHD. In 2019, the prevalence of ADHD was 1.14%, which is more than 84 million people with ADHD worldwide (Global Burden of Disease Collaborative Network, 2021). This disorder is characterized by an ongoing pattern of inattention and/or hyperactivity and impulsivity that impairs functioning or development, resulting in cognitive impairments related to response inhibition, cognitive and motor control, reward processing and emotion recognition (American Psychiatric Association (APA), 2013). Although ADHD can be diagnosed throughout life, about 80% of all ADHD patients are diagnosed at 4 to 11 years old (Kessler et al., 2007). ADHD often co-occurs with depression, anxiety and ASD (Kooij et al., 2019; Reale et al., 2017).

ASD is a highly heritable neurodevelopmental disorder (Ronald & Hoekstra, 2011). The number of people with ASD was more than 28 million in 2019 globally, with a prevalence of 0.38% (Global Burden of Disease Collaborative Network, 2021). It is characterized by deficits in social communication and interaction, stereotyped and repetitive patterns of behavior, and sensory anomalies, as stated in the DSM-5 (American Psychiatric Association (APA), 2013). Most diagnoses are determined during childhood, with males having a higher prevalence than females (Christensen et al., 2018). However, as individuals can vary considerably in their symptoms, and most research is done in men, autistic women are usually underrepresented (Taylor & DaWalt, 2020).

The abovementioned four disorders not only negatively influence educational achievements and increase social withdrawal in individuals with these disorders, but they also

create a high emotional and financial pressure on family and society (Sahakian et al., 2015). Despite much research and progress in neuroscience, no effective treatments for the highly comorbid neuropsychiatric disorders depression, anxiety, ASD, and ADHD have been discovered (Cuijpers, 2017). Therefore, it is critical to develop a deeper insight into the pathophysiology underlying these disorders.

A possible common factor in their etiology is the serotonergic system. Serotonin (5-HT) plays a crucial role throughout neurodevelopment and is involved in the maturation of circuitries related to psychiatric disorders (Gaspar et al., 2003; Kepser & Homberg, 2015; Whitaker-Azmitia, 2001). 5-HTergic signaling dysfunction has been linked to the pathophysiology of all four neuropsychiatric disorders (Banerjee & Nandagopal, 2015; Cowen & Browning, 2015; Deneris & Wyler, 2012; Garbarino et al., 2019). Because serotonin in the early fetal brain appears to be regulated by maternal-fetal interactions, the maternal 5-HTergic system, rather than the offspring's, may play a role in downstream effects on brain development and possibly affect offspring behavior (Gleason et al., 2011). Besides, the maternal 5-HT system appears to be linked to the quality of maternal care, implying that 5-HT may also play a role in the pathophysiology of neuropsychiatric disorders (Caldji et al., 1998; Masís-Calvo et al., 2013). Therefore, in this essay, the research question 'how does the maternal 5-HTergic system influence maternal care and with that the offspring's behavior, in both rodents and humans, specifically in the development of neuropsychiatric disorders?' is aimed to be investigated.

Serotonergic system

Serotonin as a neurotransmitter and neurotrophic factor

5-HT is one of the most classical monoamine neurotransmitters and hormones in the central nervous system (CNS) and peripheral tissues (Lv & Liu, 2017). Since its discovery more than 70 years ago, serotonin has been extensively studied in the CNS for its crucial role in embryos and adults (Rapport et al., 1948). Within the brain, 5-HT serves as a neurotransmitter that modulates neural activity and a wide range of neuropsychological processes (Berger et al., 2018). Serotonin regulates nearly all human behavioral processes as all brain regions express multiple serotonin receptors. Serotonergic neurons in the CNS are positioned perfectly to regulate the activity of a wide variety of human brain circuits, which partly explains the pleiotropic behavioral effects of serotonin in the brain (Mengod et al., 2006). The behavioral and neuropsychological processes that are regulated by 5-HT include mood, reward, perception, aggression, anger, appetite, memory, attention, and sexuality, as well as other processes (Canli & Lesch, 2007; Roth et al., 2004).

Serotonin not only functions as a neurotransmitter, but it also shows particular neurotrophic abilities during development. Serotonergic neurons are one of the first neurons to develop (Gaspar et al., 2003), and pharmacological studies demonstrated that 5-HT can regulate various developmental processes such as cell division, neural proliferation and migration, programmed cell death, cell differentiation, and synaptogenesis (Azmitia, 2001; Lauder, 1993; Levitt et al., 1997; Lipton & Kater, 1989; Vitalis & Parnavelas, 2003).

Serotonin is not only present in the CNS but also in the peripheral nervous system (PNS), where it is even more abundant (95%) compared to 5% in the CNS (Pourhamzeh et al., 2021). Because serotonin cannot cross the blood-brain-barrier (BBB), the CNS and PNS 5-HT systems are entirely independent (Sahu et al., 2018).

5-HT synthesis in the CNS occurs in the serotonergic neurons of the raphe nuclei of the brain stem (fig. 1). 5-HT is synthesized from the precursor molecule tryptophan, an essential amino acid. The fully synthesized 5-HT is taken up into vesicles in the axon. After an action potential, 5-HT is released into the synapse, where it can interact with both the presynaptic and the postsynaptic receptors. Free 5-HT is removed from the synapse and taken back to the presynaptic neuron by 5-HT transporters (5-HTT), also called Serotonin Reuptake Transporters (SERTs) (Pourhamzeh et al., 2021). Because serotonin and serotonin receptors

are involved in regulating almost all brain functions, dysregulation of this system has been linked to the pathogenesis of many psychiatric and neurological disorders (Roth, 1994).

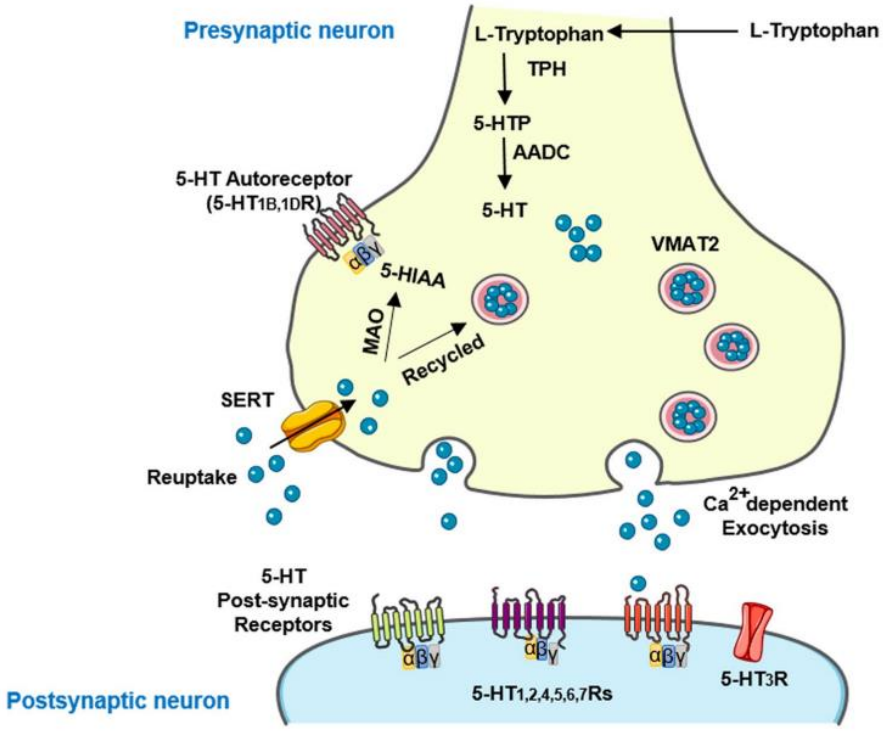


Figure 1. The synthesis and metabolism of 5-HT. Tryptophan, an essential amino acid, is the precursor molecule that is involved in the synthesis of 5-HT. It can cross the BBB and in the CNS, tryptophan hydroxylase type 2 (TPH2) hydroxylate tryptophan into 5-hydroxytryptophan (5-HTP), which then is transformed into 5-HT by l-aromatic acid decarboxylase (AADC). 5-HT is taken up into vesicles and after an action potential, it is released into the synapse, where it can interact with the presynaptic and postsynaptic receptors. All 5-HTRs are heteroreceptors expressed on non-serotonergic neurons post-synaptically and autoreceptors located on the serotonergic neurons pre-synaptically. 5-HT can be reuptaken by SERTs, located on the axon terminal and soma of the serotonergic neurons (Pourhamzeh et al., 2021).

Role of serotonin in neuropsychiatric disorders

As mentioned above, 5-HT regulates a wide spectrum of functions, including mood, cognition, anxiety, learning, memory, and sleep. Polymorphisms in the SERT gene have been associated with depression, anxiety, autism, and suicidality (White et al., 2008). When low concentrations of 5-HT are generated, or SERT pumps work harder and faster than usual, available synaptic 5-HT levels drop. To block the reuptake of 5-HT, selective serotonin reuptake inhibitors (SSRIs) are applied, and they have been administered extensively worldwide to treat various psychiatric disorders, such as major depressive disorder (MDD), anxiety disorders, and obsessive-compulsive disorder (OCD) as well as other psychiatric and nonpsychiatric disorders (Lorman, 2018).

Multiple studies have shown that anxiety disorders are linked to 5-HT disruptions (Abela et al., 2020; Ohmura et al., 2020). According to the developmental role of 5-HT neurotransmission, dysregulation during developmentally crucial periods could have long-term effects on brain functioning, especially for the anxiety phenotype in adulthood (Teissier et al., 2017). 5-HT_{1A} receptors (5-HT_{1A}Rs) are commonly studied receptors in the treatment of anxiety (Raab et al., 2016), as fewer 5-HT_{1A}Rs have been discovered in the forebrain and raphe nuclei of patients with panic disorder and in the amygdala of patients with social anxiety disorder (Lanzenberger et al., 2007; Nash et al., 2008). Signaling via 5-HT_{1A} autoreceptors appears to be essential and sufficient for the establishment of anxiety-like behaviors (Richardson-Jones et al., 2010). Furthermore, when 5-HT_{2c} receptors in the bed nucleus of the stria terminalis are activated, it leads to 5-HT release from the dorsal raphe nucleus (DRN), which enhances fear

and anxiety (Marcinkiewcz et al., 2016). 5-HT_3 receptors are also found to be involved in triggering antipsychotic signs, and inhibiting these receptors has beneficial effects by reducing glutamate release in the striatum (Ohno et al., 2015). Thus, blocking specific 5-HT receptors might be a potential candidate for treating anxiety disorders. Another factor that plays a role in anxiety disorders are increased levels of SERTs, which have been found in patients with GAD. Chronic treatment of SSRIs that block SERTs leads to anxiolytic effects (Harmer et al., 2017).

The cause of depression is hypothesized to be the hypofunction of serotonergic neurons. However, the pathogenesis of depression is complex and this hypothesis has been criticized as the efficacy and response of typical antidepressants affecting 5-HT was delayed and insufficient (Liu et al., 2017). It has been reported that patients with MDD have altered 5-HTRs and SERTs as well as excessive activity of presynaptic autoreceptors (Lin et al., 2014; Sharp et al., 2007). 5-HT_{1A} pre- and postsynaptic receptors appear to play a major role in the mediation of depressive-like behaviors (Samuels et al., 2015). Buspirone, a partial 5-HT_{1A} agonist, is currently used as an anti-depressant (Celada et al., 2013), and after selective blockade of 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors as well as stimulation of 5-HT_{2B} and 5-HT_4 receptors, anti-depressant effects have been observed (Aznar & Hervig, 2016; Belmer et al., 2018; Gupta et al., 2016; Hamati et al., 2020; Madsen et al., 2015; McCorvy et al., 2011).

ADHD is one of the most common disorders in children, and it is hypothesized that chronic reductions in available 5-HT are related to the clinical manifestations of ADHD. Lower concentrations of 5-HT in blood have been reported in patients with ADHD (Wang et al., 2018). 5-HT is linked to a variety of behaviors, including impulsivity, inhibition, and attention, and it interacts with the dopaminergic system to mediate and regulate impulsive behavior (Hou et al., 2018). Moreover, 5-HT activity in the orbitofrontal-striatal circuitry contributes to the pathophysiology of ADHD (Curatolo et al., 2010). As a first-line treatment for ADHD, methylphenidate (Ritalin) is the most safe and effective candidate in children and adolescents, while amphetamines are the preferred option in adults (Cortese et al., 2018). However, also SSRIs are sometimes used for children or adults with both ADHD and depression.

In ASD, one of the most common and earliest manifestations is hyperserotonemia, which is defined as elevated concentrations of 5-HT in the blood. Children with ASD have increased levels of 5-HT in their blood but decreased levels in their brains. Before the age of five years, the 5-HT levels in the brain of autistic children are only one-third of the standard amount (Marler et al., 2016). Although a number of factors can cause ASD, abnormalities in the serotonergic system during development play an important causal factor and can have long-term effects on brain functioning in adulthood. However, the precise role of the 5-HTergic system in the pathophysiology of ASD is unknown.

Overall, 5-HT evidently plays a significant role in the pathophysiology of neuropsychiatric disorders. Therefore it will be interesting to evaluate whether the maternal 5-HTergic system is also involved in the development of neuropsychiatric disorders in the offspring.

Effect of the maternal 5-HTergic system on offspring

In adulthood, 5-HT cannot cross the BBB, but during the first half of pregnancy in humans, 5-HT from the mother's placenta can be transferred to the fetal brain via the fetal periphery (Bonnin & Levitt, 2011; Côté et al., 2007). Therefore, it is likely that the maternal serotonergic system significantly impacts fetal brain development, as serotonin plays a role in neurodevelopment. Since many disorders appear to have a developmental origin (Rebello et al., 2014), this maternal-fetal interaction may play a role in the onset of the four neuropsychiatric disorders mentioned above. Moreover, the maternal 5-HTergic system seems to be implicated in the quality of maternal care/caregiving behavior (Cents et al., 2014; Morgan et al., 2018), implying that maternal care may also be involved in the pathophysiology of neuropsychiatric disorders.

Maternal care

Effect of the serotonergic system on maternal care

Variability in maternal care exists naturally in both rodents and humans. In humans, maternal caregiving behavior is normally distributed (Hane & Fox, 2006). Rat studies have also shown that variations are stable across litters and are passed down from mothers to offspring (Champagne et al., 2003). Quality of maternal care in rats is primarily assessed through the licking and grooming behavior of the mother, as well as nursing behavior. Nursing is often characterized by arching the back and legs splayed out, called arched-back nursing (Meaney, 2001). Maternal behavior is found to be indirectly and directly regulated by the serotonergic system (Angoa-Pérez & Kuhn, 2015). For example, a study with mice from Angoa-Pérez et al. (2014) found that mothers with TPH2 depletion, which is an enzyme responsible for the synthesis of serotonin in the brain, displayed disruptions in pup retrieval/huddling, nest building, and high arched-back nursing (fig. 2). They found that wildtype mothers had more high arched-back nursing compared to TPH2 KO mice. High-arched back nursing is characterized as the most relevant position for nursing compared to low-arched back nursing. Noticeably, most behaviors that are used to assess maternal behavior are worse in female mice without brain serotonin, such as worse pup retrieval, huddling and high-arched back nursing (Angoa-Pérez et al., 2014). In humans, the maternal serotonergic system also seems to be involved in the quality of caregiving behavior. For example, mothers carrying a particular variant of the serotonergic gene, the S allele, which will be discussed further in following paragraphs, showed higher maternal sensitivity towards their children (Cents et al., 2014).

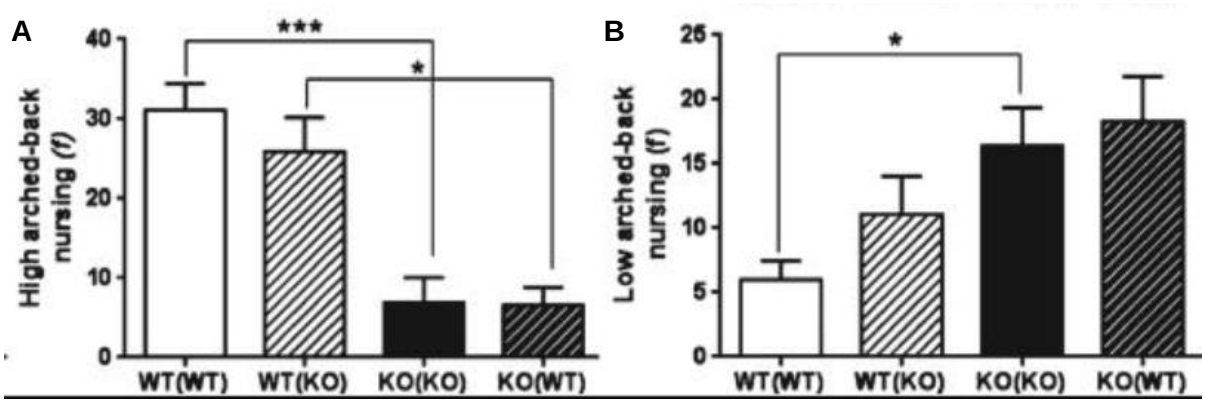


Figure 2. TPH2$^{-/-}$ dams demonstrate impaired instinctual maternal behavior that are resistant to rescue by cross-fostering. TPH2$^{+/+}$ (WT) mothers and TPH$^{-/-}$ (KO) mothers were evaluated for maternal behaviors. A) High-arched back nursing and B) low-arched back nursing. The genotypes of the mothers and their pups are appointed as follows: WT(WT), WT mothers rearing their own WT pups; WT(KO), WT mothers rearing cross-fostered KO pups; KO(KO), KO mothers rearing their own KO pups and KO(WT), KO dams rearing cross-fostered WT pups. Data are expressed as mean ± SEM. *P < 0.05, ***P < 0.0001. (Angoa-Pérez et al., 2014)

Effect of maternal care on offspring's health

Litters from low licking and grooming mothers had higher anxiety- and depressive-like behavior than litters that were exposed to high licking and grooming mothers (Caldji et al., 1998; Champagne & Meaney, 2007; Masís-Calvo et al., 2013; Weaver et al., 2006). This was measured in the open field test, the elevated plus maze, and the forced swim test. As shown in figure 3, rats that were exposed to high licking and grooming (HLG) mothers spent significantly more time in the center and the open arms of the elevated plus maze (EPM) compared to the rats that were exposed to low licking and grooming (LLG) mothers (Masís-Calvo et al., 2013). LLG rats spent significantly more time in the closed arms, indicating they experienced more anxiety compared to HLG rats.

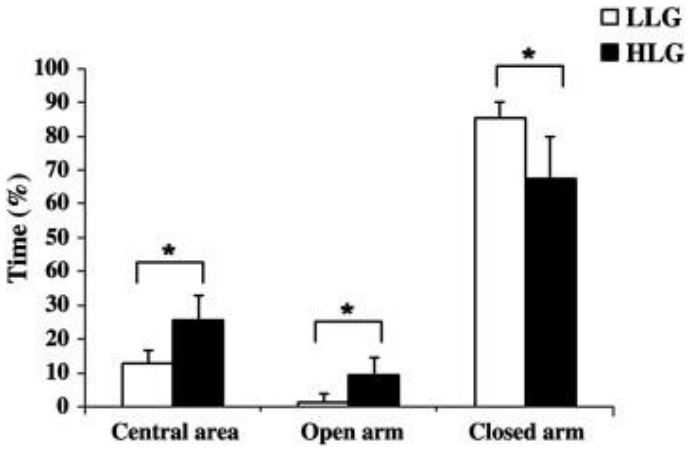


Figure 3. Time spent in the central area, open arm and closed arm in the EPM in litters exposed to low and high licking/grooming mothers. Median value ± IQR/2, LLG: N = 17; HLG: N = 22. *p < 0.05. (Masís-Calvo et al., 2013).

Rodents

The 5-HTT$^{-/-}$ rodent model

To examine whether the serotonergic system affects maternal care and the health of the offspring, rodent models can be used. Advantages of using rodent models are that most environmental factors can be regulated, and the main and interactive effects of maternal 5-HT genotype-induced changes can be studied. One of the most commonly used models is the 5-HTT$^{-/-}$ rodent model, also known as the SERT knockout (KO) model. The 5-HTT gene of the rat is 92% homologous to the human 5-HTT gene (Lesch et al., 1993). As 5-HTT$^{-/-}$ rats exhibit a total absence of 5-HTT, it leads to an enormous increase in extracellular 5-HT levels throughout the brain of up to six to ten times as numerous (Homberg et al., 2007; Shen et al., 2004). The 5-HTT rodent model was primarily used to study the genotype of the offspring and its association with neuropsychiatric disorders. This rodent model has shown that the absence of 5-HTT is associated with increased anxiety-like behavior, and they exhibit more anhedonia-like behavior and decreased social play behavior compared to the 5-HTT$^{+/+}$ rats (Homberg et al., 2007; Olivier et al., 2008). Furthermore, research in this rodent model has been conducted in recent years to examine a connection between the maternal 5-HT and neuropsychiatric disorders in offspring (Hanswijk, 2022).

Maternal care in rodents

Maternal care, particularly provided before postnatal day 10, is the most significant contributor to the early life environment in rats (Curley & Champagne, 2016; Masís-Calvo et al., 2013). As mentioned briefly before, maternal care in rodents consists primarily of grooming, licking, and nursing. Variations in maternal care have shown that it can have a significant impact on the development of the offspring. The frequency of licking/grooming (LG) and arched-back nursing is highly correlated across animals, so mothers can be defined according to both behaviors: high or low licking/grooming-arched-back nursing (LG-ABN) mothers (Meaney, 2001).

Role of maternal serotonin on maternal care

To discover whether maternal care behavior in the 5-HTT genetic rodent model is affected, Hanswijk (2021) observed maternal care behavior three times a day from postnatal day 2 to 8 in rats, where 5-HTT$^{-/-}$ dams were compared to 5-HTT$^{+/+}$ dams. All offspring had a 5-HTT$^{+/-}$ genotype. Total licking and grooming provided by 5-HTT$^{-/-}$ dams to their litters was significantly lower compared to the total amount that was provided by the 5-HTT$^{+/+}$ dams (fig. 3; $p = 0.009$). Furthermore, a fostering procedure was performed to establish whether the maternal 5-HTT genotype affects offspring through the intrauterine environment (placenta-derived 5-HT) or the postnatal environment (maternal care quality). In short, there were three different groups in which the dam that provides the maternal care was different in each group. In the non-fostering group, the biological dam cared for their offspring, while in the in-fostering and cross-fostering groups, a foster dam provided the maternal care to litters with the same 5-HTT genotype as

their own offspring and to litters with the opposite 5-HTT genotype, respectively. Here, they found no significant effect between the licking and grooming behavior of 5-HTT$^{-/-}$ and 5-HTT$^{+/+}$ dams. However, a possible explanation for this might be the small sample size, as there were only 2, 3, or 4 pups per group. This led to high observed power in the study without the fostering procedure (ɪ-β = 0.79), while the finding in the study with the fostering method showed a low observed power (ɪ-β = 0.39).

In another study by Muzerelle et al. (2021), the contribution of serotonin to maternal care was investigated using mice with a null mutation in the tryptophan hydroxylase-2 (Tph2) gene resulting in a genetic serotonin depletion in the brain. In this study, the amount of time pup licking was the same in the Tph2 KO dams compared to the control (Tph2$^{+/+}$) dams, but Tph2

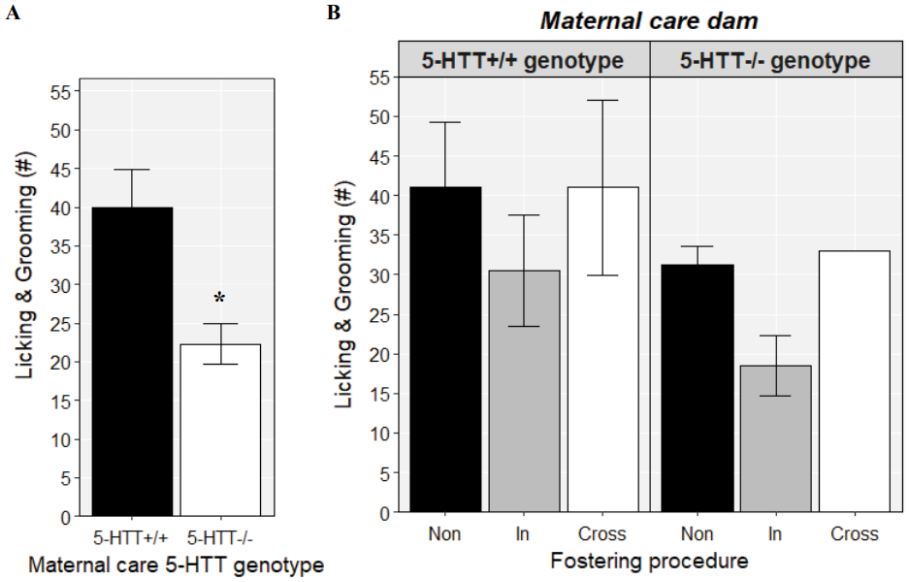


Figure 3. Effect of maternal 5-HTT genotype on maternal care. A) Dams with the 5-HTT$^{-/-}$ genotype lick and groom their offspring significantly less often then 5-HTT$^{+/+}$ dams (p = 0.009). **B)** After the fostering procedure, this difference in licking and grooming was barely visible. Data presented as mean ± SEM. (Hanswijk, 2022)

KO mice spent significantly less time nursing compared to the control mice (fig. 4D and 4E, respectively). Other maternal behaviors, like nest building and spending time in their nest were also altered in the Tph2 KO dams compared to the controls (fig. 4B and 4C). The nest building scores of Tph2 KO mothers were lower than those of the controls, and pups from the KO mothers were scattered around the nest, indicating a defect in huddling. Furthermore, Tph2 KO dams spent significantly more time outside the nest compared to control dams. Moreover, the survival rate of the pups was 0% with the Tph2 KO dam compared to 60% with the control dams (fig. 4A; (Muzerelle et al., 2021). However, the pups' genotype was not controlled for;

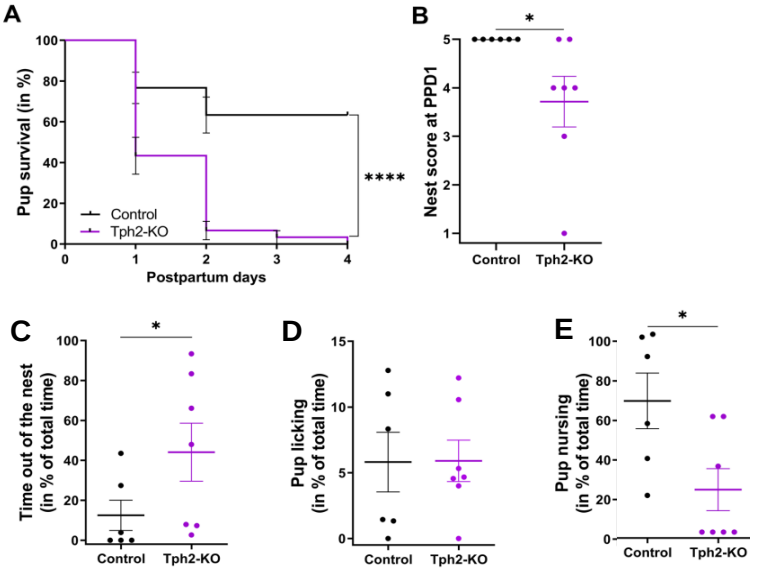


Figure 4. Reproductive success and maternal behaviors are altered in TPH2-KO dams. (A) All the litters from TPH2-KO dams were lost by postpartum day 4, in contrast to control dams. **(B)** Nest building scores at PPD1 were significantly higher in controls compared to Tph2-KO dams. **(C)** Tph2-KO dams spent more time outside the nest compared to control dams. **(D/E)** Both KO and control dams dedicated the same time to pup licking, but the KO dams spent significantly less time nursing. All data presented as mean ± SEM. (Muzerelle et al., 2021)

They had different genotypes in both groups since Tph2 KO dams and control dams were crossed with WT males. This difference in the genotype of the pups could have influenced the survival rate and potentially the maternal behaviors.
Overall these data show that maternal serotonin has an effect on maternal care behaviors, which then potentially have an influence on the offspring's behavior.

Influence of maternal 5-HTergic system on offspring's behavior
In the same study by Hanswijk et al. (2022), where they investigated the differences in maternal care, they also studied the role of maternal 5-HT genotype in anxiety- and depressive-like behavior in adult male 5-HTT$^{+/-}$ offspring. Again, a fostering procedure was performed where the non- and in-fostering groups were combined since no differences in maternal care were observed. In different behavioral tests, the adult male 5-HTT+/- offspring were examined for anxiety- and depressive-like behavior. As shown in figure 5A, offspring from 5-HTT$^{-/-}$ dams that were also exposed to 5-HTT$^{-/-}$ care spent more time on the open arms compared to all other groups. However, offspring from 5-HTT$^{+/+}$ dams that also received 5-HTT$^{-/-}$ care spent significantly less time on the open arms than offspring from similar dams but exposed to 5-HTT$^{+/+}$ care. This shows that exposure to maternal care with the opposite 5-HTT genotype as the biological dam leads to increased anxiety-like behavior in offspring. Also, the latency towards the open arm was lower in offspring exposed to maternal care from dams with the same genotype as the offspring's biological mothers, indicating lower anxiety behavior (fig. 5C). Furthermore, offspring were exposed to two other behavioral tasks examining symptoms of depression (anhedonia and learned helplessness). However, in these tasks, no group differences were discovered. This indicates that maternal 5-HT genotype does not influence offspring's depressive-like behavior.

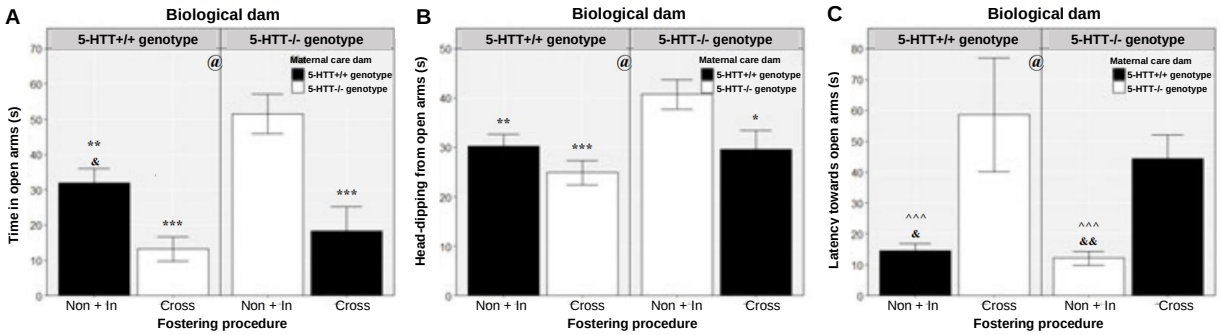


Figure 5. Associations between maternal 5-HTT genotype and care and adult male 5-HTT$^{+/-}$ offspring's anxiety-like behaviors. A) In the EPM test, offspring from 5-HTT$^{-/-}$ mothers, receiving 5-HTT$^{-/-}$ care spent more time on the open arms and **B)** spent more time performing head-dips on the open arms compared to the other groups. **C)** Offspring receiving maternal care from mothers with the same 5-HTT genotype as their biological mother showed the lowest latency towards the open arms. Data presented as mean ± SEM. * = p ≤ 0.05, ** = p ≤ 0.01, and *** = p ≤ 0.001 versus maternal dam 5-HTT-/- non- + in-fostering; & = p ≤ 0.05, && = p ≤ 0.01 versus maternal dam 5-HTT+/+ cross-fostering; ^^^ = p ≤ 0.0001 versus maternal dam 5-HTT-/- cross-fostering. (Hanswijk et al., 2022)

Maternal care associated with offspring's anxiety- and depressive-like behavior
To investigate the effect of maternal care on the offspring's behavior independent of the mother's genotype, multiple studies examined the effect of maternal care on offspring in different behavioral tasks for anxiety- and depressive-like behavior. In a study by Francis et al. (1999), offspring of high LG-ABN mothers and low LG-ABN mothers were examined in a novel open field test to assess anxiety. They did a cross-fostering study with a group in which the biological offspring of high LG-ABN and low LG-ABN were either reared by their biological mothers, the high control (H/C) and low control (L/C); cross-fostered back onto their own mothers, high/w (H/w) and low/w (L/w); cross-fostered to dams of the same group, high-high (H/H) and low-low (L/L); or cross-fostered across groups, high-low (H/L) and low-high (L/H).

All offspring reared by low LG-ABN dams showed less exploration time in the center of the novel open field, indicating more fearfulness compared to offspring reared by high LG-ABN dams (fig. 6). Furthermore, biological offspring from low LG-ABN dams reared by high LG-ABN dams were significantly less fearful in the novel open field test compared to any of the offspring reared by low LG-ABN mothers, indicating maternal care plays a role in the development of neuropsychiatric disorders, like anxiety.

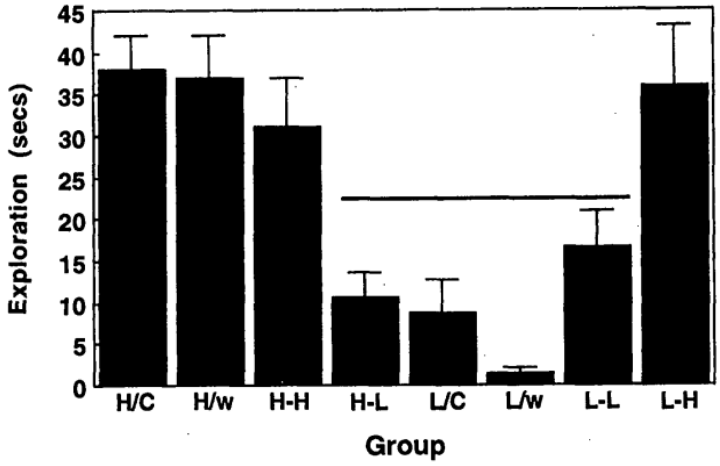


Figure 6. The amount of time (sec) spent in the inner area of the novel open field. Groups lying below the solid line differ significantly from those above the line. Data presented as mean ± SEM. (Francis et al., 1999)

Another study examined the relationship between maternal care and depressive-like behavior in the forced swim test (FST) and the sucrose preference test (SPT). The FST was used to assess the rodent's response to the threat of drowning, with rodents in a more depressive state supposedly giving up more easily and being immobile, whereas healthy rodents swim around and try to escape (Can et al., 2011). The SPT is a reward-based test used as an indicator of anhedonia (Liu et al., 2018). As shown in figure 7A, a correlation between the dams' nursing behavior and the offspring's immobility in the FST was found (Ronovsky et al., 2017), indicating more depressive-like behavior in offspring that received less maternal care. Surprisingly, in the SPT, offspring with a lower sucrose preference received more maternal care (fig. 7B), indicating that mice receiving more maternal care show anhedonia or depressive-like behavior. However, in this study, pregnant female mice received poly(I:C) to induce immune activation that modulates maternal care, which may have had an effect on the behavior of the offspring. It would have been better to use cross-fostering since that rules out interventions during pregnancy and genotype and more accurately shows how maternal care plays a role. Also, the forced swim test might not be an accurate test to assess depressive-like behavior, as immobility could also be interpreted as saving energy as mice learn they cannot escape and

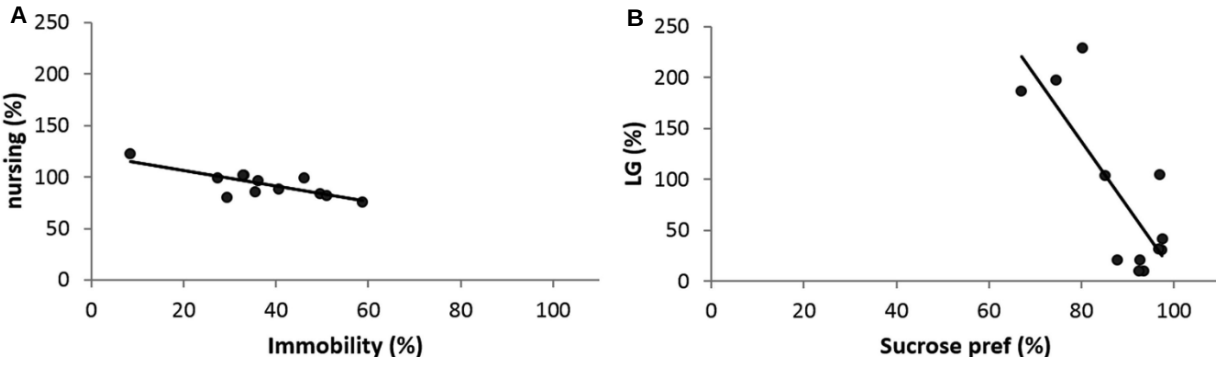


Figure 7. Correlation between first generation (F1) and second generation (F2). A) dam nursing behavior and offspring immobility in the FST. B) correlation between F1 dam licking and grooming (LG) behavior and F2 offspring sucrose preference in the SPT. (Ronovsky et al., 2017)

remember that when they are immobile, they are taken out of the water by the researcher, especially when they have previous experience with the environment.
Masís-Calvo and colleagues also studied the effects of maternal care on anxiety- and depressive-like behavior (Masís-Calvo et al., 2013). They tested rats in three behavioral tests: the open field test (OFT) and the elevated plus maze (EPM) to assess anxiety-like behavior and the FST to assess coping style behavior. In the OFT, no significant differences were found between offspring from low licking and grooming (LLG) dams and offspring from high licking and grooming (HLG) dams, suggesting there was no association between maternal care quality and anxiety-like behavior. However, in the EPM, offspring from HLG dams spent significantly more time in the central area and open arms and less time in the closed arms compared to offspring from LLG dams (fig. 8), suggesting a shorter duration of licking and grooming represents increased anxiety in offspring. In the FST, no significant differences were found between the two groups, indicating maternal care did not influence immobility behavior.

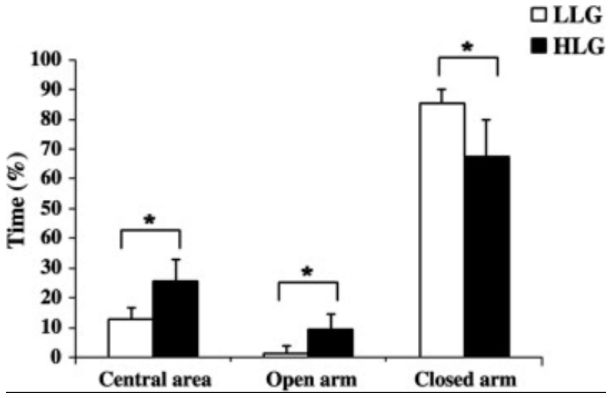
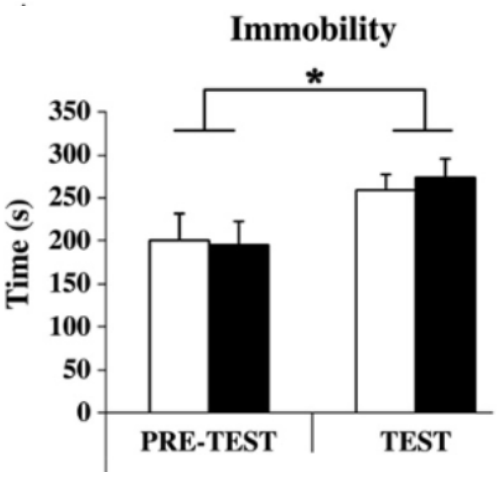


Figure 8. Amount of time spent in the different areas of the EPM in low and high LG groups. Data presented as median value ± IQR/2 (interquartile ranges/2). N=17 and N=22, respectively. *p<0.05. (Masís-Calvo et al., 2013)

However, as stated before, the FST might not be an accurate model to test depressive-like behavior, and as shown in figure 9, immobility duration in the test was higher compared to the immobility duration in the pre-test, implying rats learned that they cannot escape and are lifted out of the water by the researcher.

Figure 9. Immobility time (s) observed in the FST in low and high LG groups. Data presented as median value ± IQR/2. N=17 and N=22, respectively. *Within groups comparisons between PRE-TEST and TEST p<0.01). (Masís-Calvo et al., 2013)



Humans

5-HTTLPR gene variance

In humans, the *SLC6A4* gene encodes the 5-HTT (SERT). Within the gene's promoter region, there is a 5-HTT-linked polymorphic region (5-HTTLPR) that consists of two variants, the short (S)-allelic variant and the long (L)-allelic variant. The number of repeats differs between the two 5-HTTLPR variants, where the L-allele has 16 repeats, and the S-allele only has 14 repeats. Consequently, 5-HTT expression is about 50% lower in people with the S-allele

compared to the expression in people with the L-allele (Murphy & Moya, 2011). Furthermore, the single nucleotide polymorphism (SNP), i.e. rs25531, is another genetic variation that affects 5-HTT function, which substitutes a single base (A > G) within the 5-HTTLPR L allele. This L_G variant results in about the same 5-HTT expression as the 5-HTTLPR S allele variant (Hu et al., 2006). Regarding 5-HTT mRNA expression and function, the L_AL_A genotype differs significantly from the other genotypes (SS, SL_G, L_GL_G, L_AL_G, but not from SL_A). L_AL_A and SL_A have the highest 5-HTT availability, the highest 5-HT storage, and the lowest extracellular 5-HT availability (Hu et al., 2006).

Role of 5-HTTLPR gene variance on neuropsychiatric behaviors

Many studies have investigated whether 5-HTTLPR gene variance is involved in the pathophysiology of neuropsychiatric disorders. For example, according to multiple studies, 5-HTTLPR S/L or S/S genotypes seem to be associated with amygdala-related social and communication deficits, manifesting in ASD (Brune et al., 2006; Tordjman et al., 2001; Velasquez et al., 2017; Wiggins et al., 2014). Although very inconsistent, 5-HTTLPR gene variance may also be involved in ADHD. Some studies found a link between the 5-HTTLPR polymorphisms and inattentive symptoms, while others found an association with hyperactivity and impulsivity symptoms (Chen et al., 2019; Gadow et al., 2013; Li et al., 2007). In people with depression and anxiety, a link with the 5-HTTLPR gene was also observed. In a study by Caspi et al. (2003), they found that individuals with HTTLPR S/L or S/S genotype displayed more depressive symptoms, diagnosable depression, and suicidality in response to stressful live events compared to individuals with the 5-HTTLPR L/L genotype. For anxiety, differences between men and women were found; the S allele and SS genotype appeared to be more often associated with an increased risk of anxiety in women, but not in men (Gressier et al., 2016).

Maternal genotype influencing offspring's behavior

The hypothesis that the 5-HTTLPR gene variance in offspring is involved in the pathophysiology of neuropsychiatric disorders is often studied, as mentioned above, but the potential involvement of maternal 5-HTTLPR genotype in these disorders in offspring has not received much attention. Hanswijk et al. (2021) examined the association between maternal 5-HTTLPR genotype and clinical and cognitive measures of ADHD and comorbid ASD in typically-developing and ADHD-diagnosed offspring. First, they observed that offspring from mothers with low-expressing 5-HTTLPR genotypes (SS, L_GS, L_GL_G, and L_AL_G) showed lower anxiety levels than those from mothers with high-expressing genotypes (L_AL_A and L_AS). Therefore, the offspring's anxiety levels were included in the sensitivity analyses as it was a potential mediator. As shown in figure 10, they found that the maternal 5-HTTLPR genotype was not associated with clinical ADHD measurements of the offspring, but they did find that female offspring from mothers with low-expressing 5-HTTLPR genotypes displayed slightly higher stereotypic scores, which is a clinical measure of ASD, than female offspring from mothers with high-expressing 5-HTTLPR genotypes.

Furthermore, there were some associations between maternal 5-HTTLPR genotype and offspring's cognitive measures that are related to ADHD and ASD. Adult male offspring from mothers with low 5-HTTLPR genotypes expression made fewer errors and required fewer trials to complete the reversal-learning task compared to adult male offspring from high-expressing 5-HTTLPR genotype mothers (fig. 11), indicating that male offspring from high-expressing 5-HTTLPR genotype mothers are more likely to have a reduction in cognitive flexibility, that is characterized in ASD and ADHD. This supports the finding by Kistner-Griffin et al. (2011), who found that the maternal 5-HTTPLR L-allele induced the risk for offspring's ASD, but this does not comply with the finding, as discussed earlier, that increased stereotyped behavior was associated with low-expressing 5-HTTLPR genotype instead of high-expressing genotype.

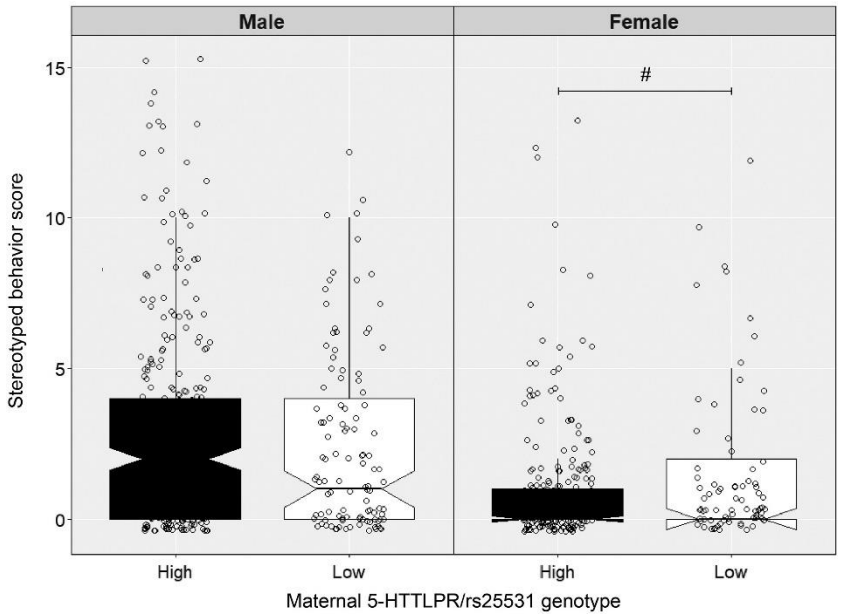


Figure 10. Association between stereotyped behavior and maternal 5-HTTLPR/rs25531 genotype. The black box represents the maternal high expressing 5-HTTLPR genotypes (L_AL_A and L_AS) and the white box represents the maternal low expressing 5-HTTLPR genotypes (SS, L_GS, L_GL_G and L_AL_G). These boxes indicate the interquartile range and the whiskers show the 95% confidence interval. #: post hoc test p≤0.1. (Hanswijk et al., 2021)

In the identification of facial emotions task, it was revealed that girls from low-expressing 5-HTTLPR mothers demonstrated an increased accuracy in recognizing happy faces compared to girls from high-expressing 5-HTTLPR mothers (fig. 12). Also, adult offspring from low-expressing 5-HTTLPR mothers reported slower recognition times compared to adult offspring from high-expressing 5-HTTLPR mothers, but after sensitivity analysis which included the offspring's anxiety levels, this finding disappeared.

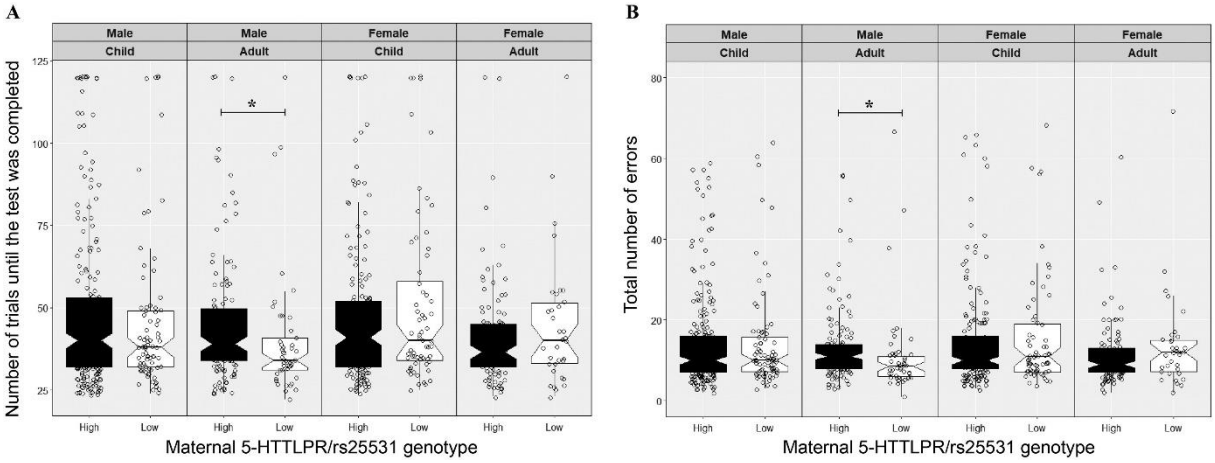


Figure 11. Associations between maternal 5-HTTLPR/rs25531 genotype and deficits in cognitive flexibility. A) Number of trials until the reversal learning task was completed. B) Total number of errors in the reversal learning task. The black box represents the maternal high expressing 5-HTTLPR genotypes (L_AL_A and L_AS) and the white box represents the maternal low expressing 5-HTTLPR genotypes (SS, L_GS, L_GL_G and L_AL_G). These boxes indicate the interquartile range and the whiskers show the 95% confidence interval. *: sensitivity and post hoc tests p≤0.05. (Hanswijk et al., 2021)

Thus, these findings show that maternal 5-HTT genotype, but not child 5-HTT genotype, appear to be associated with stereotyped behavior, cognitive flexibility, reward processing, and emotion recognition that are cognitive measures related to neurodevelopmental disorders like ADHD and ASD, although most associations are only visible in specific subgroups such as offspring's age, sex and anxiety levels.

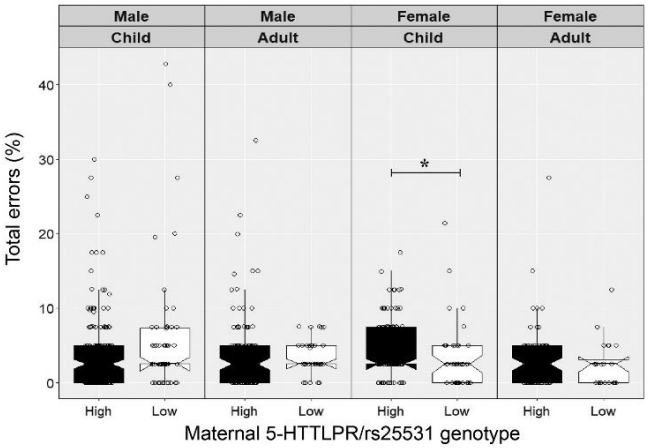


Figure 12. Association in offspring between maternal 5-HTTLPR/rs25531 genotype and recognizing happy faces. The black box represents the maternal high expressing 5-HTTLPR genotypes (L_AL_A and L_AS) and the white box represents the maternal low expressing 5-HTTLPR genotypes (SS, L_GS, L_GL_G and L_AL_G). These boxes indicate the interquartile range and the whiskers show the 95% confidence interval. *sensitivity and post hoc tests p ≤ 0.05. (Hanswijk et al., 2021)

Role of 5-HTTLPR on parental care

One of the hypotheses that the maternal 5-HT system contributes to the offspring's neurodevelopment and altered behavior is thought to be through neurotrophic factors, but environmental factors, such as maternal care, may also mediate the association between maternal 5-HTTLPR genotype and neurodevelopmental disorders in offspring. For example, mothers carrying the 5-HTTLPR S-allele exhibited less positive parenting behavior in response to disruptive child behavior than mothers with the 5-HTTLPR L/L genotype (Morgan et al., 2018). Positive and negative parenting was assessed by using the Dyadic Parent Child Interaction Coding System (DPICS; Eyberg et al., 2005). In contrast, another study observed that mothers that carried the 5-HTTLPR S allele were more sensitive towards their children (Cents et al., 2014), which was supported by another study that found that both mothers carrying the S allele as well as the L_G allele had a higher maternal sensitivity than mothers carrying only the L_A allele (Mileva-Seitz et al., 2011). Maternal sensitivity was observed and assessed using the Ainsworth's 9-point rating scales for sensitivity and cooperation and the Erickson 7-point rating scales for supportive presence and intrusiveness (Ainsworth et al., 1975; Egeland et al., 1990). Furthermore, in this last study by Mileva-Seitz and collegues, highly-significant gene-environment interactions were found as well in association with maternal behavior. Mothers with the L_AL_A genotype and providing negative early care quality

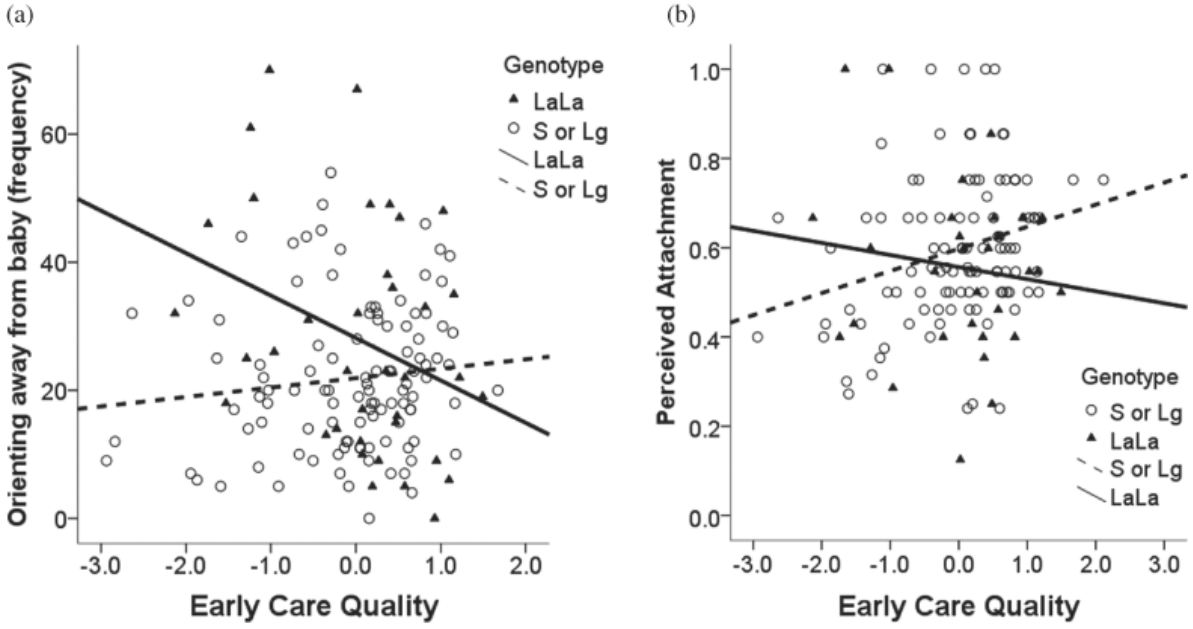


Figure 13. Correlation between early care quality and (a) frequency of the mother orienting away from their baby and (b) mothers' perceived attachment to the infant. (Mileva-Seitz et al., 2011)

oriented away more frequently from their children (fig. 13a), and mothers carrying the S allele and providing greater early care quality scored higher on their perceived attachment to their child (fig. 13b), assessed by video-recorded mother-infant interactions at six months post partum.

Parental care on offspring's behavior

These differences in maternal care between mothers with different 5-HTTLPR gene expressions can have an influence on the behavior and development of neuropsychiatric disorders in their offspring as over the years, studies have demonstrated that not only the transmission of risk genes is essential, but also the maternal environment on offspring's neural, cognitive, emotional, and social changes in later life, with one of the main maternal environmental factors being parental care (Belsky & de Haan, 2011; Tolan et al., 2013). In a study with 6483 adolescents from age 13 to 18 years, high maternal care was associated with a lower chance of depression and eating- and behavioral disorders, while high maternal control was associated with a higher risk of depression, anxiety, and eating- and behavioral disorders (Eun et al., 2018). Some behaviors including maternal control are physical and verbal manipulation of children's behaviors and negative displays, anger and rejection. Moreover, paternal behavior was also analyzed, where high paternal care was associated with a lower chance of social phobia and alcohol abuse or dependence, while high paternal control was associated with higher chances of agoraphobia and alcohol abuse or addiction but also lower chances of ADHD. Also, results from a study from Shaw et al. (2004) suggested that a lack of parental emotional support in children was associated with increased levels of depressive symptoms and chronic conditions in adulthood, while children with abundant support were likely to have relatively good health throughout adulthood (Shaw et al., 2004). Another study observed that there was an association between lack of parental care and four different anxiety disorders, i.e. panic disorder with and without agoraphobia (PDAG), generalized anxiety disorder (GAD), social phobia (SOP), and simple/specific phobia (SP) (Heider et al., 2008). The association between parental care and anxiety disorders is similar to the association between parental care and depression (Sato et al., 1998), and a study that investigated parental care as a potential risk for 13 psychiatric disorders suggested that the increased risk of disorders during adulthood that was caused specifically by a lack of care is non-disorder specific (Enns et al., 2002).

Discussion

The aim of this essay was to investigate whether the maternal 5-HTergic system influenced maternal care and hence the vulnerability for the development of neuropsychiatric disorders in offspring. By examining both rodent and human studies, there is much evidence stating the serotonergic system has an effect on maternal care and on the behavior of offspring. There are already many studies that have investigated a potential role of the maternal serotonergic system during pregnancy, where it affects the development of the child (Rakers et al., 2020; St-Pierre et al., 2016; Vehmeijer et al., 2019), but the focus of this essay was to assess the effect of the postnatal environment on the behavior of the offspring, specifically maternal care.

In rodents, evidence was found that at least two different serotonergic rodent models, the 5-HTT$^{-/-}$ rat and the Tph2 KO mouse, had a negative effect on maternal care behavior, such as licking and grooming, nursing, nest building, and spending time with the pups (Hanswijk, 2022; Muzerelle et al., 2021). As offspring from maternal 5-HTT$^{-/-}$ rats showed increased anxiety and many studies observed an association between maternal care and anxiety- and depressive-like behaviors in mice and rats (Francis et al., 1999; Ronovsky et al., 2017), it can be suggested that the maternal 5-HTergic system influences maternal care and with that the development of neuropsychiatric disorders in offspring. One possible explanation for the lack of maternal care in 5-HTT$^{-/-}$ rats is the activation of different 5-HT receptors, as 5-

$HTT^{-/-}$ rats have more extracellular 5-HT concentrations that activate different receptors. In particular the $5\text{-}HT_{2A}$ has been studied by Gao and colleagues, who found that the activation of this receptor disrupted maternal care (Gao et al., 2018). However, as more receptors are involved in 5-HT signaling and may have a possible role in maternal care behavior, it could be an important future study to investigate which other receptors are also implicated.
Furthermore, $5\text{-}HTT^{-/-}$ rats show anxiety- and depressive-like behavior (Olivier et al., 2008), which might contribute to the impairment of the quality of maternal care. However, more research should be done to examine which 5-HT receptors are further involved in disruptive maternal care, so treatments can be conducted to prevent impaired maternal care and reduce the risk of neuropsychiatric disorders in offspring. Furthermore, depressive-like symptoms in rodents were difficult to measure, as the forced swim test can no longer be identified as an accurate experiment for depression-like behavior. Therefore, better tests should be created to help understand the effect of the serotonergic system on depressive-like behavior.

In humans, lower anxiety levels were found in offspring from mothers with low-expressing 5-HTTLPR genotypes compared to offspring from high-expressing 5-HTTLPR genotype mothers. However, no association was found between clinical ADHD in offspring and the genotype of the mother, although only a few studies have studied this (Hanswijk et al., 2021). Besides, some cognitive measures that are related to ADHD as well as to ASD were found. Also, slightly higher stereotypic behavior, a typical symptom of ASD, in female offspring was found from mothers with low-expressing 5-HTTLPR genotype. However, this is in contrast with the finding from another study showing that mothers with high-expressing 5-HTTLPR genotype induced the risk for ASD in their offspring (Kistner-Griffin et al., 2011). Further research is therefore needed to explain these inconsistent effects.

Lower parental care and higher parental control were associated with worse mental health and behavioral disorders in their children, and a lack of parental emotional support and parental care was associated with more depressive and anxiety symptoms, while children with abundant support from their parents had good health throughout adulthood (Eun et al., 2018; Heider et al., 2008; Shaw et al., 2004). It was also suggested that the increased risk of adulthood disorders caused by lack of care is non-disorder specific (Enns et al., 2002). Thus, these findings indicate that 'lack of' parental care greatly influences the development of depression, anxiety, and other neuropsychiatric disorders in offspring. However, findings about the role of 5-HTTPLR on parental care are inconsistent as one study found that mothers carrying the S-allele showed less positive parenting, while other studies observed that mothers with this genotype were more sensitive towards their children (Cents et al., 2014; Mileva-Seitz et al., 2011; Morgan et al., 2018). Another review supported these contradictory findings as two studies, including Cents et al. (2014) and Mileva-Seitz et al. (2011), found mothers carrying the S allele were less sensitive to their children while two other studies, from Morgan et al., (2018) and Bakermans-Kranenburg & van IJzendoorn (2008), observed more sensitivity towards their infants from parents carrying the S allele (Landoni et al., 2022). Therefore, it is difficult to explain whether neuropsychiatric disorders in children from mothers with different 5-HTTLPR gene expression are caused by lack of paternal/maternal care, which was a possible factor in rodents, or that other factors have a big influence. Besides, parenting is highly complex and only looking at sensitivity towards their children might not give an accurate representation of the parental care quality they provide.
To further investigate this issue, future research could examine the influence of parental care by exploring paternal care in children from different 5-HHTPLR gene-expressing mothers. By receiving only paternal care and no maternal care, it can be examined whether only intrauterine factors played a role in neuropsychiatric disorders in children from mothers with different 5-HTTLPR gene expression or whether postnatal care had a significant influence on neuropsychiatric disorders in children. A limitation of the rodent studies was that only maternal care and no paternal care could be investigated, as males often are not involved in rearing

offspring. Thus, it is difficult to study in rodents whether the offspring's behavior is mainly caused by intrauterine factors, or also by maternal care. This is different in humans, where often fathers also have a big influence on parental care. Therefore, it could be an exciting study in primates as this is easier and faster to arrange than in humans.

Interestingly, in the unpublished study by Hanswijk et al. (2022), they found that offspring that received maternal care by dams with the opposite 5-HTT genotype as their biological mother showed an increase in anxiety-like behavior (Hanswijk et al., 2022), indicating that when the early postnatal environment is different from the intrauterine environment, it affects brain development, which results in increased anxiety-like behavior. This is interesting when translating it to humans, as adopted and foster children are also raised in an environment that is different from their intrauterine environment. Indeed, several studies have found significant differences between nonadopted and adopted children in social, emotional, behavioral, and cognitive functioning (Andresen, 1992; Brodzinsky, 1993; Verhulst et al., 1990a), although also no differences were found between adopted and nonadopted children in some other studies (Borders et al., 1998; Elonen & Schwartz, 1969). In addition, it was found that when a child was older at placement, they were more likely to develop emotional or behavioral problems than when they were younger (Brand & Brinich, 1999; Verhulst et al., 1990b). This suggests that when the early postnatal environment is different from the intrauterine environment, it does not necessarily increase the risk for neuropsychiatric disorders, as only placement at a later age showed a significant difference between nonadopted and adopted children. Also, it should be pointed out that adopted children often already have experienced more adversity and a lot of external factors play a role in the development of neuropsychiatric disorders, which makes it challenging to study only the effect of the intrauterine environment and parental care on disorders in these children.

In summary, maternal care in rodents is affected by the serotonergic system in mothers and plays a role in the development of neuropsychiatric disorders in offspring. Moreover, offspring receiving maternal care from a mother with an opposite 5-HTT genotype as their biological mother demonstrated increased anxiety levels, suggesting offspring raised in a different postnatal environment than their intrauterine environment experience increased anxiety, which will be an interesting study in humans for children that are adopted. Although future research should further explore how the increased extracellular serotonin in 5-HTT$^{-/-}$ dams affects maternal care, recent studies have shown that activation of the 5-HT$_{2A}$ receptor disrupts maternal behavior. The disruptions in maternal care and its association with neuropsychiatric disorders in offspring were not replicated and were inconsistent in human 5-HTTLPR studies. A possible explanation for this could be that parenting is highly complex. Therefore, future research could look into different types of parenting to further explore the association between parental care and neuropsychiatric disorders in offspring. Lastly, as not only maternal care but also paternal care is provided in humans, it is easier to study whether parental care from different 5-HTTLPR expressing parents significantly influences offspring's behavior besides the intrauterine environment.

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