Bachelor Thesis

Maternal sleep during pregnancy

Neurobiological, cognitive and behavioural effects of sleep disruption and deficit

Author: M.E.H. Meyer

Student number: S3400204

Major: Bsc Biology - Behaviour and Neuroscience

Research Cursus: Neuroscience Research

Supervisor: Prof. dr. J.D.A Olivier

Date: 05-07-2020

Abstract

Physical and psychological complaints especially towards the end of pregnancy can lead to a disruptive night sleep and sleep deficits in pregnant women. Sleep deprivation can often be restored by NREM sleep taking over REM sleep, but sleep disruption reduces the ability to produce high amplitude slow waves in NREM sleep and therefore has long lasting effects. Hormonal changes during pregnancy can affect sleep architecture. Estrogen decreases time spend in REM sleep while progesterone increases NREM sleep. The suppression of REM sleep might be beneficial as it stabilizes both maternal and fetal autonomic nervous functions such as blood pressure, heart rate, and respiratory rate. Sleep deprivation increases the allostatic load and is considered both a result of stress and a stressor per se.

During pregnancy, the hypothalamic-pituitary adrenal axis (HPA axis) is hyporesponsive to stress. This adaptation occurs at several levels, including a reduced positive feedback of glucocorticoids. During pregnancy the maternal innate immune response is also restrained, to protect the half-foreign embryo. Pregnancy hormones in relation with the HPA axis and the maternal immune response cause cognitive changes in the maternal brain that have positive effects on maternal behaviour from an evolutionary perspective. Sleep deprivation increases HPA axis activity and inflammation, which takes away the buffer of the mitigates stress response. This could prevent evolutionary beneficial cognitive changes and even lead to adverse pregnancy outcomes such as Postpartum Depression. To improve sleep quality during pregnancy, cognitive behavioural therapy or pharmacotherapy can be considered.

In conclusion, the interaction between pregnancy hormones, the HPA axis response and the immune system are the main mediators causing the negative neurobiological, cognitive and behavioural effects of maternal prenatal sleep deprivation.

Index

Chapter 1: Preface

1.1 Introduction

Pregnancy is for most woman a very special experience and growing life inside their bodies can have a big emotional impact. It can be the reason for a lot of excitement, fears, concerns, questions, curiosities and the making of life-changing decisions. Some women think pregnancy is the most beautiful experience one could ever be part of, while others hate the nine month process because of how brutal it can be for the body. Complaints like backache, constipation, faintness, indigestion, incontinence or leg aches and crams are quite common (*'NHG Pharmacy', n.d.*). All these physical burdens, combined with emotional factors like anxiety, can make it very difficult for pregnant women to get a good night's sleep.

The well-known side effects and complaints of pregnancy are not the only causes of sleep deficits in pregnant woman. The environment and social context we live in also have a great impact, of which negative associations are often stronger for women than for men (Hale et al., 2015). People cannot do without sleep for lengthy periods of time but they can compress sleep duration as a result of a demanding working and/or family life (*Chatzitheochari & Arber, 2009*). Chatzitheochari & Arber found an inverse relationship between working hours and sleep duration (*2009*). Due to the invention of artificial light, it makes it easy for us to stay longer awake and to ignore and manipulate our natural sleeping rhythm so that we eventually develop a sleep deficit (*Kantermann, 2013*).

More women have a fulltime job nowadays and want to continue working as long as possible during their pregnancy, because it is better for their career, or because then they will have more time free from work after delivery. All these factors can lead them to feel more stressed and get less sleep during their pregnancy (*reviewed in: Cappuccio et al., 2010*).

We know that sleep is crucial for a healthy life. It might seem that human sleep is a period in which our brain and body rests, but this is not the case (*Meerlo, et al., 2015*). When we sleep our body and brain are metabolically very active so that all systems, organs, tissues and mind can be supported or compromised. Sleep boosts our immune system, balances metabolism and hormones, regulates blood sugar levels and blood pressure, combats fatigue and supresses cancer cell growth. The effects of sleep on our brain can aid in problem-solving, influencing memory retention, the ability to concentrate, regulate emotions, improve coping skills and inspire creativity (*Mosey, 2020*).

Especially the studies where the effects of sleep deprivation were studied, show us the importance of sleep, as they almost all conclude that lack of sleep has negative outcomes (*Scott et al., 2006; Guadagni et al., 2014; Boonstra et al., 2007*). Therefore, when pregnant women get less sleep, this might also affect their mental and physical health. The effects of sleep deficit may be even more disastrous in pregnant women than in non-pregnant women. The pregnant body is in a constant challenging state of maintaining a homeostasis that allows the fetus to get as much resources as possible, without neglecting or destroying the needs of the mother. This costs a lot of energy and makes the body and mind vulnerable to experience the negative effects of sleep much sooner than non-pregnant women do (*Ziomkiewicz et al., 2018*).

In short, a lot of factors are involved in developing a disturbed sleeping pattern and eventually a sleep deficit in pregnant women. Sleep deprivation can have negative outcomes for both the mother and the child. This thesis will focus on maternal prenatal sleep and its neurobiological, cognitive and behavioural effects in pregnant women.

Chapter 2: Maternal sleep during pregnancy

2.1 Regular sleep behaviour

Sleep is a behaviour that can have a varying presence, quality, intensity and function between species and across the lifespan (*Siegel, 2009*). In many animal species sleep is a way to maximize energy savings by reduced body and brain energy consumption and increased survival by seeking out a safe sleeping site instead of just wandering around. When we are awake, we respond to our environment and all its impulses. We make use of our senses and use the information we get to adjust our behaviours. During sleep, depending on the sleep phase, we do not really respond to our environment anymore, and physiological and biochemical changes inside the body occur (*Pace-Schott, et al., 2002*). Hormones are released and a variety of recuperative processes are conducted, that among other things support brain function (*reviewed in: Frank, 2006*). Some species like marine mammals, terrestrial animals and birds that migrate for long distances, or large herbivores and animals with exposed sleeping sites seem to be able to perform these recuperative processes when they are awake, but humans have to be asleep (*Siegel, 2008*).

As we are sleeping 1/3 of our lives (*Aminoff et al., 2011*), it is reasonable to say that sleep plays a very prominent part in human life. Although everyone deals with sleep every day, the reason why we sleep remains a bit mysterious. There are a lot of theories, and there is a rising amount of research conducted on this subject of which some researchers focus only on portions of sleep behaviour, while other researchers take a more holistic approach. Despite the wealth of research on sleep, there still remains a lot unknown.

The sleep-wake cycle is controlled by intrinsic biological clocks that determine the timing of daily biochemical, physiological, and behavioural changes. Our circadian clock has a 24 h cycle and can be resynchronized or entrained by external cues such as the light to dark cycle or by internal cues like the pineal hormone melatonin (*Pace-Schott, et al., 2002*). When disruptions in this circadian system occur due to things like shift work, jet lag, and lifestyles, it can impair cognitive function (*Reid et al., 2011*). In mammals, the main circadian regulator in the brain is the suprachiasmatic nucleus (SCN). This bilateral hypothalamic nucleus lies immediately above the optic chiasm (*Klein et al., 1991*), and determines the timing of sleep-wake cycles while simultaneously synchronizing many other local brain clocks to a complementary circadian rhythm (*reviewed in: Kyriacou & Hastings, 2010*). Neurochemical distinct nuclei located in the basal forebrain, preoptic area, lateral hypothalamus, and brainstem are for example part of intricate neurocircuitry that are anatomically linked to the SCN *(Saper et al., 2010*). These brain areas induce and maintenance arousal and the different sleep stages (*Mong et al., 2011*). During a typical full night of sleep the brain switches between these different sleep stages for a couple of times in a cyclic manner (*Feinberg & Floyd, 1979*). This can be measured with the help of an EEG (electroencephalogram) (*Teplan, M., 2002*). An EEG measures voltages generated by the currents that flow during synaptic excitation of the dendrites of many pyramidal neurons in the cerebral cortex, which lies right under the skull and makes up most of the brain's mass. It takes many thousands of underlying neurons, activated together, to generate an EEG signal big enough to be measured at all. Therefore, the amplitude of the EEG signal is strongly dependent on how synchronous the activity of the underlying neurons is. With an EEG the electro-activity in the brain can be measured, of which human have a few dominant frequencies (*Bear, et al., 2016*).

Human frequencies of electro-activity can be divided into two main forms of sleep that are very different and both have their own function: rapid-eye-movement (REM) sleep and non-rapid-eye-movement sleep (NREM) in which slow wave activity (SWA) takes place. About 25% of the total sleep time is spent in REM and 75% is spent in NREM (*Bear, et al., 2016*). In the REM sleep state, the EEG looks very active. It is a state in which the body, except for your eyes and respiratory muscles, is immobilized, and in which you can have vivid, detailed dreams. During the NREM sleep period, movement is minimal, temperature and energy consumption is lowered and parasympathetic activity increases (*Siegel, J. M. 2005*). While REM sleep contains only one state, non-REM sleep can be divided into 4 different stages that are varying from light to deep sleep as

you can see in figure 1 (*Bear, et al., 2016*). Stage 1 sleep is the lightest and the sleep stage in which the transition of wake-sleep is made. Stage 2 sleep is slightly deeper and one of its characteristics include the 8-14 Hz oscillation of the EEG, which is generated by the thalamic pacemaker and called the spindle. Stage 3 sleep, is deeper and shows large-amplitude, slow delta rhythms. Then at last, stage 4. This is the deepest stage of sleep, with large EEG rhythms of 2 Hz or less. When all these 4 stages have been gone through, the sleep will be lighter again and stage 3, stage 2 and stage 1 occur where after REM sleep with its fast EEG beta and gamma rhythms and sharp, frequent eye movements begins again. The amount of NREM sleep each cycle is in the beginning of the night high, but decreases gradually as sleep progresses (*Bear, et al., 2016*).

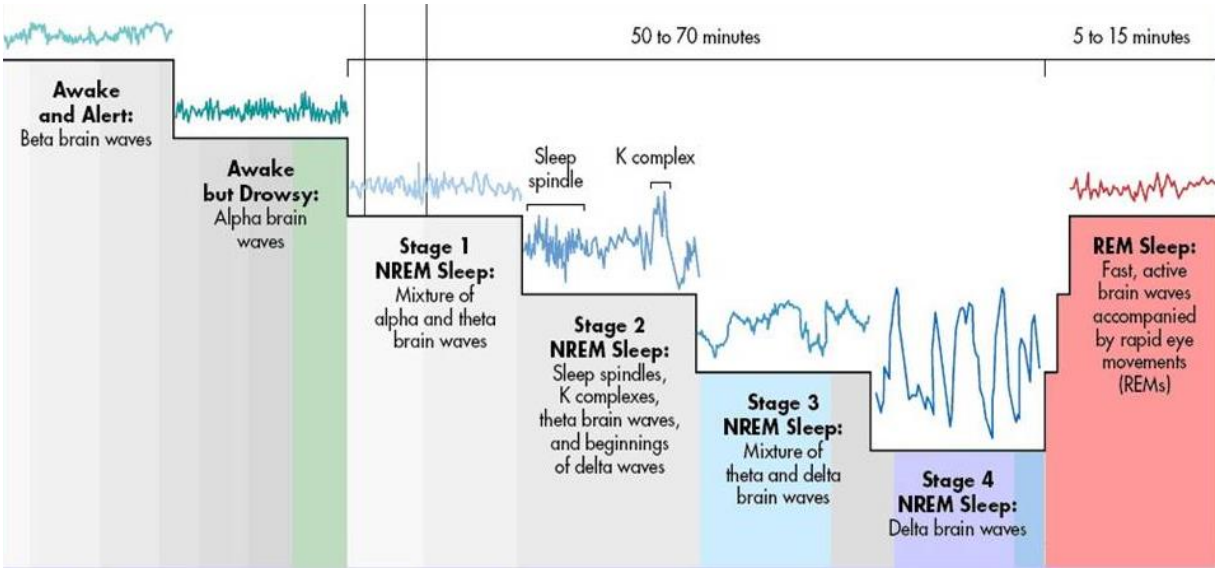

Fig. 1. Sleep stages with respect to EEG. Different characteristics of EEG rhythms are visible for each sleep stage together with the time spent in NREM and REM sleep. (*Cháberová, 2017*).

When we experience sleep loss, we compensate for this sleep loss the next time we sleep by increasing the amount of NREM sleep. After short sleep deprivation the SWA also increases which can totally recover the sleep lost within a couple of hours. In principal, there is a clear relationship between the waking duration and the amount of SWA in NREM sleep, but there are also observations that indicate that the occurrence of SWA in NREM sleep can change during a life time. These changes all occur without affecting sleep homeostatic responsiveness (*Deboer, 2013*). The quality of sleep and waking in contrast, might be a factor that has an influence on the homeostatic responsiveness. Disturbed sleep reduces the ability to produce high amplitude slow-waves in NREM sleep (*Deboer, 2013*), which might have negative consequences concerning metabolism, endocrine functions and immune function (*AlDabal, 2011*), but also mood regulation, motor function and cognitive performance such as executive attention, working memory, and divergent higher cognitive functions (*Durmer & Dinges, 2005*).

2.2 Sleep and pregnancy

According to the National Sleep Foundation, adults need 7 to 9 hours of sleep per 24 hours (*National Sleep Foundation, n.d.*). The need for sleep and sleep duration varies between individuals and could depend on age (*reviewed in: Mander et al., 2017*), gender (*Mallampalli & Carter, 2014*) and also in pregnancy (*Won, 2015*). The reproductive state of the body of a pregnant woman changes sleep in many ways, which will be elaborated in chapter 2.2.1. In general, the quality of sleep worsens throughout pregnancy, mostly because as the pregnancy goes on, the amount and intenseness of involved physical disturbing factors increase (**Fig. 2**) (*Sahota, et al., 2003*). But next to the physical complaints of being pregnant, hormones can also have an impact on prenatal sleep. This will be elaborated in subchapter 2.2.2.

2.2.1 Sleep throughout the different trimesters of pregnancy

The duration of a normal pregnancy is 40 weeks and can be divided in 3 trimesters of each 3 months. Each trimester is marked by specific fetal developments and maternal physiological changes (*UCSF Health, n.d.*). When we compare the way women of these different trimesters sleep, there are some variations visible.

In the beginning of pregnancy, the first trimester: 0-13 weeks, women tend to sleep more than they did before pregnancy. Women often feel very tired and they start to feel the effects of pregnancy on their bodies. This makes the realization of the pregnancy easier, which could bring psychological stress and fear. Complaints of fatigue and/or nausea are in this trimester associated with disturbed sleep (*Pien & Schwab, 2004*). The total hours of sleep at night increase with 0.7 hours during the first trimester, but the sleep efficiency decreases together with NREM and SWA compared to the prepregnancy period. It seems like the longer sleep duration is necessary to compensate for the decreasing sleep efficiency (*Oyiengo, et al., 2014*). During the second trimester of pregnancy (14-26 weeks), the amount of sleep begins to go back to the amount it used to be before the pregnancy. This is beneficial for the women because they feel less tired throughout the day. But when the pregnancy goes on the women tend to experience more physical disturbing factors that can cause more nocturnal awakenings than usual. In the third semester (27-40 weeks), these factors become at their worst and could involve snoring, restless legs syndrome, frequent urge to urinate, backache, fetal movements, heartburn or discomfort in general. The amount and intensity of physical disturbing factors will only increase during pregnancy until the number of awakenings is two-folded from pre-conception to the third trimester. This indicates a lower sleep efficiency in late pregnancy than in a non-pregnant control group (*Baratte-Beebe & Lee, 1999*).

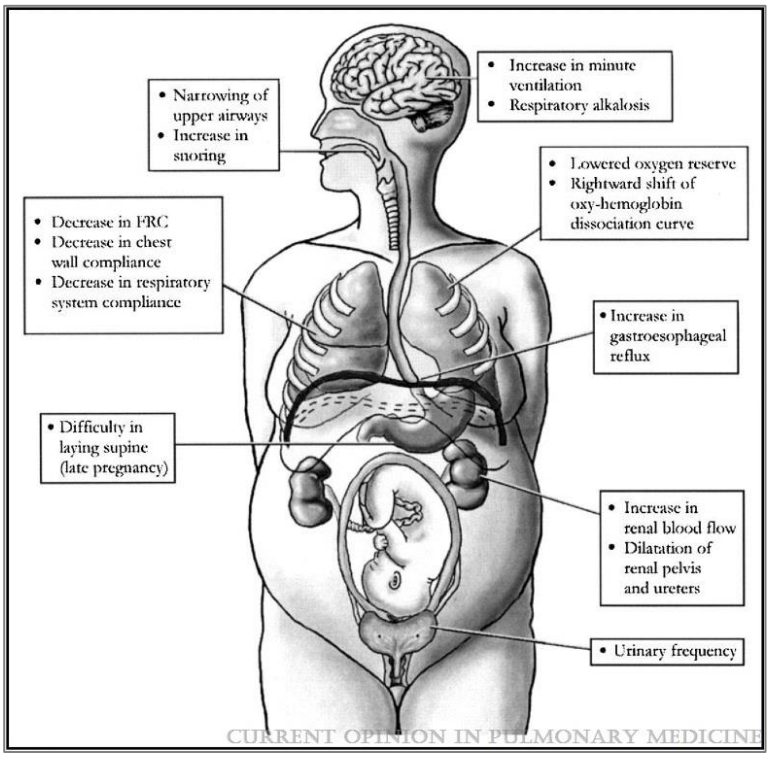

Fig. 2. Factors influencing sleep during pregnancy. A variety of hormonal, physiologic, and physical changes could contribute to sleep disturbances during pregnancy (Sahota, et al., 2003).

As explained above, during pregnancy there is a drastic change in the duration of sleep, where sleep duration during the first semester significantly increases, but shows a big decrease towards the end of pregnancy (*Hedman et al., 2002*). The reason for this change is often for a large part due to the physical changes, but other less obvious factors like psychological stress could be involved too. The change in the duration of sleep could also reflect specific hormonal changes, that not only have an influence on the duration of the total amount of sleep, but can also affect the sleep architecture during pregnancy. Findings of Lee and colleagues show that especially

multipara mothers were quickly able to get into deeper, more restorative stages of sleep after awakening (*2000*). This supports the restorative theory of deep sleep in pregnancy, in which deep sleep takes precedence over REM sleep during opportunities for recovery from sleep deprivation. Nonetheless, the NREM sleep (stages 3 and 4) was diminished throughout pregnancy in both multipara mothers and novice mothers compared to baseline and postpartum. Lee and colleagues also found that the sleep of multiparas before pregnancy was less efficient compared to nulliparas, even though their children slept through the night, and that at 3 months postpartum the nulliparas did not return to their prepregnancy sleep patterns (*2000*). They returned to baseline characteristics for multipara women (*Lee, 2000*). This indicates that pregnancy can have a long-lasting effect on the sleep architecture of women.

2.2.2 Hormonal changes during pregnancy and their effects on sleep architecture

Women experience from puberty to the menopause hormonal fluctuations. When women become pregnant, there is a major change in these cycle fluctuations. Suddenly the body has to be prepared for making life and caring for this offspring. The first change that happens is the production of the hormone hCG (human chorionic gonatropin) by the syncytiotrophoblast after fertilization and nesting of the fertilized egg in the uterus wall. This hCG production maintains the corpus luteum and stimulates progesterone production of the corpus luteum for the first 6 to 8 weeks of pregnancy (*Pierce, et al., 1963*). It has not been shown in humans yet, but Lukács showed in a rat model that hCG cause a longer sleeping time and decreased activity level (*2001*). Therefore, the observed longer sleep duration during the first trimester of human pregnancy might be related to the rising levels of the hCG hormone. Progesterone is important during pregnancy as keeps, among other things, the decidua intact. After 6-8 weeks of pregnancy, the placenta takes over the production of progesterone. This progesterone is secreted in the maternal circulation (*Davis, 1996*) and it has been shown by several studies that progesterone can affect sleep as it possesses hypnogenic properties (*Friess et al., 1997*) and diminishes REM latency (*Lee, et al. 1990*).

The placenta takes up cholesterol from the mother. Cholesterol is important for fetal growth and can be converted in the fetal adrenal gland to dehydroepiandrosterone (DHEA). DHEA then goes back to the placenta which confers it into estradiol and secretes it into the maternal circulation. Both progesterone and estrogen levels in the maternal circulation are changing throughout pregnancy (*O'Leary et al., 1991*). Progesteron and estrogen are important for the fetal growth, maintenance of pregnancy and preparation for lactation and delivery, but they also have an influence on the maternal nervous system and can account for specific alterations in maternal sleep architecture during pregnancy see text below.

Brain areas that are involved in causing NREM sleep are forebrain structures, of which in particularly the preoptic area (*Sherin et al., 1996*) and the γ-aminobutyric acid neurons located in the cortex contribute to the generation of slow-wave activity. Cholinergic neurons in the pons are responsible for the REM sleep state and it accompanying neurophysiologic phenomena (*Shouse, et al., 1992*). The onset of REM sleep is also accompanied by cessation of activity in brainstem noradrenergic and serotonergic neurons (*Hobson et al., 1975*). The hormonal influences and mechanical and somatic factors that affect the sleep-wakefulness cycle during pregnancy are shown in the figure 3 (**Fig. 3**) (*Santiago, et al., 2001*).

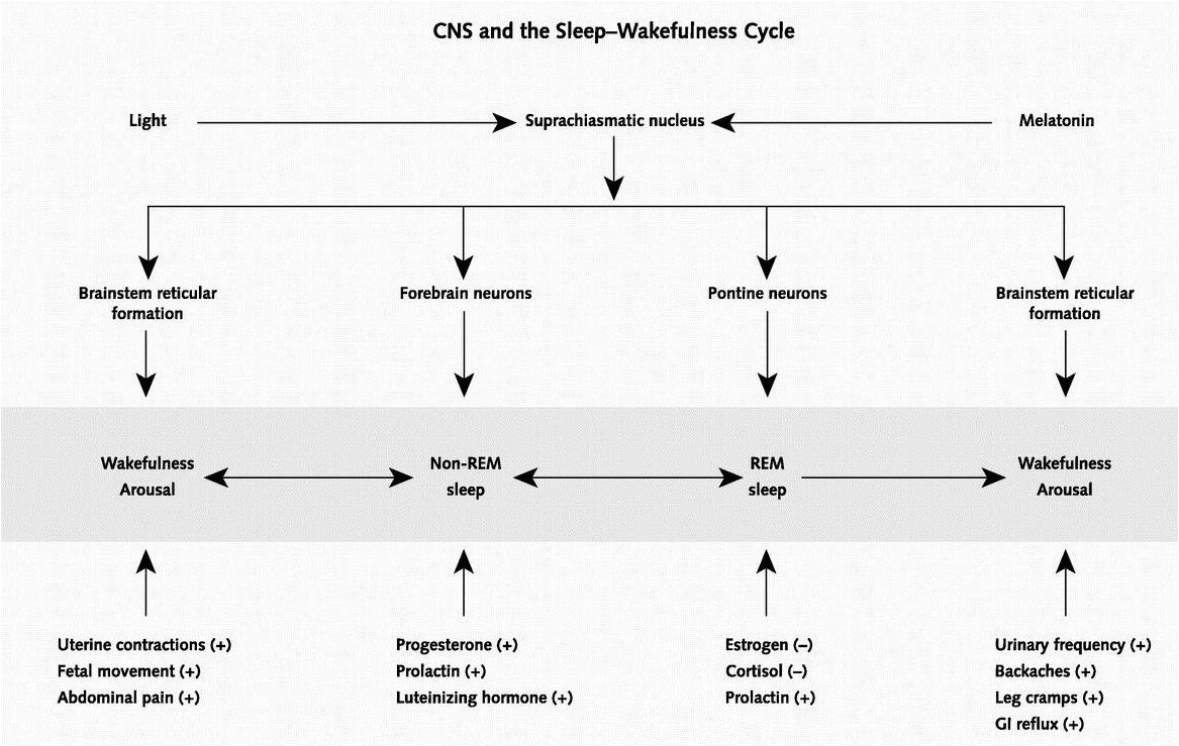

Fig. 3. Pregnancy Influences on sleep. The SCN is influenced by light and melatonin. It interacts with brain neurons to generate a circadian timing for wakefulness and arousal and for REM and NREM sleep. Bidirectional changes in physiologic states can occur, with the exception of REM sleep and wakefulness. Physiologic and hormonal events in pregnancy promote (+) or reduce (-) time spent in each state through as yet unclear neural mechanisms. GI = gastrointestinal (Santiago, et al., 2001).

Estrogen decreases REM sleep (*Nishina et al., 1996*), probably by influencing an increase in brainstem noradrenaline turnover (*Heritage et al., 1980*). Progesterone, on the other hand has a kind of hypnotic, sedating or anaesthetic effect and induces sleep (*Nishina et al., 1996*). Progesterone specifically increases NREM sleep (*Friess et al., 1997*), because it facilitates action of its neuroactive metabolites, such as allopregnanolone on GABAA receptor functioning in the brain (*Lancel et al., 1996*). When these GABAA receptors are activated by the ligands, chloride channels that regulate chloride ion influx, open up and cause a hyperpolarisation of the cell membrane (*Brunton et al., 2014*). In the progression of pregnancy rising progesterone levels are accompanied by increased levels of allopregnalolone both in the blood and in the brain (*Concas et al., 1998*). The combination of progesterone and estrogen is synergistic and increases wakefulness and decreases spontaneous NREM and REM sleep. This can result decrease in slow-wave sleep or even an absence of stage 4 for during sleep (*Hertz et al., 1992*). The effects of progesterone and estrogen are for a part dependent on the time of the day, of which they have the most significant effect in most rodent species during the dark phase (*Hadjimarkou et al., 2008*). As is explained earlier in this thesis in chapter 2.1, sleep can be seen as a homeostatically regulated behaviour modulated by the circadian clock. Estrogen suppresses REM sleep in the dark phase and alters the dynamics of REM sleep recovery by suppressing the homeostatic drive for REM sleep in the active phase. This implicates a role of the circadian system and possibly the SCN in modulating the effects of estrogen on sleep and arousal (*Hadjimarkou et al., 2008*). During REM sleep, autonomic nervous functions such as blood pressure, heart rate, and respiratory rate, vary greatly (Snyder et al., 1964). The suppression of REM sleep during pregnancy facilitated by hormones such as estrogen and its metabolites may be favourable because it stabilizes both maternal and fetal functions (*Nishina et al., 1996*).

Chapter 3: Effects of change in sleep during pregnancy on the mother

3.1 Mechanisms involved

3.1.1 Sleep deprivation as a stressor

Sleep is crucial for the maintenance of homeostatic function and counterbalances the negative effects of stress. Sleep deprivation can cause inefficient management of the systems that promote adaptation through allostasis, which causes an increased allostatic load (*McEwen, 2006*). The allostatic load is the cumulative wear and tear on body systems. When the allostatic load increases, there are higher levels of proinflammatory cytokines, evening cortisol as well as insulin and blood glucose levels and it increases sympathetic tone and decreases parasympathic tone (*McEwen, 2006*). Chronic sleep deficits can therefore contribute to pregnancy complaints and with that, cause even more chronic sleep disruption, shorter sleep duration and insomnia. On the other hand, sleep loss can also affect nervous structures like the amygdala (*Drevets, 1999*) and hippocampus (*Duman, 2004*), brain areas involved with the interpretation and regulation of stress responses. The effect of sleep loss on the amygdala and hippocampus cause an extra activation of the stress system and therefore sleep deprivation can be considered a psychological stressor per se. Maternal sleep deficits experienced during pregnancy may lead to a vicious cycle, in which chronic sleep loss during pregnancy is considered both the result of stress and a stressor per se (**Fig.4**) (*reviewed in: Palagini et al., 2014*). It contributes to changes and structural remodelling of brain areas and can therefore contribute to cognitive problems, which can further exacerbate pathways that will lead to disease (*McEwen, 2006*).

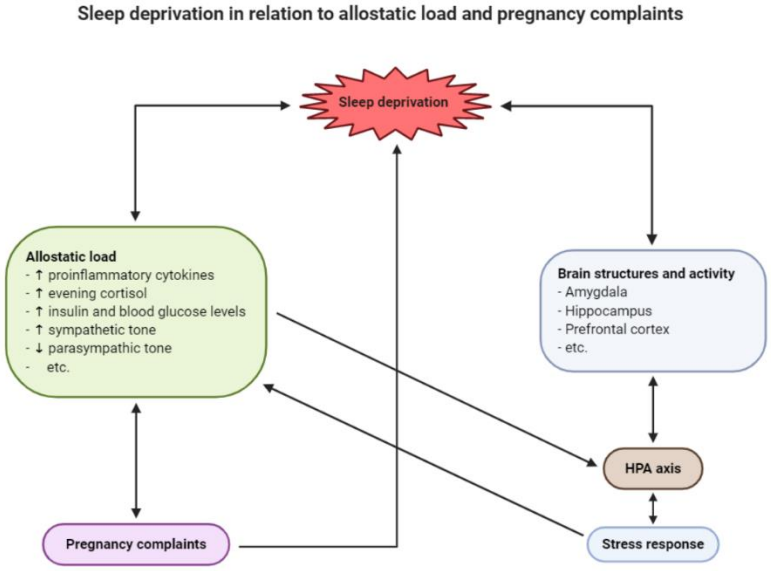

Fig. 4. Network of mediators involved in the stress response caused by sleep deprivation. Double pointed arrows indicate that each system regulates the others in a reciprocal manner, creating a nonlinear network (*Figure created by Melanie Meyer)*

Important factors for negative pregnancy outcomes due to sleep deficits are the over activation of the hypothalamic-pituitary-adrenal axis (HPA axis) and impairments of the proinflammatory system (*Palagini et al., 2014*). These pathways will be elaborated in the next subchapters.

3.1.2 HPA-axis

Stressors during pregnancy could be physical, for example when pregnant women are in pain and have backaches, or stressors could be psychological, for example when these women experience work pressure or fear for delivery and when they doubt their capacities to become a good mother, but as is mentioned in chapter 3.1.1, disturbed sleep can also be a stressor. Physical stressors rely mostly on direct brain inputs, whereas psychological stressors are more processed by limbic brain regions (*reviewed in: Herman & Cullinan, 1997*). Stress can have a rapid response which is initiated by the hypothalamus that activates the sympathetic nervous system (SNS). Neurons in the spinal cords causes activation of the adrenal medulla, this then results in release of the hormones adrenaline and noradrenaline. These hormones cause a more conscious feeling of stress, as the heart rate and sweating increases, just as there is more heavily breathing (*Wolf, 2008*). Chronic stressors like chronic sleep deprivation are more likely to activate the HPA axis, of which the effects are more sustainable. Dependent on the type of chronic stressor which determines the activity in areas of the brain like the prefrontal cortex,

hippocampus and amygdala, the brain can cause a release of cortisol to the blood via the HPA axis. These cortisol concentrations in the blood travel to targets in the periphery where it cause physiological changes as a response to the stressor. Cortisol can also modulate the HPA axis function through several negative feedback mechanism of which most targets are in the brain (*Herman et al., 2005*). When the allostatic load increases, the hypothalamic paraventricular nucleus (PVN) will be activated and produce a cocktail of adrenocorticotrophic hormone (ACTH) secretagogues, of which the most important ones are corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP), into the pituitary portal circulation (*McEwen et al., 1968*). This stimulates the pituitary to produce adrenocorticotropic hormone (ACTH), which on its turn stimulates the adrenal cortex to produce glucocorticoids (GC) (*Joëls & Krugers, 2007*), of which cortisol is the primary type in humans (*Corwin & Pajer, 2008*). Since GCs are small, lipophilic molecules, they can pass through cell membranes and the blood-brain barrier to reach its targets in the brain such as the hypothalamus and pituitary or limbic structures such as the hippocampus and the prefrontal cortex. After entering the cell, cortisol can bind to two different intracellular receptors, which are the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). After binding to the receptor, the cortisol-receptor complex travels to the nucleus of the cell and affects the gene transcription inside the nucleus, leading to changes in the production of specific proteins. Since the receptors MR and GR are found throughout the body, cortisol can have various effects on different parts of the body and brain (*Wirth, 2014*). Cortisol has a negative feedback on the pituitary, hippocampus and hypothalamus, which leads to decreased activity of the HPA system. On the other hand, cortisol creates a positive feedback on the amygdala, the prefrontal cortex (PFC) and the brain stem, which leads to increased activity of the HPA axis (*Wolf, 2003*). The MR is a high affinity receptor and has high expression levels in some brain regions, such as in all the hippocampal subfields, the central amygdala and some others, but other parts of the brain have much less expression of MR. The GR has a much lower affinity but is more widespread in its expression on different parts of the body. Due to its low affinity, GR will only be activated due to high levels of cortisol, which can happen when the body experiences chronic stress. The different characteristics of MR and GR are especially important for cells which express both receptors, such as cells in the hippocampal CA1 region, the dentate gyrus and the central amygdala (*Joëls & Krugers, 2007*).

During late pregnancy, it seems that, the HPA axis is hyporesponsive to stress. Several animal studies showed reduced ACTH and corticosterone responses to stress in pregnant rats (*Neumann et al., 1998; Johnstone et al., 2001*). Towards the end of pregnancy, mRNA levels of CRH in the parvocellular region of the paraventricular nucleus (pPVN) are lower. The same is true for the median eminence of CRH and anterior pituitary pro-opiomelanocortin (POMC, the ACTH precursor) mRNA and CRH receptor levels (*Johnstone et al., 2001*). The physiological adaptations of the HPA axis during pregnancy occur at several levels including the limbic feedback systems, CRH/vasopressin neurons within the hypothalamus, corticotrophs of the adenohypophysis, and cortical cells of the adrenal gland. The reduced HPA-activity is probably more an effect of a reduced positive feedback than an increased effectiveness of glucocorticoid negative feedback. This is because even though there are more GR receptors in the dentate gyrus (amount of MR receptors stay the same) and more activity of 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1, normally enhances corticosterone negative feedback signal) in the PVN and anterior pituitary were measured during pregnancy, the 11b-HSD inhibitor did not modify the stress response. Therefore, there is a reduced positive feedback of the HPA axis in pregnancy (*Johnstone et al., 2001*).

From rat studies it is known that an altered ACTH-corticosterone relationship seems present in pregnancy, and the same was found in humans (*Carr et al., 1981*). This might find its cause in a lower sensitivity of the adrenal gland to ACTH because of the hormone estrogen, of which levels are higher in pregnancy (*Waddell & Atkinson, 1994*). Also, normally opioids potentiate the HPA-axis responses to stress, but in pregnancy they have a net inhibitory effect on the HPA axis activity. This is because in pregnancy the levels of progesterone rise and progesterone can be converted to the neurosteroid allopregnanolone, which prevents activation of CRH neurons and oxytocin neurons in the hypothalamus (**Fig. 5**) (*Brunton et al., 2014*). Allopregnanolone stimulate noradrenergic A2 (NTS) neurons in the brainstem that project to CRH neurons and magnocellular oxytocin neurons in the PVN, and to oxytocin neurons in the supraoptic nuclei (SON). Allopregnanolone also acts as an allosteric modulator at postsynaptic GABAA receptors, including those in the hypothalamus. This also reduces the release of CRH. Normally the interleukin-1β (IL1β) activate these brainstem neurons through a prostaglandin-dependent pathway, but in pregnancy, there is an increased opioid (enkephalin) inhibition acting presynaptically on the upregulated μ-opioid receptor on the noradrenergic nerve terminals, causing IL1β to fail evoking noradrenaline release from their terminals in the PVN. The effect of progesterone and enkephalin therefore can suppress HPA axis responses (*Brunton & Russell, 2008*).

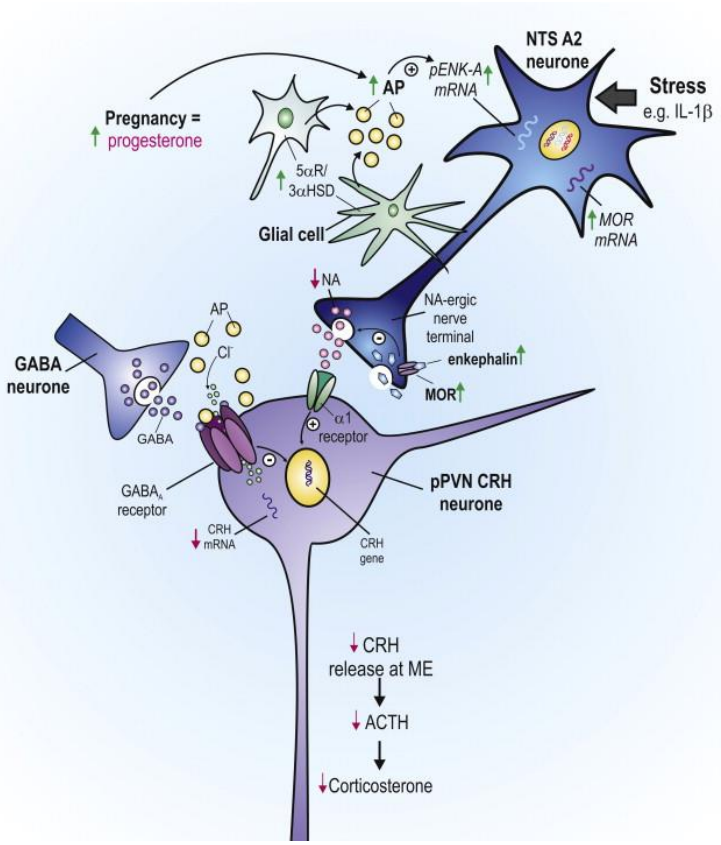

Fig. 5. Allopregnanolone-opiod mechanism involved in suppressed HPA axis responses in late pregnant rats. (*Brunton et al., 2014*)

Studies have shown that sleep restriction, in contrast to all the effects of pregnancy on the HPA axis described above, can lead to a moderate activation of the HPA axis and with that elevated glucocorticoid levels (*Minkel et al., 2014*). Although sleep deprivation can act as a moderate stressor, it does not lead to habituation of the HPA axis to a homotypic stimulus and sensitization to a heterotypic stimulus. Sleep deprivation is therefore not an usual stressor (*Meerlo et al., 2002*). In rats it has been shown that one effect of chronic sleep restriction is a significant reduced ACTH response, while the corticosterone response remains unaffected. This means that there is some kind of change in the brain that cause an attenuated ACTH response, but at the same time an increased adrenal sensitivity to ACTH so that the cortisol levels stay unaffected. These changes in the brain could reflect a reduced CRH release in response to stress, a reduced pituitary sensitivity to CRH, or a gradual increase in GR numbers in certain brain areas due to sleep loss which lead to a more rapid and stronger negative feedback on the HPA axis (*Meerlo, et al., 2002*).

In conclusion, both pregnancy and sleep deprivation may cause an increased sensitivity to ACTH of the adrenal glands. But while pregnancy mitigate the activation of the HPA axis to stress, sleep deprivation increases the stress response.

3.1.3 Immune System

During pregnancy, the number of immune responses is down-regulated to protect the half-foreign embryo from the maternal immune system (*Navarrete et al., 2007*). Pregnancy is associated with alternations in circulating cytokine levels of which these fluctuations can vary by trimester (*Okun & Coussons-Read, 2007*). Sleep deprivation affects this functional cellular innate immune response and is associated with elevated levels of proinflammatory cytokines (*Irwin et al., 2010*). Unabated inflammation can cause undesirable side effects, so to prevent this the proinflammatory response is normally suppressed by the reciprocal production of anti-inflammatory cytokines like IL-4 and IL-10 (*reviewed in: Opal & DePalo, 2000*). The alternation from basal levels of cytokines because of sleep deprivation indicate an activated inflammatory system (*Mullington et al., 2010*). Sleep deprivation shifts the balance between proinflammatory and anti-inflammatory cytokines, which could impact the health of pregnant women. Even a modest disturbance of sleep produces a reduction of natural immune responses and T-cell cytokine production that could last even after a night of recovery sleep (*Irwin et al., 1996*). Inflammatory markers that increase because of sleep deprivation are interleukin-1 (IL1), IL-2, IL-6, tumornecrosis factor a (TNFa), and C-reactive protein (*M. R. Irwin, 2006; Meier-Ewert et al., 2004; Okun & Coussons-Read, 2007*). Chronically elevated proinflammatory cytokines and exposure of cells to these proinflammatory cytokines induce a decrease of the GR function in the central nervous system. This leads to a decrease in the sensitivity for rising cortisol of the hypothalamic CRH-secreting cells and blunting of the normal negative feedback response of the hypothalamus to cortisol (*Pace, et al., 2007*). This decrease in function of the GR function is among others mediated via the GR-mediated gene transcription and activity of the p38 mitogen-activated kinase (MAPK) pathway. IL-1a induces GR impairment via this p38 pathway, which is not yet fully understood, although it has been proposed that the early events of signal transduction are similar to IL-1 activation of NF-kB and JNK (*Wang, et al., 2003*). Activation of p38 MAPK pathways by proinflammatory cytokines was found to result in GR phosphorylation that in turn is associated with reduced sensitivity to glucocorticoids (*Irusen et al., 2002*). At the same time stimulate proinflammatory cytokines like IL-1, IL-2, IL-6, and TNFa cortisol secretion directly by acting on the cells of the adrenal cortex and indirectly via stimulation of CRH from the hypothalamus and ACTH from the anterior pituitary (*McCANN et al., 2006*). IL-2 is a more potent known stimulator of ACTH release than CRH on a molar-to-molar basis. (*Corwin & Pajer, 2008*)

As becomes clear in the text above, the innate immune response is associated with the HPA axis. However, the HPA activation has also a prominent effect on the inflammatory response. Especially the glucocorticoids play here a role as they inhibit the proinflammatory cytokines by blocking the genes responsible for their production and by inducing the production of NF-kB, a protein that binds and neutralizes important cytokine transcription factors. Cytokines known to be downregulated by cortisol and other glucocorticoids include IL-1, IL-2, TNF-, and IFN-γ (*Corwin & Pajer, 2008*). Moreover, glucocorticoids favour the production of the anti-inflammatory cytokines, especially at low concentrations of glucocorticoids (*Elenkov & Chrousos, 2002*).

In the next chapter (chapter 3.2) will be elaborated on why the interaction of the innate immune response with the HPA axis is crucial for proper maternal behaviour and the wellbeing of mothers.

3.2 Outcomes of pregnancy and sleep deficit on mother

3.2.1 Effects on cognition and behaviour

Sleep is important in daily life functioning. When sleep is disturbed this may affect cognitive performance, including in pregnant women.

Numerous studies studied cognitive performance during pregnancy of which most studies concluded that pregnant women often score lower on specific cognitive tasks compared to non-pregnant women (*reviewed in: Anderson & Rutherford, 2012*). Ziomkiewicz and colleagues suggest that this is caused by life history trade-offs (2018). They say that elevated cortisol levels during pregnancy impair maternal cognitive function due to a long-term effect on hippocampal structure and function. Elevated cortisol levels during pregnancy enhance energy flow from the mother through the placenta to sustain foetal development (*Gangestad et al., 2012*). Ziomkiewicz and colleagues hypothesize that there is a trade-off in the energy availability for the fetus and for the mother, which leads to maternal cognitive changes. The limited energy available for the maternal brain is used to enhance cognitive processes that are beneficial for the health of the mother and the fetus, which leaves less energy for cognitive processes that are less essential (**Fig. 6**) (*Ziomkiewicz et al., 2018*).

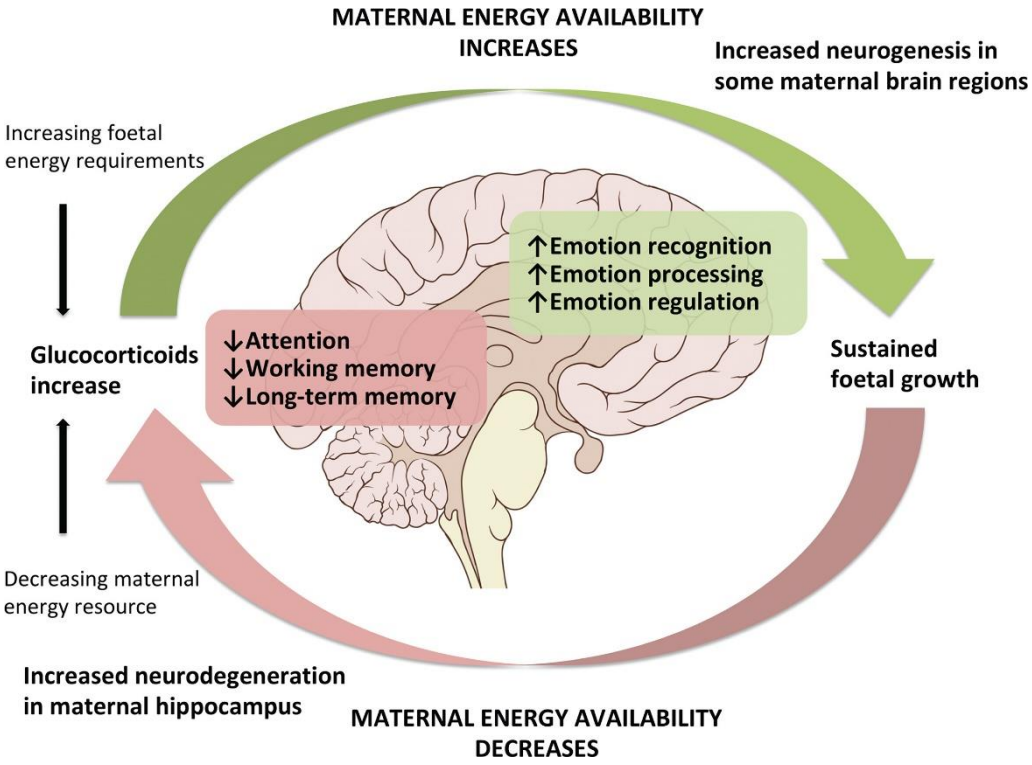

Fig. 6. Energy distribution between competing maternal and foetal demands effecting maternal cognition. To sustain foetal growth and prepare for motherhood, the mother experiences limited energy availability for costly but non-essential cognitive functions. Negative cognitive changes (pink box) caused by increased neurodegeneration arise as a consequence. Any spare energy supports the cognitive changes necessary for maternal and offspring survival (green box) with accompanying increased neurogenesis in specific maternal brain regions. (*Ziomkiewicz et al., 2018*).

The presented evolutionary perspective in the study of Ziomkiewicz and colleagues which states that some changes in cognition that happen during pregnancy dependent on energy trait-offs, are beneficial for the survival of the mother and her offspring is supported by other studies. For example, most kind of memory in pregnancy show a deficit, while recognition memory is actually better during pregnancy. Anderson & Rutherford showed that pregnant women have a better recognition of novel faces and especially for same-race faces, using a disguised recognition task were participants viewed male faces and female faces and then identified their ethnicity/race (*2011*) (**Fig. 7 and Fig. 8**). This change in cognition where pregnancy causes a better recognition of novel faces can influence behaviour in pregnant women positively, as it is important for survival

to be good in recognizing persons and situations that are safe and that are dangerous (*Anderson & Rutherford, 2012*). A better recognition for novel faces has protective function as it makes the women more socially competent. These ideas correspond to the findings of Otgaar and colleagues where their results support the idea that memory is enhanced by processing information in terms of fitness value, while at the same time, it may increase the risk for memory distortions (*2010*).

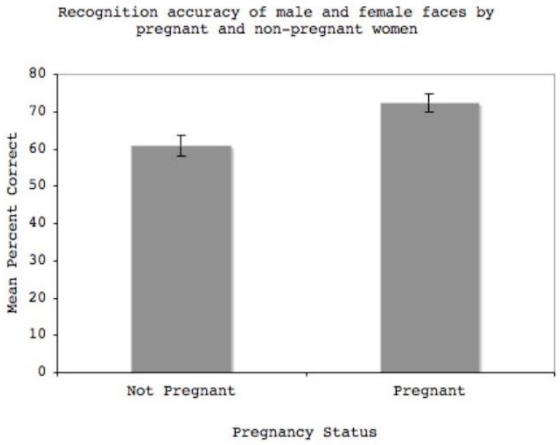

Fig. 7. Recognition accuracy of male and female faces by pregnant and non-pregnant women. Error bars indicate SEM. From the participants that viewed male faces were 20 pregnant and 20 non-pregnant. From the participants that viewed female faces were 19 pregnant and 19 non-pregnant (*Anderson & Rutherford, 2011*).

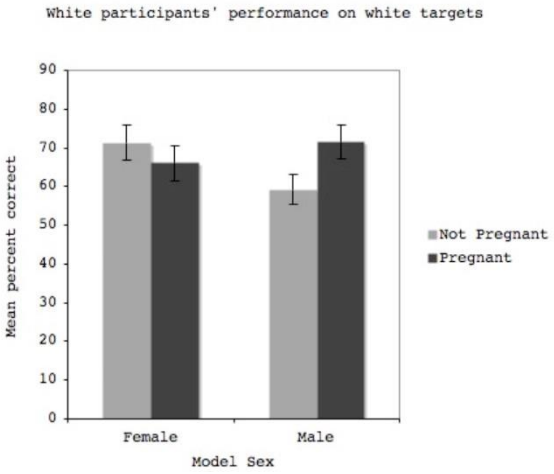

Fig. 8. Recognition accuracy of White male and female faces by White pregnant and non-pregnant women. Error bars indicate SEM. (*Anderson & Rutherford, 2011*).

The reproductive status of pregnancy influences cognition and behaviour among other things, because of the changes in immune responses and the different concentrations of hormones circulating in the different trimesters.

Especially during the first semester pregnant women show an increased ethnocentrism and in-group bias (*Navarrete et al., 2007*). The 206 pregnant female American participants joining the study of Navarrete et al. were presented two essays (*2007*). One essay presented the negative experiences and opinions of a foreigner critical of the United States and its citizens, while the other presented an American's positive appraisal of America and its values. Following the essay, the participants evaluated which author was likeable, intelligent, knowledgeable, moral, well adjusted, and truthful, as well as the extent to which they would want to work which each author. It appeared that the week of pregnancy was correlated with in-group attraction and out-group negativity (*Navarrete et al., 2007*). The evolutionary mechanism behind this could be that it is disease avoidant. During pregnancy, the number of maternal immune responses are initially restrained to protect the half-foreign embryo (*Wai Loke & King, 1997*). This leaves the mother and the fetus more vulnerable to intracellular pathogens such as viruses and some bacteria (*Navarrete et al., 2007*). When pregnancy progresses, the fetal immune system develops and changes in immune function become more localized at the maternal-fetal interface which diminishes the dangers presented by infection. Therefore, especially during the first trimester of pregnancy mothers and their foetuses are vulnerable for diseases. A lot of these diseases can be avoided by behavioural changes (*Fessler, et al., 2002*) such as an increased ethnocentrism and in-group bias. Interaction with outgroup members is often a greater threat of disease transmission because the likelihood that one already possesses antibodies to pathogens carried by conspecifics is a function of past interaction, and interactions with in-group members are more frequent than with outgroup members (*Navarrete et al., 2007*). Outgroup members, particularly when they are immigrants, also may correspond to locally maladaptive practices such as hygienic behaviors, diet, patterns of food storage and preparation, medicinal traditions, mortuary practices, and sexual behaviors. Cultural dissimilarity may therefor increase the risk of disease (*Faulkner et al., 2004; Navarrete et al., 2007*).

The changes in cognition and behaviour during pregnancy is for a great part mediated by changes in hormonal levels because of the reproductive state that have an effect on the brain. Several studies showed the effects of hormones on cognitive processes such as memory and contagion avoiding processes (*Khadilkar & Patil, 2019*; *Jones, et al.,* 2005). For example, when progesterone levels are high in pregnancy, this has an effect on the women's rate of others people's fear and disgust (*Conway et al., 2007*), it makes them better in identifying negative emotions. Progesterone therefore correlates with accuracy in the identification of emotions, which can serve as a protective mechanism to socially threatening stimuli during pregnancy and have a survival advantage (*Lustig et al., 2018*). In non-pregnant women, a better accuracy in identifying negative emotions can be more stressful. But because the stress response in pregnant women is mitigated, pregnant women actually benefit from facilitated emotion encoding without the costs associated with increased anxiety (*Anderson & Rutherford, 2012*). When pregnant women are sleep deprived, the buffer of a mitigated stress response can fall away which make them more vulnerable to the negative effects of social stimuli. Additionally found the study of Lustig et al. (*2018*) that women with higher progesterone levels were more vulnerable to the effects of sleep restriction on emotion processing tasks and the study of Carter et al. (*2012*) reported that one night of sleep deprivation reduced progesterone in women. This shows that sleep deprivation has negative impact on the adaptive cognitive changes happening during pregnancy both via the stress response and hormone levels.

Since both the state of pregnancy and sleep deprivation have effects on cognition, it is interesting to see what happens when there is a combination between the two. This thesis hypothesizes that sleep deprivation during pregnancy can inhibit or even negatively affect the cognitive changes occurring in pregnancy, because it levels out the buffer of the normal mitigated stress response of pregnant women. This can influence maternal behaviour unbeneficial from an evolutionary perspective. Maternal behaviour in humans is very complex and depends not only on behavioural adaptive mechanisms, but also on sociocultural and environmental factors. Nonetheless it might be useful to understand maternal behaviour in rodents so that we can get an insight in the fundamentals of maternal behaviour during pregnancy. In the rodent behavioural repertoire, maternal behaviour is a specific behaviour that comes to expression from the end of pregnancy to the time of weaning. In rats it is defined as any action performed by a dam in order to nurture, warm, feed, and protect its litter and can be divided in two basic categories: maternal care and maternal aggression (*Pires, et al., 2015*). Sleep restriction during pregnancy in female rats affects especially the behaviour of the second category: maternal aggression. It increases defensive aggression and decreases self-grooming when compared to non-sleep-restricted lactating rats. Self-grooming is a well-known behaviour associated with high stress situation (*Katz & Roth, 1979*). Sleep restriction during pregnancy can therefore be said to induce an anxiolytic condition during the postpartum period and to increase defensive aggressive behaviour while still maintaining maternal care (*Pires, et al., 2015*). There might be behavioural adaptive mechanisms that allows for the maintenance of proper maternal care even when the dam has been exposed to environmental challenges like sleep deprivation during pregnancy (*Pires, et al., 2012*). If the same is for humans and if these adaptive mechanisms are strong enough to have effect even in combination with other sociocultural and environmental factors, remains a subject for further research.

3.2.2 Effects on mood

Sleep disruption or deficiency during pregnancy has been considered a significant risk factor for the occurrence of mood disturbances, as well as the recurrence of depression. (*Swanson et al., 2011*)

Depression in women after pregnancy is common: approximately 10–15% of childbearing women experience postpartum depression (*Nielsen et al., 2000*). Epidemiology studies have indicated that there appears to be an association between sleep disturbance and depression (*Breslau et al., 1996*). Mothers who developed postpartum depression showed a decreased total sleep from the end of pregnancy to early postpartum weeks, while non-depressed mothers had an increase in total sleep time during the same time period (*Wolfson et al., 2003*).

Chrousos and Gold in 1992 were the first to propose a psychoneuroimmunology model which suggests that dysregulation in the immune system or the HPA axis or both may contribute to the development of Postpartum Depression (*Chrousos & Gold, 1992*). During pregnancy, when the development of the fetus continues, the fetal adrenal gland plays an increasing critical role in controlling the maternal HPA axis. The fetal adrenal gland secretes under the influence of progesterone, significant amounts of cortisol. This cortisol stimulates cells of the trophoblast and placenta to increase their production of CRH (*Mastorakos & Ilias, 2003*). Production of CRH causes a self-propagating cycle where elevated CRH levels stimulate further fetal cortisol production and more CRH secretion. This then suppresses maternal CRH production and with that the HPA axis of the mother after delivery of the infant. On the other hand, the innate immune response in healthy postpartum women, is stimulated by labor and delivery and causes an increase in the production of proinflammatory cytokines. Within a few weeks to months these women recover from childbirth and the inflammation regresses. With recovery, the HPA axis hormones also return to normal levels and assist in limiting inflammation, which leads to normal postpartum emotional regulation (**Fig. 9**) (*Corwin & Pajer, 2008*). Sleep deficits in the prenatal and postnatal period can induce an exaggerated inflammatory response after labor and delivery, and an inadequately suppressed HPA axis function. These disturbed functions can alone, or both lead to postpartum depression (**Fig. 10**) (*Corwin & Pajer, 2008*).

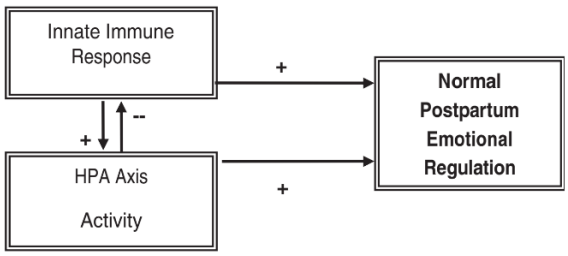

Fig. 9. Normal relationship between the inflammatory response and the HPA axis. After childbirth, the anti-inflammatory milieu abruptly shifts to a proinflammatory state. The HPA axis is suppressed following delivery, but normalizes after a few weeks where after the HPA axis hormones assist in limiting inflammation (--). Together, these steps assure normal postpartum emotional regulation (*conceptual framework by Corwin & Pajer, 2008*).

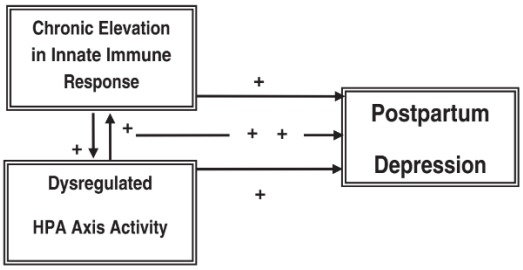

Fig. 10. Dysregulated relationships between the inflammatory response, the HPA axis and Postpartum Depression. Sleep deficits can lead to an exaggerated proinflammatory response by labor and delivery, and an inadequately suppressed HPA axis. Together or alone can these factors lead to postpartum depression (*conceptual framework by Corwin & Pajer, 2008*).

Depression is typically characterized as a disorder of noradrenaline and serotonin neurotransmission with first-line treatment focused on normalizing neurotransmitter function (*Kulmatycki, et al., 2006*). Proinflammatory cytokines may alter neurotransmitter function by reduction of the serotonin synthesis (*Maes et al., 2002*). Serotonin is synthesized from tryptophan, which is an essential amino acid and moves via the systemic circulation and active transport from the periphery to the brain, and is there converted into serotonin. Cytokines can induce the stimulation of indoleamine-2,3-dioxygenase, an enzyme that switches the synthesis of serotonin from tryptophan to kynurenine and quinolinic acid. This results into a decreased production of serotonin by this mechanism and may lead to development of depression (*Kulmatycki, et al., 2006*). Cytokine-induced activation of indoleamine-2,3-dioxygenase may also impair the negative feedback of corticosteroids on the HPA axis through production of quinolinic acid, a potent *N*-methyl-D-aspartate receptor agonist, causing hippocampal atrophy and loss of glucocorticoid receptors (*Pariante & Miller, 2001*).

3.3 Treatments

Sleep disruption and deficit is common in pregnancy and has been associated with adverse pregnancy outcomes, both for the mother and her child. It is therefore important to find ways to improve the sleep quality of the mother. Because the sleep disruption and deficit can be caused by various different factors as described in this essay, we have to determine for each woman individually what kind of treatment is appropriate. During pregnancy many drugs are avoided on account of fears for teratogenicity (*Oyiengo et al., 2014*). Probably a lot of pregnancy complaints can be obviated with treatments that involve no drugs. One option is to study is the daily life of the pregnant women to find out what kind of bad habits she might have and if these habits could be unlearned or prevented. However, when complaints of sleep disruption and insomnia are extreme, other treatments could be considered. Cognitive behavioural therapy for insomnia is a skill-based nonpharmacologic insomnia-focused psychotherapy and the study of Manber et al. (*2019*) shows that it can be an effective treatment for insomnia during pregnancy. Manber and colleagues allocated participants randomly to cognitive behavioural therapy for insomnia (a first-line, empirically supported psychosocial intervention that addresses sleep-related behaviours and cognitions) or to a control intervention consisting of imagery exercises that paired patient-identified distressing night-time experiences with patient-identified neutral images. Women assigned to the cognitive behavioural therapy for insomnia experienced significantly greater reductions in insomnia severity, faster remission of insomnia disorder and a significantly greater decline in Edinburgh Postnatal Depression Scale scores compared to the control group (*Manber et al., 2019*).

When cognitive behavioural therapy does not help pharmacotherapy can be considered. It is important to take the risk on teratogenicity and other negative outcomes on the child into account, although sometimes the negative effects of sleep disruption and deficits outweigh the risk for the child due to pharmacological treatment. Pharmacotherapy for insomnia such as the hypnotic benzodiazepine receptor agonists: Zaleplon, Zolpidem, Zopiclone, deserve attention as they are not associated with an increased risk for congenital malformations (*Wikner & Källén, 2011*). They work among others on the GABAA receptors on the CRH neurons in the PVN and cause a hyperpolarisation and decrease the excitability of the neurons. Benziazepine receptor agonists have a broad spectrum of action (*Lüllmann & Mohr, 2005*). Ramelteon, Amytriptyline, Trazodone, Doxepin, Diphenhydramine and Temazepam, also deserve attention. Their effects on human pregnancy safety and lactation are not always clear, so further studies on these substances are important. The study of (*Khazaie et al., 2013*) show that treatment with Trazadone or Diphenhydramine during the third trimester both can prevent Postpartum Depression by improving the sleep profile of women that experienced insomnia, which are promising results.

Chapter 4: Discussion, conclusion and implications

Physical and emotional complaints especially towards the end of pregnancy in the third trimester can lead to a disruptive night sleep and sleep deficits. Although sleep deprivation can often be restored by NREM sleep taking over REM sleep, sleep disruption reduces the ability to produce high amplitude slow waves in NREM sleep and therefore has effects on the allostatic load. Hormonal changes during pregnancy can have effects on sleep architecture. Estrogen decreases time spent in REM sleep while progesterone increases NREM sleep. The suppression of REM sleep might be beneficial as it stabilizes both maternal and fetal autonomic nervous functions such as blood pressure, heart rate, and respiratory rate. Sleep deprivation because of disruption increases the allostatic load and is considered both a result of stress and a stressor per se. When we look into the effects of sleep deprivation in humans, often rodent models are used to gain insights into which mechanisms are involved and how. In humans, pregnant women often experience sleep disruption and deficits for a longer period of time because of pregnancy, but also because of the attention demanding child in the postpartum period. It is therefore important to make sure that in future research the rodent models are specifically tested on chronic sleep disruption and deprivation, as short sleep deprivation often has different effects. Important factors that play a role in the effects of negative pregnancy outcomes because of sleep disruption and deficits are the HPA axis and the immune system. During pregnancy, the HPA axis is hyporesponsive to stressors. This adaptation occurs at several levels, including a reduced positive feedback of glucocorticoids. The altered ACTH-corticosterone relationship during pregnancy can be caused by progesterone metabolites like allopregnanolone which prevents activation of CRH neurons in the PVN. Sleep deprivation in contrast to pregnancy, activates the HPA axis, likely because of changes in the brain that cause an increased ACTH response and also by increasing the sensitivity of ACTH by the adrenal glands. Sleep deprivation alters our immune response too and elevates levels of proinflammatory cytokines. Since our innate immune response is associated with the HPA axis, sleep deprivation and elevated proinflammatory cytokines can cause blunting of the negative feedback response of the hypothalamus to glucocorticoids. Sleep deprivation can induce an increase of the GR function via activation of the p38 MAPK pathway or directly and indirectly stimulate glucocorticoid secretion. The HPA axis can in its turn also influence levels of proinflammatory cytokines for example by blocking gene activity. The precise pathways, mechanisms and interactions concerning pregnancy hormones, HPA axis and immune system remain subjects for further research. Here it is important to take the effects of circadian rhythms of our brain and bodies and these factors into consideration as it might have a great impact.

The limited energy available for the maternal brain because of pregnancy is used to enhance cognitive processes that are beneficial for the health of the mother and the fetus, which leaves less energy for cognitive processes that are less essential. These life history trade-offs concerning cognition are influenced by pregnancy hormones and can enhance cognition by processing information in terms of fitness value and therefore have positive effects on behaviour from an evolutionary perspective. During pregnancy, the number of maternal immune responses are initially restrained to protect the half-foreign embryo, which leaves the mother and fetus more vulnerable to intracellular pathogens. Cognitive changes during pregnancy such as increased ethnocentrism and in-group bias can lead to behavioural changes that diminish the danger of diseases. Pregnant women also tend to become more socially competent and the mitigated stress response in pregnancy allows for the maintenance of proper maternal care. Sleep deprivation can take away the buffer of this mitigated stress response and make pregnant women more vulnerable for the negative effects of this social competence, although studies in rats indicate that there might be adaptive mechanisms against the effects of exposal to environmental challenges like sleep deprivation. It would be interesting to dive more into these adaptive mechanisms and see if similar adaptations occur in humans. Moreover, when this is the case, we could look whether these adaptation mechanisms can be enhanced so that they also counterbalance the negative effects of other environmental and sociocultural factors.

Sleep disruption or deficiency during pregnancy remains a significant risk factor for the occurrence of mood disturbances. It can cause a dysregulation of the immune system, the HPA axis or both, which can contribute to the development of Postpartum Depression in mothers. For

this reason, effects of the untreated conditions of sleep deprivation on the health of the pregnant woman and the fetus have to be taken into consideration when deciding to treat sleep disruptions and deficits. To improve sleep quality during pregnancy, treatment has to be adjusted to each pregnant women individually. Knowledge of the mothers sleep alterations and its effects is useful for informing expecting mothers in their predelivery check-ups. Consideration of nonpharmacologic treatments and interventions like cognitive behavioural therapy against sleep deprivation could be effective, but needs to be further researched to make it more efficient. When nonpharmacologic treatments are not effective, pharmacotherapy for insomnia with the use of hypnotic benzodiazepine receptor agonists can be promising. Pregnancy often makes women more cautious that could cause fears for teratogenity and other negative treatment outcomes of pharmacotherapy. These fears need to be taken seriously as there still remains a lot unknown about all the mechanisms and pathways involved with sleep deprivation and pharmacotherapy. In addition, further research on the effects of pharmacotherapy is needed as for most treatments the translation from a rodent to human model still remains a big step.

This thesis did not elaborate on the effects of maternal sleep deprivation during pregnancy and postpartum on the development of the fetus and child, which is also a very interesting to look into. Since sleep deprivation has a negative effect on the physical and psychological health of the mother, it might also affect the fetus and child in a negative way. This is more reason to guide women during their pregnancies and in the postpartum period into having a good night sleep and to further investigate and research treatment options against sleep disruption and deficits during pregnancy. On the other hand, certain negative effects of sleep deprivation, might have positive effects on the development of the fetus/child. The maternal brain is a major force in driving essential physiological changes during pregnancy and adaptations of the mother so that the mother's experience of stress and metabolism is in favor of the fetus and child. These positive effects weigh probably a lot smaller than the negative effects, but still deserve attention in further research as they might provide us insights into pathways and mechanisms that we can use against the negative effects of sleep deprivation.

In conclusion, deprivation of maternal prenatal sleep has several negative neurobiological, cognitive and behavioural effects in pregnant women. During pregnancy the HPA axis and the innate immune response are mitigated. Sleep deprivation is a chronic stressor that activates the HPA axis and cause inflammation. This could prevent cognitive changes that normally lead to evolutionary adaptive maternal behaviours and sleep deprivation could eventually lead to adverse maternal pregnancy outcomes like Postpartum Depression. Next to conducting research on the pathways, mechanisms and treatments involved with sleep deprivation during pregnancy, it is important to consider how our society influences the sleep of pregnant women. With knowledge about the negative outcomes of sleep deprivation during pregnancy, we can adjust our policies and inform women and all concerned parties such as medical doctors before, during and after pregnancy on the effects and treatments of sleep deprivation during pregnancy.

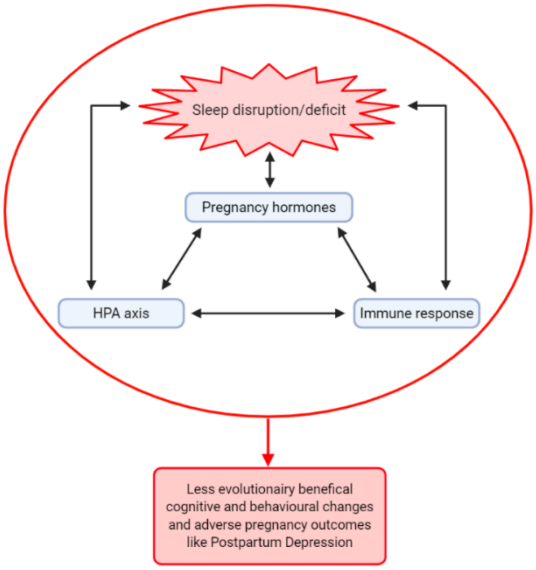

Fig. 11. Overview of sleep deprivation during pregnancy in relation to the HPA axis, the immune response and its outcomes. (*Figure created by Melanie Meyer*)

Chapter 5: Acknowledgements and References

5.1 Acknowledgements

I wish to thank Professor dr. J.D.A Olivier, for her assistance during the process of writing this thesis.

5.2 References

AlDabal, L. (2011). Metabolic, Endocrine, and Immune Consequences of Sleep Deprivation. *The Open Respiratory Medicine Journal*, *5*(1), 31–43. https://doi.org/10.2174/1874306401105010031

Aminoff, M. J., Boller, F., & Swaab, D. F. (2011). Foreword. *Handbook of Clinical Neurology*, vii. https://doi.org/10.1016/b978-0-444-52006-7.00047-2

Anderson, M. V., & Rutherford, M. D. (2011). Recognition of Novel Faces after Single Exposure is Enhanced during Pregnancy. *Evolutionary Psychology*, *9*(1), 147470491100900. https://doi.org/10.1177/147470491100900107

Anderson, M. V., & Rutherford, M. D. (2012). Cognitive Reorganization during Pregnancy and the Postpartum Period: An Evolutionary Perspective. *Evolutionary Psychology*, *10*(4), 147470491201000. https://doi.org/10.1177/147470491201000402

Baratte-Beebe, K. R., & Lee, K. (1999). Sources of Midsleep Awakenings in Childbearing Women. *Clinical Nursing Research*, *8*(4), 386–397. https://doi.org/10.1177/10547739922158377

Bear, M., Connors, B., & Paradiso, M. A. (2016). *Neuroscience: Exploring the Brain, Enhanced Edition* (Fourth Edition). Wolters Kluwer.

Boonstra, T. W., Stins, J. F., Daffertshofer, A., & Beek, P. J. (2007). Effects of sleep deprivation on neural functioning: an integrative review. *Cellular and Molecular Life Sciences*, *64*(7–8), 934–946. https://doi.org/10.1007/s00018-007-6457-8

Breslau, N., Roth, T., Rosenthal, L., & Andreski, P. (1996). Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young Adults. *Biological Psychiatry*, *39*(6), 411–418. https://doi.org/10.1016/0006-3223(95)00188-3

Brunton, P. J., & Russell, J. A. (2008). The expectant brain: adapting for motherhood. *Nature Reviews Neuroscience*, *9*(1), 11–25. https://doi.org/10.1038/nrn2280

Brunton, P. J., Russell, J. A., & Hirst, J. J. (2014). Allopregnanolone in the brain: Protecting pregnancy and birth outcomes. *Progress in Neurobiology*, *113*, 106–136. https://doi.org/10.1016/j.pneurobio.2013.08.005

Bublitz, M. H., Bourjeily, G., D'Angelo, C., & Stroud, L. R. (2016). Maternal Sleep Quality and Diurnal Cortisol Regulation Over Pregnancy. *Behavioral Sleep Medicine*, *16*(3), 282–293. https://doi.org/10.1080/15402002.2016.1210147

Cappuccio, F., Miller, M. A., & Lockley, S. W. (2010). *Sleep, Health, and Society*. Retrieved from https://books.google.nl/

Carr, B. R., Parker, C. R., Jr., Madden, J. D., MacDonald, P. C., & Porter, J. C. (1981). Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. *American Journal of Obstetrics and Gynecology*, *139*(4), 416–422. https://doi.org/10.1016/0002-9378(81)90318-5

Carter, J. R., Durocher, J. J., Larson, R. A., DellaValla, J. P., & Yang, H. (2012). Sympathetic neural responses to 24-hour sleep deprivation in humans: sex differences. *American Journal of Physiology-Heart and Circulatory Physiology*, *302*(10), H1991–H1997. https://doi.org/10.1152/ajpheart.01132.2011

Cháberová, J. (2017). Analysis of Sleep Polysomnography Data Using Advanced Signal Processing Algorithms Descriptive features extraction for automatic sleep stages scoring. *Master Thesis*, 0. Retrieved from https://core.ac.uk/reader/81647120

Chang, J. J., Pien, G. W., Duntley, S. P., & Macones, G. A. (2010). Sleep deprivation during pregnancy and maternal and fetal outcomes: Is there a relationship? *Sleep Medicine Reviews*, *14*(2), 107–114. https://doi.org/10.1016/j.smrv.2009.05.001

Chatzitheochari, S., & Arber, S. (2009). Lack of sleep, work and the long hours culture: evidence from the UK Time Use Survey. *Work, Employment and Society*, *23*(1), 30–48. https://doi.org/10.1177/0950017008099776

Chrousos GP, Gold PW. The Concepts of Stress and Stress System Disorders: Overview of Physical and Behavioral Homeostasis. JAMA. 1992;267(9):1244–1252. doi:10.1001/jama.1992.03480090092034

Common Ailments of Pregnancy and Their Management - NHG Pharmacy. (n.d.). Retrieved 21 April 2020, from https://www.pharmacy.nhg.com.sg/page.aspx?id=680+

Concas, A., Mostallino, M. C., Porcu, P., Follesa, P., Barbaccia, M. L., Trabucchi, M., … Biggio, G. (1998). Role of brain allopregnanolone in the plasticity of -aminobutyric acid type A receptor in rat brain during pregnancy and after delivery. *Proceedings of the National Academy of Sciences*, *95*(22), 13284–13289. https://doi.org/10.1073/pnas.95.22.13284

Conway, C. A., Jones, B. C., DeBruine, L. M., Welling, L. L. M., Law Smith, M. J., Perrett, D. I., … Al-Dujaili, E. A. S. (2007). Salience of emotional displays of danger and contagion in faces is enhanced when progesterone levels are raised. *Hormones and Behavior*, *51*(2), 202–206. https://doi.org/10.1016/j.yhbeh.2006.10.002

Corwin, E. J., & Pajer, K. (2008). The Psychoneuroimmunology of Postpartum Depression. *Journal of Women's Health*, *17*(9), 1529–1534. https://doi.org/10.1089/jwh.2007.0725

Davis, D. C. (1996). The Discomforts of Pregnancy. *Journal of Obstetric, Gynecologic & Neonatal Nursing*, *25*(1), 73–81. https://doi.org/10.1111/j.1552-6909.1996.tb02516.x

Deboer, T. (2013). Behavioral and Electrophysiological Correlates of Sleep and Sleep Homeostasis. *Sleep, Neuronal Plasticity and Brain Function*, 1–24. https://doi.org/10.1007/7854_2013_248

Drevets, W. C. (1999). Prefrontal Cortical-Amygdalar Metabolism in Major Depression. *Annals of the New York Academy of Sciences*, *877*(1 ADVANCING FRO), 614–637. https://doi.org/10.1111/j.1749-6632.1999.tb09292.x

Duman, R. S. (2004). Depression: a case of neuronal life and death? *Biological Psychiatry*, *56*(3), 140–145. https://doi.org/10.1016/j.biopsych.2004.02.033

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive Consequences of Sleep Deprivation. *Seminars in Neurology*, *25*(01), 117–129. https://doi.org/10.1055/s-2005-867080

ELENKOV, I. J., & CHROUSOS, G. P. (2002). Stress Hormones, Proinflammatory and Antiinflammatory Cytokines, and Autoimmunity. *Annals of the New York Academy of Sciences*, *966*(1), 290–303. https://doi.org/10.1111/j.1749-6632.2002.tb04229.x

Faulkner, J., Schaller, M., Park, J. H., & Duncan, L. A. (2004). Evolved Disease-Avoidance Mechanisms and Contemporary Xenophobic Attitudes. *Group Processes & Intergroup Relations*, *7*(4), 333–353. https://doi.org/10.1177/1368430204046142

Feinberg, I., & Floyd, T. C. (1979). Systematic Trends Across the Night in Human Sleep Cycles. *Psychophysiology*, *16*(3), 283–291. https://doi.org/10.1111/j.1469-8986.1979.tb02991.x

Fessler, D. T., Bayley, T., Dye, L., Brown, J., Flaxman, S., Leeners, B., ... & Tepper, B. (2002). Reproductive immunosuppression and diet: An evolutionary perspective on pregnancy sickness and meat consumption. *Current anthropology*, *43*(1), 19-61.

Frank, M. G. (2006). The Mystery of Sleep Function: Current Perspectives and Future Directions. *Reviews in the Neurosciences*, *17*(4), 0. https://doi.org/10.1515/revneuro.2006.17.4.375

Friess, E., Tagaya, H., Trachsel, L., Holsboer, F., & Rupprecht, R. (1997). Progesterone-induced changes in sleep in male subjects. *American Journal of Physiology-Endocrinology and Metabolism*, *272*(5), E885–E891. https://doi.org/10.1152/ajpendo.1997.272.5.e885

Gangestad, S. W., Caldwell Hooper, A. E., & Eaton, M. A. (2012). On the function of placental corticotropin-releasing hormone: a role in maternal-fetal conflicts over blood glucose concentrations. *Biological Reviews*, *87*(4), 856–873. https://doi.org/10.1111/j.1469-185x.2012.00226.x

Guadagni, V., Burles, F., Ferrara, M., & Iaria, G. (2014). The effects of sleep deprivation on emotional empathy. *Journal of Sleep Research*, *23*(6), 657–663. https://doi.org/10.1111/jsr.12192

Hadjimarkou, M. M., Benham, R., Schwarz, J. M., Holder, M. K., & Mong, J. A. (2008). Estradiol suppresses rapid eye movement sleep and activation of sleep-active neurons in the ventrolateral preoptic area. *European Journal of Neuroscience*, *27*(7), 1780–1792. https://doi.org/10.1111/j.1460-9568.2008.06142.x

Hale, L., Emanuele, E., & James, S. (2015). Recent Updates in the Social and Environmental Determinants of Sleep Health. *Current Sleep Medicine Reports*, *1*(4), 212–217. https://doi.org/10.1007/s40675-015-0023-y

Hedman, C., Pohjasvaara, T., Tolonen, U., Suhonen-Malm, A. S., & Myllylä, V. V. (2002). Effects of pregnancy on mothers' sleep. *Sleep Medicine*, *3*(1), 37–42. https://doi.org/10.1016/s1389-9457(01)00130-7

Heritage, A., Stumpf, W., Sar, M., & Grant, L. (1980). Brainstem catecholamine neurons are target sites for sex steroid hormones. *Science*, *207*(4437), 1377–1379. https://doi.org/10.1126/science.7355296

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis. *Trends in Neurosciences*, *20*(2), 78–84. https://doi.org/10.1016/s0166-2236(96)10069-2

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(8), 1201–1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Hertz, G., Fast, A., Feinsilver, S. H., Albertario, C. L., Schulman, H., & Fein, A. M. (1992). Sleep in Normal Late Pregnancy. *Sleep*, *15*(3), 246–251. https://doi.org/10.1093/sleep/15.3.246

Hobson, J., McCarley, R., & Wyzinski, P. (1975b). Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science*, *189*(4196), 55–58. https://doi.org/10.1126/science.1094539

Irusen, E., Matthews, J. G., Takahashi, A., Barnes, P. J., Chung, K. F., & Adcock, I. M. (2002). P38 Mitogen-activated protein kinase–induced glucocorticoid receptor phosphorylation reduces its activity: Role in steroid-insensitive asthma. *Journal of Allergy and Clinical Immunology*, *109*(4), 649–657. https://doi.org/10.1067/mai.2002.122465

Irwin, M. R. (2006). Sleep Deprivation and Activation of Morning Levels of Cellular and Genomic Markers of Inflammation. *Archives of Internal Medicine*, *166*(16), 1756. https://doi.org/10.1001/archinte.166.16.1756

Irwin, M., McClintick, J., Costlow, C., Fortner, M., White, J., & Gillin, J. C. (1996). Partial night sleep deprivation reduces natural killer and celhdar immune responses in humans. *The FASEB Journal*, *10*(5), 643–653. https://doi.org/10.1096/fasebj.10.5.8621064

Joëls, M., & Krugers, H. J. (2007). LTP after Stress: Up or Down? *Neural Plasticity*, *2007*, 1–6. https://doi.org/10.1155/2007/93202

Johnstone, H. A., Wigger, A., Douglas, A. J., Neumann, I. D., Landgraf, R., Seckl, J. R., & Russell, J. A. (2001). Attenuation of Hypothalamic-Pituitary-Adrenal Axis Stress Responses in Late Pregnancy: Changes in Feedforward and Feedback Mechanisms. *Journal of Neuroendocrinology*, *12*(8), 811–822. https://doi.org/10.1046/j.1365-2826.2000.00525.x

Jones, B. C., Perrett, D. I., Little, A. C., Boothroyd, L., Cornwell, R. E., Feinberg, D. R., … Moore, F. R. (2005). Menstrual cycle, pregnancy and oral contraceptive use alter attraction to apparent health in faces. *Proceedings of the Royal Society B: Biological Sciences*, *272*(1561), 347–354. https://doi.org/10.1098/rspb.2004.2962

Kantermann, T. (2013). Circadian Biology: Sleep-Styles Shaped by Light-Styles. *Current Biology*, *23*(16), R689–R690. https://doi.org/10.1016/j.cub.2013.06.065

Katz, R. J., & Roth, K. A. (1979). Stress induced grooming in the rat — An endorphin mediated syndrome. *Neuroscience Letters*, *13*(2), 209–212. https://doi.org/10.1016/0304-3940(79)90043-0

Khadilkar, S. V., & Patil, V. A. (2019). Sex Hormones and Cognition: Where Do We Stand? *The Journal of Obstetrics and Gynecology of India*, *69*(4), 303–312. https://doi.org/10.1007/s13224-019-01223-5

Khazaie, H., Ghadami, M. R., Knight, D. C., Emamian, F., & Tahmasian, M. (2013). Insomnia treatment in the third trimester of pregnancy reduces postpartum depression symptoms: A randomized clinical trial. *Psychiatry Research*, *210*(3), 901–905. https://doi.org/10.1016/j.psychres.2013.08.017

Klein D.C., Moore R.Y., Reppert S.M. (1991). *Suprachiasmatic nucleus: the mind's clock*. Oxford University Press, USA.

Kulmatycki, K. M., & Jamali, F. (2006). Drug disease interactions: role of inflammatory mediators in depression and variability in antidepressant drug response. *J Pharm Pharm Sci*, *9*(3), 292-306.

Kyriacou, C. P., & Hastings, M. H. (2010). Circadian clocks: genes, sleep, and cognition. *Trends in Cognitive Sciences*, *14*(6), 259–267. https://doi.org/10.1016/j.tics.2010.03.007

Lancel, M., Faulhaber, J., Holsboer, F., & Rupprecht, R. (1996). Progesterone induces changes in sleep comparable to those of agonistic GABAA receptor modulators. *American Journal of Physiology-Endocrinology and Metabolism*, *271*(4), E763–E772. https://doi.org/10.1152/ajpendo.1996.271.4.e763

Lee, K. (2000). Parity and sleep patterns during and after pregnancy. *Obstetrics & Gynecology*, *95*(1), 14–18. https://doi.org/10.1016/s0029-7844(99)00486-x

Lee, K. A., Shaver, J. F., Giblin, E. C., & Woods, N. F. (1990). Sleep patterns related to menstrual cycle phase and premenstrual affective symptoms. *Sleep*, *13*(5), 403-409.

Lukács, H. (2001). Rat as Model for Studying Behavior Effects of hCG. *Seminars in Reproductive Medicine*, *19*(01), 111–120. https://doi.org/10.1055/s-2001-13918

Lüllmann, H., & Mohr, K. (2005). *Sesam Atlas van de farmacologie* (2e Nederlandse druk ed.). Amersfoort, Nederland: ThiemeMeulenhoff bv.

Lustig, K. A., Stoakley, E. M., MacDonald, K. J., Geniole, S. N., McCormick, C. M., & Cote, K. A. (2018). Sex hormones play a role in vulnerability to sleep loss on emotion processing tasks. *Neurobiology of Sleep and Circadian Rhythms*, *5*, 94–104. https://doi.org/10.1016/j.nbscr.2017.10.001

Maes, M., Verkerk, R., Bonaccorso, S., Ombelet, W., Bosmans, E., & Scharpé, S. (2002). Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. *Life Sciences*, *71*(16), 1837–1848. https://doi.org/10.1016/s0024-3205(02)01853-2

Mallampalli, M. P., & Carter, C. L. (2014). Exploring Sex and Gender Differences in Sleep Health: A Society for Women's Health Research Report. *Journal of Women's Health*, *23*(7), 553–562. https://doi.org/10.1089/jwh.2014.4816

Manber, R., Bei, B., Simpson, N., Asarnow, L., Rangel, E., Sit, A., & Lyell, D. (2019). Cognitive Behavioral Therapy for Prenatal Insomnia. *Obstetrics & Gynecology*, *133*(5), 911–919. https://doi.org/10.1097/aog.0000000000003216

Mander, B. A., Winer, J. R., & Walker, M. P. (2017). Sleep and Human Aging. *Neuron*, *94*(1), 19–36. https://doi.org/10.1016/j.neuron.2017.02.004

McCANN, S. M., KIMURA, M., KARANTH, S., YU, W. H., MASTRONARDI, C. A., & RETTORI, V. (2006). The Mechanism of Action of Cytokines to Control the Release of Hypothalamic and Pituitary Hormones in Infection. *Annals of the New York Academy of Sciences*, *917*(1), 4–18. https://doi.org/10.1111/j.1749-6632.2000.tb05368.x

McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. *Metabolism*, *55*, S20–S23. https://doi.org/10.1016/j.metabol.2006.07.008

MCEWEN, B. S., WEISS, J. M., & SCHWARTZ, L. S. (1968). Selective Retention of Corticosterone by Limbic Structures in Rat Brain. *Nature*, *220*(5170), 911–912. https://doi.org/10.1038/220911a0

Meerlo, P., Benca, R. M., & Abel, T. (Reds.). (2015). Sleep, Neuronal Plasticity and Brain Function. *Current Topics in Behavioral Neurosciences*. https://doi.org/10.1007/978-3-662-46878-4

Meerlo, P., Koehl, M., Van Der Borght, K., & Turek, F. W. (2002). Sleep Restriction Alters the Hypothalamic-Pituitary-Adrenal Response to Stress. *Journal of Neuroendocrinology*, *14*(5), 397–402. https://doi.org/10.1046/j.0007-1331.2002.00790.x

Meier-Ewert, H. K., Ridker, P. M., Rifai, N., Regan, M. M., Price, N. J., Dinges, D. F., & Mullington, J. M. (2004). Effect of sleep loss on C-Reactive protein, an inflammatory marker of cardiovascular risk. *Journal of the American College of Cardiology*, *43*(4), 678–683. https://doi.org/10.1016/j.jacc.2003.07.050

Minkel, J., Moreta, M., Muto, J., Htaik, O., Jones, C., Basner, M., & Dinges, D. (2014). Sleep deprivation potentiates HPA axis stress reactivity in healthy adults. *Health Psychology*, *33*(11), 1430–1434. https://doi.org/10.1037/a0034219

Mong, J. A., Baker, F. C., Mahoney, M. M., Paul, K. N., Schwartz, M. D., Semba, K., & Silver, R. (2011). Sleep, Rhythms, and the Endocrine Brain: Influence of Sex and Gonadal Hormones. *Journal of Neuroscience*, *31*(45), 16107–16116. https://doi.org/10.1523/jneurosci.4175-11.2011

Mosey, T. (2020, March 11). The Gut-Sleep Connection. Retrieved 20 April 2020, from https://www.ideafit.com/mind-recovery/the-gut-sleep-connection/

Mullington, J. M., Simpson, N. S., Meier-Ewert, H. K., & Haack, M. (2010). Sleep loss and inflammation. *Best Practice & Research Clinical Endocrinology & Metabolism*, *24*(5), 775–784. https://doi.org/10.1016/j.beem.2010.08.014

National Sleep Foundation. (n.d.). How Much Sleep Do We Really Need? Retrieved 24 April 2020, from https://www.sleepfoundation.org/articles/how-much-sleep-do-we-really-need

Navarrete, C. D., Fessler, D. M. T., & Eng, S. J. (2007). Elevated ethnocentrism in the first trimester of pregnancy. *Evolution and Human Behavior*, *28*(1), 60–65. https://doi.org/10.1016/j.evolhumbehav.2006.06.002

Neumann, I. D., Johnstone, H. A., Hatzinger, M., Liebsch, G., Shipston, M., Russell, J. A., … Douglas, A. J. (1998). Attenuated neuroendocrine responses to emotional and physical stressors in pregnant rats involve adenohypophysial changes. *The Journal of Physiology*, *508*(1), 289–300. https://doi.org/10.1111/j.1469-7793.1998.289br.x

Nielsen, D., Videbech, P., Hedegaard, M., Dalby, J., & Secher, N. J. (2000). Postpartum depression: identification of women at risk. *BJOG: An International Journal of Obstetrics and Gynaecology*, *107*(10), 1210–1217. https://doi.org/10.1111/j.1471-0528.2000.tb11609.x

Nishina, H., Honda, K., Okai, T., Kozuma, S., Inoué, S., & Taketani, Y. (1996). Characteristic changes in sleep patterns during pregnancy in rats. *Neuroscience Letters*, *203*(1), 5–8. https://doi.org/10.1016/0304-3940(95)12249-4

O'Leary, P., Boyne, P., Flett, P., Beilby, J., & James, I. (1991). Longitudinal assessment of changes in reproductive hormones during normal pregnancy. *Clinical Chemistry*, *37*(5), 667–672. https://doi.org/10.1093/clinchem/37.5.667

Okun, M. L., & Coussons-Read, M. E. (2007). Sleep disruption during pregnancy: How does it influence serum cytokines? *Journal of Reproductive Immunology*, *73*(2), 158–165. https://doi.org/10.1016/j.jri.2006.06.006

Opal, S. M., & DePalo, V. A. (2000). Anti-Inflammatory Cytokines. *Chest*, *117*(4), 1162–1172. https://doi.org/10.1378/chest.117.4.1162

Otgaar, H., Smeets, T., & van Bergen, S. (2010). Picturing survival memories: Enhanced memory after fitness-relevant processing occurs for verbal and visual stimuli. *Memory & Cognition*, *38*(1), 23–28. https://doi.org/10.3758/mc.38.1.23

Oyiengo, D., Louis, M., Hott, B., & Bourjeily, G. (2014). Sleep Disorders in Pregnancy. *Clinics in Chest Medicine*, *35*(3), 571–587. https://doi.org/10.1016/j.ccm.2014.06.012

Pace-Schott, E. F., & Hobson, J. A. (2002). The Neurobiology of Sleep: Genetics, cellular physiology and subcortical networks. *Nature Reviews Neuroscience*, *3*(8), 591–605. https://doi.org/10.1038/nrn895

Palagini, L., Gemignani, A., Banti, S., Manconi, M., Mauri, M., & Riemann, D. (2014). Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. *Sleep Medicine*, *15*(8), 853–859. https://doi.org/10.1016/j.sleep.2014.02.013

Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological Psychiatry*, *49*(5), 391–404. https://doi.org/10.1016/s0006-3223(00)01088-x

Pearson, R., & Lewis, M. B. (2005). Fear recognition across the menstrual cycle. *Hormones and Behavior*, *47*(3), 267–271. https://doi.org/10.1016/j.yhbeh.2004.11.003

PIERCE, G. B., Jr, & MIDGLEY, A. R., Jr (1963). THE ORIGIN AND FUNCTION OF HUMAN SYNCYTIOTROPHOBLASTIC GIANT CELLS. *The American journal of pathology*, *43*(2), 153–173.

Pires, G. N., Alvarenga, T. A., Maia, L. O., Mazaro-Costa, R., Tufik, S., & Andersen, M. L. (2012). Inhibition of self-grooming induced by sleep restriction in dam rats. *The Indian journal of medical research*, *136*(6), 1025.

Pires, G. N., Tufik, S., & Andersen, M. L. (2015). Effects of REM sleep restriction during pregnancy on rodent maternal behavior. *Revista Brasileira de Psiquiatria*, *37*(4), 303–309. https://doi.org/10.1590/1516-4446-2014-1629

Reid, K. J., McGee-Koch, L. L., & Zee, P. C. (2011). Cognition in circadian rhythm sleep disorders. *Progress in Brain Research*, 3–20. https://doi.org/10.1016/b978-0-444-53817-8.00001-3

Roozendaal, B. (2002). Stress and Memory: Opposing Effects of Glucocorticoids on Memory Consolidation and Memory Retrieval,. *Neurobiology of Learning and Memory*, *78*(3), 578–595. https://doi.org/10.1006/nlme.2002.4080

Sahota, P. K. , Jain, S. S. & Dhand, R. (2003). Sleep disorders in pregnancy. Current Opinion in Pulmonary Medicine, 9(6), 477-483.

Santiago, J. R., Nolledo, M. S., Kinzler, W., & Santiago, T. V. (2001). Sleep and sleep disorders in pregnancy. *Annals of Internal Medicine*, *134*(5), 396-408.

Saper, C. B., Fuller, P. M., Pedersen, N. P., Lu, J., & Scammell, T. E. (2010). Sleep State Switching. *Neuron*, *68*(6), 1023–1042. https://doi.org/10.1016/j.neuron.2010.11.032

Scott, J. P. R., McNaughton, L. R., & Polman, R. C. J. (2006). Effects of sleep deprivation and exercise on cognitive, motor performance and mood. *Physiology & Behavior*, *87*(2), 396–408. https://doi.org/10.1016/j.physbeh.2005.11.009

Sherin, J. E., Shiromani, P. J., McCarley, R. W., & Saper, C. B. (1996). Activation of Ventrolateral Preoptic Neurons During Sleep. *Science*, *271*(5246), 216–219. https://doi.org/10.1126/science.271.5246.216

Shouse, M. N., & Siegel, J. M. (1992). Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. *Brain research*, *571*(1), 50-63.

Siegel, J. M. (2005). REM sleep. *Principles and practice of sleep medicine*, *4*, 120-135.

Siegel, J. M. (2008). Do all animals sleep? *Trends in Neurosciences*, *31*(4), 208–213. https://doi.org/10.1016/j.tins.2008.02.001

Siegel, J. M. (2009). Sleep viewed as a state of adaptive inactivity. *Nature Reviews Neuroscience*, *10*(10), 747–753. https://doi.org/10.1038/nrn2697

Snyder, F., Hobson, J. A., Morrison, D. F., & Goldfrank, F. (1964). Changes in respiration, heart rate, and systolic blood pressure in human sleep. *Journal of Applied Physiology*, *19*(3), 417–422. https://doi.org/10.1152/jappl.1964.19.3.417

Swanson, L. M., Pickett, S. M., Flynn, H., & Armitage, R. (2011). Relationships Among Depression, Anxiety, and Insomnia Symptoms in Perinatal Women Seeking Mental Health Treatment. *Journal of Women's Health*, *20*(4), 553–558. https://doi.org/10.1089/jwh.2010.2371

Teplan, M. (2002). Fundamentals of EEG measurement. *Measurement science review*, *2*(2), 1-11.

UCSF Health. (n.d.). Pregnancy the three trimesters. Retrieved 24 April 2020, from https://www.ucsfhealth.org/conditions/pregnancy/trimesters

Waddell, B. J., & Atkinson, H. C. (1994). Production rate, metabolic clearance rate and uterine extraction of corticosterone during rat pregnancy. *Journal of Endocrinology*, *143*(1), 183–190. https://doi.org/10.1677/joe.0.1430183

Wai Loke, Y., & King, A. (1997). Immunology of human placental implantation: clinical implications of our current understanding. *Molecular Medicine Today*, *3*(4), 153–159. https://doi.org/10.1016/s1357-4310(97)01011-3

Wang, X., Wu, H., & Miller, A. H. (2003). Interleukin 1α (IL-1α) induced activation of p38 mitogen-activated protein kinase inhibits glucocorticoid receptor function. *Molecular Psychiatry*, *9*(1), 65–75. https://doi.org/10.1038/sj.mp.4001339

Wikner, B. N., & Källén, B. (2011). Are Hypnotic Benzodiazepine Receptor Agonists Teratogenic in Humans? *Journal of Clinical Psychopharmacology*, *31*(3), 356–359. https://doi.org/10.1097/jcp.0b013e3182197055

Wirth, M. M. (2014). Hormones, Stress, and Cognition: The Effects of Glucocorticoids and Oxytocin on Memory. *Adaptive Human Behavior and Physiology*, *1*(2), 177–201. https://doi.org/10.1007/s40750-014-0010-4

Wolf, O. T. (2003). HPA axis and memory. *Best Practice & Research Clinical Endocrinology & Metabolism*, *17*(2), 287–299. https://doi.org/10.1016/s1521-690x(02)00101-x

Wolf, Oliver T. (2008). The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychologica*, *127*(3), 513–531. https://doi.org/10.1016/j.actpsy.2007.08.002

Wolfson, A. R., Crowley, S. J., Anwer, U., & Bassett, J. L. (2003). Changes in Sleep Patterns and Depressive Symptoms in First-Time Mothers: Last Trimester to 1-Year Postpartum. *Behavioral Sleep Medicine*, *1*(1), 54–67. https://doi.org/10.1207/s15402010bsm0101_6

Ziomkiewicz, A., Wichary, S., & Jasienska, G. (2018). Cognitive costs of reproduction: life-history trade-offs explain cognitive decline during pregnancy in women. *Biological Reviews*, *94*(3), 1105–1115. https://doi.org/10.1111/brv.12494