# THESIS

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2021

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# Role of hypothalamic dysfunction in relation to selected neuropsychiatric disorders

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2021

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# List of abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotrophic hormone |
| AVP | Arginine vasopressin |
| BD | Bipolar disorder |
| CNS | Central nervous system |
| CRH | Corticotrophin-releasing hormone |
| g | Grams |
| GABA | Gamma aminobutyric acid |
| GAD | Generalized anxiety disorder |
| GH | Growth hormone |
| GR | Glucocorticoid receptor |
| HAMA | Hamilton Rating Scale for Anxiety |
| HPA-axis | Hypothalamic-Pituitary-Adrenal axis |
| HR | High-reactive |
| IGF | Insulin-like growth factor |
| IL-1β | Interleukin 1 beta |
| IR | Intermediate-reactive |
| LH | Luteinizing hormone |
| LR | Low-reactive |
| MDD | Major depressive disorder |
| MDDu | Major depressive disorder unmedicated |
| MR | Mineralocorticoid receptor |
| MSH | Melanocyte-stimulating hormone |
| $NK_1$ | Neurokinin 1 |
| PTH | Parathyroid hormone |
| PVN | Paraventricular nucleus |
| THPO | Thrombopoietin |
| TRH | Thyrotrophin-releasing hormone |
| TSH | Thyroid stimulating hormone |

# 1. Introduction

We maintain our health and wellbeing through combined actions of the endocrine system and the nervous system [1]. The hypothalamus plays an important role in this. Its main function is to maintain the homeostasis of the body [2] and it can be visualized as the key intersection point between the nervous system and the endocrine system [3]. In hypothalamic dysfunction there is normally also a combination of neurological and endocrine disturbance. Examples of this are mood disorders, eating disorders, abnormal behavior, and thermoregulation disorders [4].

Neuropsychiatric disorders are complex conditions that derives from multiple genetic factors interacting in the context of environmental factors that are not well understood, and which results in clinically diverse attributes [5]. Although neuropsychiatric disorders are assumed to follow from changes in brain function, the underlying biological mechanisms are to a large degree not known, and neuropsychiatric disorders are not characterized by evident neuropathology [6]. There has been an increased focus in the past decades to understand better the relationship between alterations in the hypothalamus and certain psychiatric diseases [7].

In the remaining part of chapter 1 the following main topics will be addressed:

- The endocrine system.
- The nervous system.
- The hypothalamus.
- Hypothalamic dysfunction.
- Neuropsychiatric disorders.
- Hypothalamic dysfunction and mood and behavioral disorders.

Thereafter, the literature review part of the thesis, chapters 2 – 4, focus on hypothalamic dysfunction in relation to aggression, anxiety and depression.

## 1.1 The endocrine system

The endocrine system regulates and coordinate vital bodily functions, including mood, through the production and secretion of hormones from a series of glands and tissues. Hormones are vital for maintaining homeostatic balance in the body and regulate physiological processes. The endocrine system is very complex. It consists of specialized and dedicated endocrine glands which release their secretions directly into the bloodstream, in addition to other organs and tissues like bone, adipose tissue, heart, and kidneys that have a secondary endocrine function which also release a set of hormones. The hypothalamus plays a key role in this, and has several endocrine functions which will be discussed in chapter 1.3 below [3]. Figure 1 below illustrate the major endocrine glands and tissues, and their hormones[1].

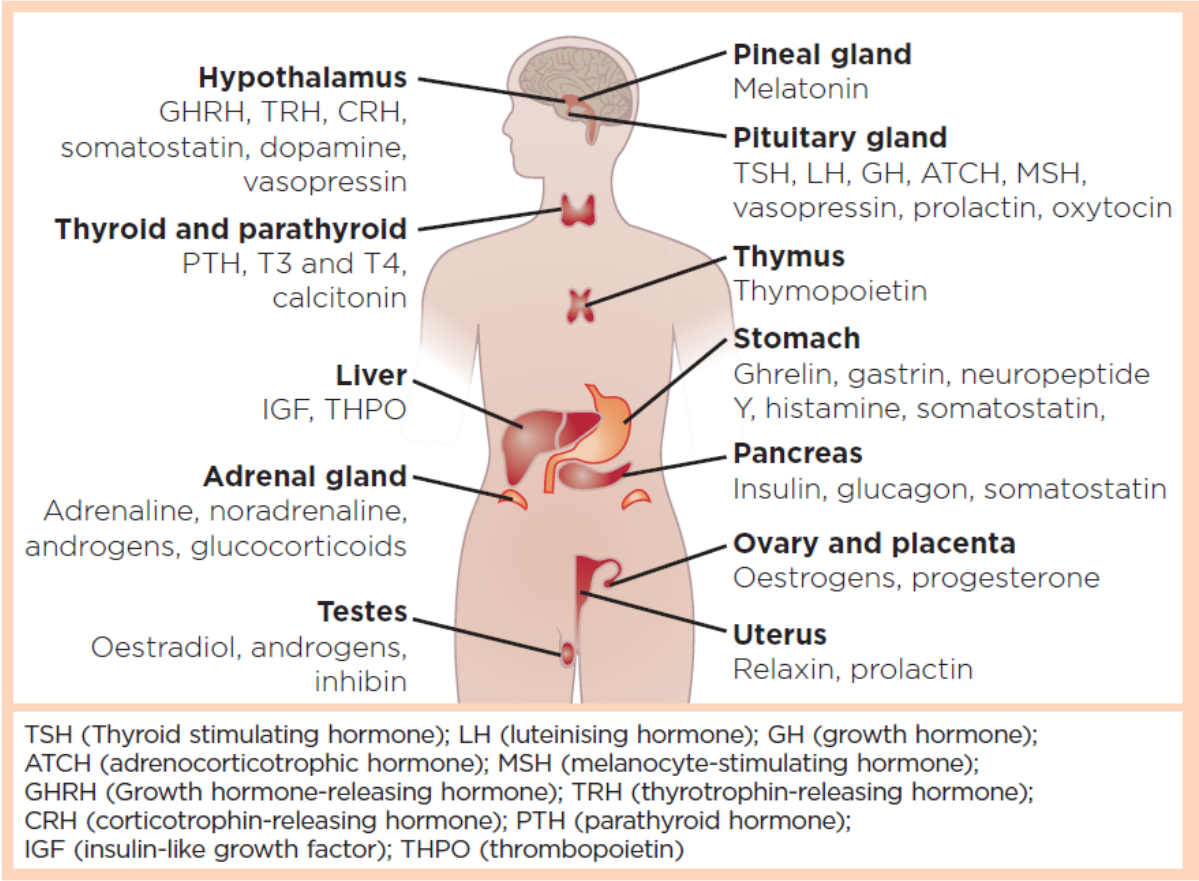


**Figure 1: Major endocrine glands and tissues, and their hormones.**
***Source: [3] page 39***
*[Used with publisher permission.]*

[1] Note that in Figure 1: Adrenocorticotrophic hormone has been abbreviated as ATCH, instead of ACTH. ACTH is used in the text throughout the thesis.

## 1.2 The nervous system

As mentioned above, we maintain our health and wellbeing through combined actions of the endocrine system and the nervous system. Changes in the external and internal environment is monitored and responded to by the nervous system. Our memory, perception and behavior are the responsibility of our nervous system. It also initiates all voluntary movements. All the neural tissues in the body, which carries information from one part of the body to another, is included in the neural system. The central nervous system (CNS), within the brain and spinal cord, is where integration and co-ordination are carried out. All the neural tissue outside the CNS is called the peripheral nervous system [1].

The peripheral nervous system is divided between afferent (or sensory) nerves and efferent (or motor) nerves. The afferent nerves transmit impulses from peripheral organs to the CNS, while the efferent nerves transmit impulses from the CNS to the peripheral organs to cause an action or an effect [8].

The efferent nerves are further divided into somatic nerves, which communicate with skeletal muscle only and which are under voluntary or conscious control [1], autonomic nerves, which is not under conscious or voluntary control, but functions continuously and without conscious control. The autonomic nervous system regulates heart rate, temperature, blood glucose and blood pressure [1, 8].

The autonomic nervous system has two parts or subdivisions, namely the sympathetic part and the parasympathetic part. Although they tend to result in opposing effect, they work together on an overall basis to achieve homeostasis. One stimulates and the other inhibits. In stressful situations sympathetic activity dominates, while during rest parasympathetic activity dominates. [9]. The autonomic nervous system contributes to maintaining regional reflex control of autonomic function assisted by modulating input from more central systems, jointly facilitating quick adjustment to heart rate, blood pressure, bowel function, bladder function, vascular reactivity, pupils, sweating, temperature regulation and sexual organs [10]. The regulator of the autonomic nervous system is the hypothalamus, which get input from sensory nerves as well as several other parts of the brain [9].

## 1.3 The hypothalamus

As highlighted, our health and wellbeing are maintained through combined actions of the endocrine- system and the nervous system [1], in which the hypothalamus plays an important role. Its main function is to maintain the homeostasis of the body [2] through the integration and coordination of several biologic systems [7]. It can be visualized as the key intersection point between the nervous system and the endocrine system [3].

The hypothalamus is part of the limbic system, which is a set of structures involved in processing emotion and memory. The limbic system also includes the hippocampus and the amygdala, and is located within the cerebrum of the brain, just below the temporal lobes, and buried under the cerebral cortex [11].

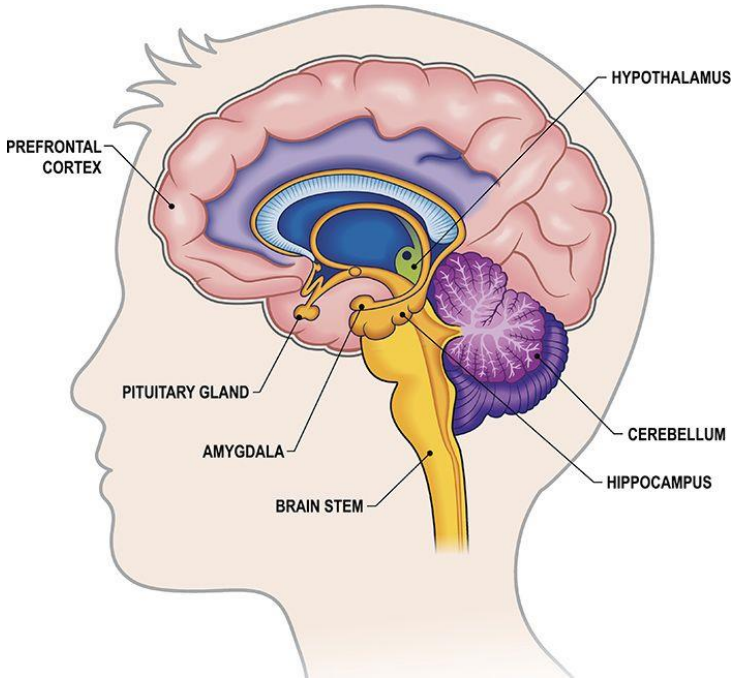


**Figure 2. The Limbic System**
***Source: [11]***
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The hypothalamus is one of the smallest and oldest parts of the brain. The total brain weight of an adult human is 1400 g, of which the hypothalamus represents just 4 g. Nevertheless, it contains highly conserved neural circuitry [12].

The hypothalamus is formed by various nervous and nucleus fibers and is involved in many complex functions through its neuronal connections, such as endocrine, autonomic, and

behavioral functions. The hypothalamus links the nervous system to the endocrine system through the pituitary gland and regulates the hormone secretion in the body through releasing and inhibitor factors [2, 13].

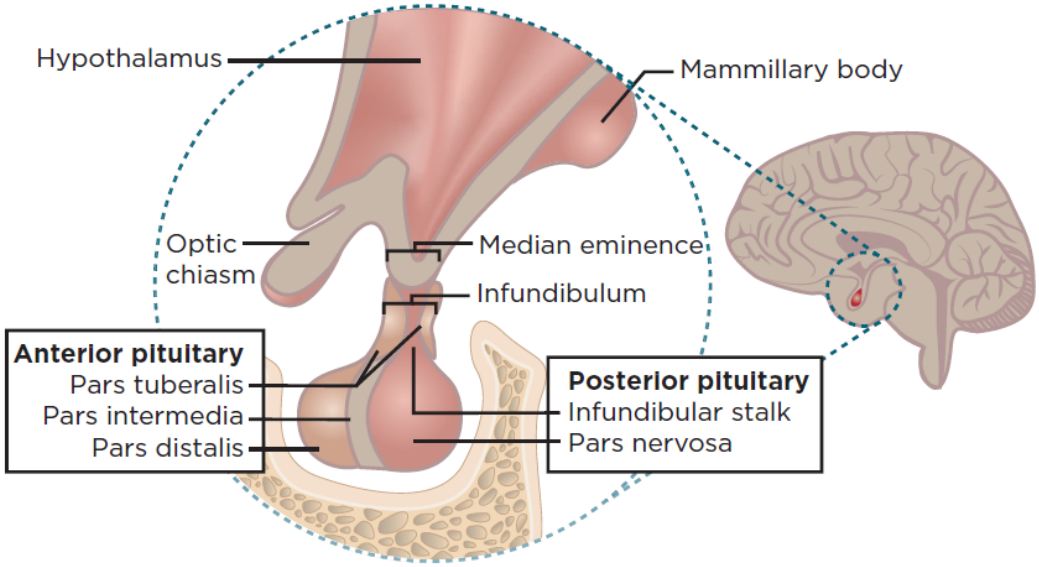


**Figure 3. Anatomy of the hypothalamus and pituitary gland**
***Source: [14] page 50***
*[Used with publisher permission]*.

The importance of the functional roles of the hypothalamus is high and cannot be overestimated [7]. It manages several important physiologic functions such as:

- Behavioral and emotional responses [3] including mood, sleep, circadian rhythm, reproduction, and sexual drive and behavior [7], how the body responds to stress [11], and in the mediation of the emotional responses [13].
- Regulation of appetite [3] and the control of hunger and thirst, food, and water intake [11].
- Regulation of body temperature [14].
- Coordination of the autonomic nervous system [3].
- The release of several essential hormones by the hypophysis [3, 13].

The below figure shows a schematic illustration of the hypothalamic nuclei.

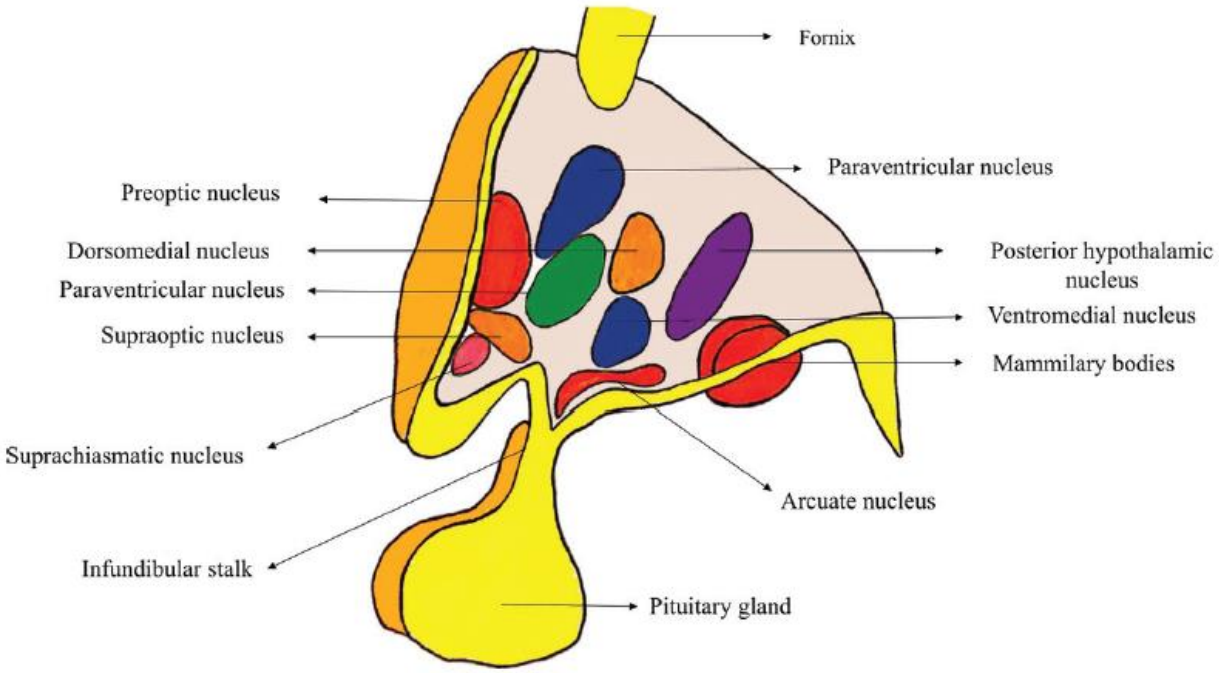


**Figure 4. Schematic representation of hypothalamic nuclei (sagittal section).**
***Source: [2] page 5***
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An explanation of the involvement of the various parts of the hypothalamic nuclei is given by Gabriela Pop, Crivii and Opincariu [2], and is summarized below:

- Blood pressure control and water balance of the body in the supraoptic nucleus.
- Thermoregulation of the body by way of sweating, as well as in eating and reproduction in the preoptic region alongside the anterior hypothalamic nucleus.
- Cardiovascular control in response to stress in the medial preoptic region.
- Circadian rhythm control in the suprachiasmatic nucleus.
- Stress and metabolism control in the paraventricular nucleus.
- Eating habits and the feeling of satiety in ventromedial nucleus.
- Orexigenic peptides secretion of ghrelin, orexin, or neuropeptide Y in the infundibular or arcuate nucleus.

In respect of the main role of the hypothalamus, Saper and Lowell states in the R1112 page of their 2014 article, that “the role of the hypothalamus is essentially integrative, meaning that it brings together a range of sensory inputs necessary to make important decisions about

basic life functions. It then compares those inputs to basic setpoints, that is, ideal levels for parameters such as body temperature, blood sodium and glucose levels, and various hormone levels. The hypothalamus then activates autonomic, endocrine, and behavioral responses that try to maintain the body at the key setpoints (homeostasis) or overcome a stressor (allostasis)" [12].

These are some of the key outputs of the hypothalamus [12]:

- Control of the autonomic nervous system
- Endocrine control
- Behavioral control

The autonomic nervous system is controlled by the hypothalamus via a set of neurons that directly stimulates both the sympathetic and the parasympathetic systems [2], in addition to different groups of cells in the brainstem that controls autonomic reflexes [12].

The hypothalamic endocrine control acts through the pituitary gland and regulates the hormone secretion in the body through releasing and inhibitor factors [2]. The role of the hypothalamus in behavior control is complex, and current thought suggest that the hypothalamus contains circuits, rather than specific centers that increase the likelihood of certain behavior [12].

## 1.4 Hypothalamic dysfunction

As described above, the hypothalamus is a complex area of the brain, involved in coordinating signals between the nervous system and the endocrine system, mainly through the pituitary gland. It also plays an important regulatory role in various neurological and psychiatric disorders [4].

Dysfunction in the hypothalamus can be seen as a group of endocrine, metabolic, neurologic, and other systemic symptoms, and signs. The hypothalamic dysfunction can be caused by a variety of pathologic processes, since many nuclei and nerve tracts are anatomically and functionally linked within the small dimension of the hypothalamus [15].

The causes of hypothalamic dysfunctions can be grouped into the following [15]:

- Congenital (acquired or genetic)
- Tumors
- Infiltrative
- Immunologic
- Nutritional, metabolic
- Infectious
- Vascular
- Traumatic
- Functional
- Other (radiation, porphyria, toluene exposure)

Since the hypothalamus regulates both endocrine and autonomic functions, a combination of endocrine and neurological disturbances are usually found in hypothalamic dysfunctions, such as mood disorders, eating disorder, abnormal behavior, and thermoregulation disorders. It should be noted that it can be difficult to differentiate between hypothalamic and pituitary dysfunction as their endocrine abnormalities are often alike [4].

## 1.5 Signs, symptoms, and manifestations of hypothalamic dysfunctions

Hypothalamic dysfunctions can include both endocrine and non-endocrine neurological features, which can be difficult to distinguish between. Hypothalamus also plays an important regulatory role in various neurological and psychiatric disorders. In fact, hypothalamic damage may result in serious clinical morbidity regardless of whether the cause is congenital or acquired [4].

Hypothalamic dysfunctions can result in the manifestation of several dysfunctions and disorders, including emotions and mood, sleep cycle, body temperature, weight, growth, water balance and milk production. Depending on the specific area affected in the hypothalamus, the hypothalamic dysfunction can be manifested as different signs and symptoms. The clinical signs and symptoms can also vary, depending on the hypothalamic nuclei and function being affected. In addition, due to the functional organization of the hypothalamus, it may be possible to trace some signs and symptoms to a specific anatomic area [16].

The Hypothalamic Pituitary Adrenal axis (HPA-axis) is affected by most hypothalamic dysfunctions. For example, several disorders may result in hypothalamic hyposecretion which leads to pituitary hyposecretion. Also, if a hypothalamic inhibitory hormone is altered, pituitary hypersecretion will follow with its clinical manifestations. For instance, oxytocin and vasopressin are two neurohormones influenced by disorders affecting hypothalamus. These hormones affect the distal tubules of the kidneys by influencing its water reabsorption, in addition to affecting contraction of the uterus during labor, reflex of milk ejection and sexual response. Diets rich in saturated fatty acids may cause dysfunctions of the mitochondria and hypothalamic inflammation that may produce dysfunction of hypothalamus, which encourage obesity [16].

The signs and symptoms of suspected hypothalamic dysfunctions are for the most part non-specific. Clinical manifestation must therefore be seen together with a patient's history and a physical examination to confirm the suspicion. The extent of genetic disorders in the family must also be considered [16].

## 1.6 Neuropsychiatric disorders

Neuropsychiatric disorders are complex conditions that derives from multiple genetic factors interacting in the context of environmental factors that are not well understood, and which results in clinically diverse attributes [5]. Although neuropsychiatric disorders are assumed to follow from changes in brain function, the underlying biological mechanisms are to a large degree not known, and neuropsychiatric disorders are not characterized by evident neuropathology [6].

Neuropsychiatry focus on understanding the neurological bases of psychiatric disorders, the psychiatric manifestations of neurological disorders, and/or the evaluation and care of persons with neurologically based behavioral disturbances [17]. Neuropsychiatric disorders are highly debilitating conditions, and it is established that they are at least moderately heritable. Although neurobiological leads are illusive in respect of common neuropsychiatric disorders, significant advances have been made in recent years in understanding the genetic architecture of neuropsychiatric disorders and the genetic loci involved. For instance, the heritability, as opposed to environmental factors of neuropsychiatric disorders has been studied on twins and have concluded that most have a significant genetic component [6].

There has been an increased focus in the past decades to understand better the relationship between alterations in the hypothalamus and certain psychiatric diseases. Multiple hypothalamic abnormalities have for instance been revealed in relation to major depressive disorders (MDD) such as volume changes of hypothalamus, increased or decreased expression of various hypothalamic hormones such as CRH, vasopressin and oxytocin and loss of neurons among others [7].

The symptoms of neuropsychiatric disorders seem to impact an individual's emotions, mood and brain function. These symptoms may be irritability, sadness, mood problems, and depression among others. Some of the common neuropsychiatric disorders are [18]:

- Anxiety
- Depression
- Uncontrolled anger
- Eating disorders
- Cognitive deficit disorders
- Attention deficit disorders
- Seizures
- Addictions

## 1.7 Hypothalamic dysfunction in mood and behavioral disorders

The functional role of the hypothalamus is high and cannot be overestimated [7]. Hypothalamus manages several important physiologic functions including behavioral and emotional responses [3] like mood, sleep, circadian rhythm, reproduction, and sexual drive and behavior [7], how the body responds to stress [11], and in the mediation of the emotional responses [13]. It has been further pointed out that a combination of endocrine and neurological disturbances is usually found in hypothalamic dysfunctions, including mood disorders and abnormal behavior [4].

In the remaining part of the thesis, I have chosen to focus on hypothalamic dysfunction in relation to aggression, anxiety and depression.

# 2. Hypothalamic dysfunction and aggression

## 2.1 Aggressive behavior

As de Boer state in page 81 of his 2018 article, aggression is "characterized by a ritualized set of species-typical behaviors performed in close interaction with another individual" [19]. In fact, one of the primary social behaviors used by animals and humans is aggression. It is used to protect young individuals, compete for food, defend their territory and to secure mates [20].

Social conflict is, for the majority of individuals, handled with controlled and appropriate types of aggressive behavior. However, a minor percentage of individuals, which in humans range from 3 to 7 %, show severe forms of aggressive behavior. In order to understand these abnormal aggressive behaviors, recognizing their modulating factors and underlying causal mechanism is of great importance [19].

Different specific actions during aggressive reactions may vary when comparing humans to animals. However, the basic neural mechanisms which motivate the aggressive behavior are, to a high degree, believed to be maintained across species [20]. Aggression comes in multiple forms and is not expressed uniformly. A commonly accepted division separates aggression into two forms: reactive and proactive aggression. The reactive aggression is considered as emotional and impulsive while proactive aggression is considered cold and gain-oriented [21].

## 2.2 Altered function of HPA axis and its role in aggression

The appearance of aggressive phenotypes is commonly found together with developmentally low or high HPA axis reactivity. In fact, abnormal aggression is often linked to abnormal functioning of HPA axis, but the information available to causally associate different HPA axis abnormalities with specific types of aggression is inadequate [21].

The HPA axis is an important part of the body´s physiological stress system as it plays an important part in the regulation of various adjustments to stress. Together with the sympathetic nervous system, the physiological, behavioral and metabolic responses to stress are regulated by the activated HPA axis. A cascade of multiple responses is involved in its

activation, beginning with the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) performed by the paraventricular nucleus (PVN) of hypothalamus after enduring stress. These two hormones reach the pituitary where they activate the production of adrenocorticotropic hormone (ACTH), which is released into the circulation. [21–23]

ACTH travels with the blood and reach its effector organ, the adrenal cortex, activating the production and release of glucocorticoids. Glucocorticoids is further involved in multiple processes in the body, including inhibition of the HPA axis and modulation of its activity. Mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) are the two receptor systems which glucocorticoids act through. They are found in high concentrations in hypothalamus and both genomic and non-genomic actions are a result of their receptor binding. The genomic actions are a result of induced or repressed expression of genes upon activation of glucocorticoid receptors which are important for the regulation of several processes, such as inflammation, behavior and metabolism. Non-genomic actions are, on the other hand, a result of activation of membrane-bound GR and MR which aid in encoding information related to stress in addition to promote behaviors like aggression and other stress-related adaptive behaviors [21, 24–28].

Increased activation of the stress systems is seen in individuals showing increased levels of reactive type aggression [29]. In a study performed on rats, corticosterone (a HPA axis hormone) was injected in the prepubertal period. During the adolescence period, the rat´s displaced elevated play fighting while in adult age, aggressive behavior was increased [30]. These results suggests that increased corticosterone levels during the rat´s development does have a causal role in aggression [21].

As mentioned earlier, the appearance of aggressive phenotypes is commonly found together with developmentally low or high HPA axis reactivity. According to Walker et al., there is a possible U-shaped relationship between aggressive behavior and the HPA axis activity [21]. Chapter 2.2 and 2.3 point to studies performed on various species with findings both supporting and contradicting this U-shaped curve.

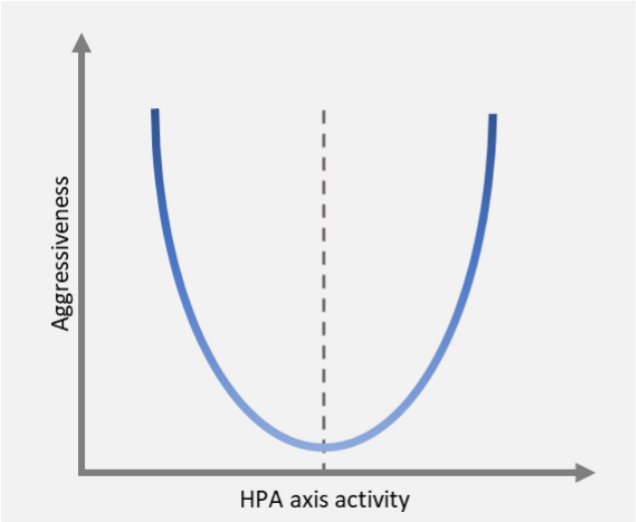


**Fig. 5. Possible U-shaped relationship between aggressive behavior and HPA axis activity.**
***Source:*** **[21]**
*[Figure by Martine Solberg Gresslien]***.**

In a study with rodents, aggressive behavior in the resident-intruder test was examined. In this study, the C57Bl/6 mice was used. These mouse lines were chosen and bred based on plasma corticosterone response following applied restraint stress for 15 minutes which resulted in three different reactivity lines, namely high reactivity (HR), intermediate reactivity (IR), and low reactivity (LR) mice. The focus of the analysis was the amount of time elapsed between entrance of the intruder mouse until the attack by the resident mouse. The results showed that LR mice performed the quickest attacks where 92% of them attacked the intruder mouse within 300 seconds. While only 42% of the HR mice performed an attack within 300 seconds, 70% of the IR mice attacked the intruder mouse within the same amount of time. The results showed that there was a negative link between aggression and high responsiveness of HPA axis, while low HPA axis responsiveness had a positive link to aggressiveness as LR mice showed elevated attack reactivity towards conspecific intruders [21, 31].

## 2.3 Developmental stress and its consequences for aggression

Serious ramifications on the HPA axis development may occur as a result of early life experiences [21]. In certain developmental periods of an individual´s life, such as prenatal, postnatal and pubertal periods, the brain is especially sensitive to stress as it goes through important changes [32]. In fact, long-term consequences on the function of HPA axis in addition to behavior may occur if exposed to stressful situations during these developmental stages. Experiencing negative situations in early life and during adolescence

can affect social behavior later in life as a result of altered HPA axis function caused by its impaired development. Additionally, aggressiveness as well as depression and anxiety may result from early life stress [33, 34].

### 2.3.1 Prenatal stress

A study on male rats from an inbred strain (DA/Han), where acute prenatal stress was applied on the 10$^{th}$ and 19$^{th}$ gestation days, showed elevated HPA axis reactivity caused by stress in addition to lowered aggression and higher degree of submissiveness [35, 36]. However, a study performed on juvenile Wistar rats revealed elevated aggression in a social interaction test when exposed to prolonged prenatal stress during the final week of gestation [37]. Another study performed on voles being exposed to various forms of prenatal stress on the 13$^{th}$ to the 15$^{th}$ day of gestation caused elevated aggression in male offspring in addition to extended stress induced HPA axis activation [38].

### 2.3.2 Early postnatal stress

Maternal separation is a study model widely used in studies on early life adversity, and in juvenile individuals, maternal separation has shown to be a major stressor that results in early postnatal stress [21]. A study on juvenile male rats being separated from their mother revealed elevated play fighting and decreased submission with an increased activity of HPA axis at basal level during the early dark phase [39]. When examined during adulthood, the rats displayed elevated aggressive behavior when exposed to the resident-intruder test, but their HPA axis responsiveness was, compared to control rats, similar [40]. In C57Bl/6 mice, the opposite results were demonstrated. A two-week separation from their mother, starting from the day of birth, results in heightened HPA axis reactivity following stress, less playfighting during juvenility as well as lower levels of aggression between males during adulthood [21]. In Balb/C mice however, a briefer maternal separation period showed elevated aggressive behavior [41].

Increased levels of impulsive aggressive behavior while engaging in play-fighting was seen in a study with young monkeys who had been separated from their mother at birth. These were hand-reared the first month after birth, followed by five months of being raised with peers of the same age [21]. In studies where infant monkeys had been treated poorly by their mother, elevated concentrations of plasma cortisol in infants and excessive aggression in the

adolescence period was seen [42]. In contrast, other studies of peer-reared monkeys with increased aggression were linked to low reactivity of the HPA axis [21].

In summary, a complex link was revealed between aggressive behavior and differences in HPA axis development in studies on early postnatal stress. Elevated aggression in rats was associated with increased stress induced HPA axis, while in monkeys both low and high HPA axis reactivity was linked with aggression [21].

### 2.3.3 Peripubertal and adolescent stress

Stress exposure in the period around puberty and during adolescent may also have consequences for aggressive behavior [43]. Post-weaning studies in male Wistar rats exposed to social isolation over a period of 7 weeks after weaning, resulted in abnormal aggression. The rat´s corticosterone concentration at basal level did not change, but after aggressive confrontations or social stress however, increased concentrations were detected [44]. Even social isolation post-weaning for less than 7 weeks may be enough to cause changes in social behaviors. A study performed on Sprague Dawley rats, which exposed rats to 4 weeks of isolation, showed socially deprived rats with increased play-fighting behavior when tested in late adolescence [45]. On the other hand, a study in mice showed no change in HPA axis function or aggressive behavior later in life, after 5 days of isolation in the early period around puberty. Accordingly, the length of isolation seems to be an interfering factor in development of aggressive behavior and changes in HPA axis regulation [21].

In various studies performed on rodents, animals were exposed to repeated social subjugation in form of social abuse or bullying. For instance, a study exposing juvenile rats to aggressive adults daily showed increased aggression and basal corticosterone concentrations following provocations of both social and physical forms [46].

In the peripubertal stress model, which was originally developed in rats, exposed the animals to various fear-inducing stressors across the prepubertal period on seven dispersed days. Male rats displayed abnormal aggressive behavior such as elevated aggression towards males, young individuals, and even against individuals expressing subordinate postures as well as females. In general, a lack of change in corticosterone concentrations at basal levels was seen, but both males and females exposed to peripubertal stress had a weakened corticosterone response to stress while showing increased aggressive behavior. Rats exposed

to stress during peripubertal and/or adolescence showed increased likelihood to increased aggressive behavior and development of increased reactivity of the HPA axis [43, 47].

Similar studies have been performed on juvenile hamsters. In a study where young individuals were exposed to an aggressive adult male in their own cage, for 20 minutes a day, displayed no change in corticosterone concentrations at basal level, but elevated corticosterone response upon stress was found. Interestingly, less attacks were performed on intruders of the same size, while elevated aggressive behavior was seen on intruders of smaller size. Even during adulthood, these individuals showed increased levels of aggressive behavior [21]. Other studies point to similar results, where hamsters defeated again and again in the period of adolescence showed increased aggressive behavior towards opponents of smaller size, and reduced aggression towards similar sized individuals [48].

In summary, the effects of stress appear to depend greatly on two factors. Firstly, on the developmental period in which an individual is exposed to stress, and secondly on the chosen species in addition to the protocol used. As there is limited research in this field, further research is needed to better understand how various types of stress impact the development of aggressive behavior over time and in relation to different stages of brain development [21].

## 2.4 Hypothalamic mechanisms involved in aggression

Haller points to findings suggesting that there are two basic types of hypothalamic mechanisms where the emotional part of the attack is what differentiates between them. Haller has reviewed hypothalamic mechanisms in rodents, cats and humans where 12 laboratory models which show abnormal attack features was analyzed, with special focus on the hypothalamus. The hypothalamic mechanisms shown to regulate attacks go through changes which are dependent on etiological factors. These hypothalamic mechanisms are: general activation levels and the neurotransmitters serotonin (local), dopamine, substance P, glutamate, GABA, and vasopressin [48].

The first type of hypothalamic mechanism involved in the emotional part of attack is linked to elevated arousal i.e., emotional/reactive aggression. It showed elevated mediobasal hypothalamic activation as well as elevated hypothalamic vasopressinergic neurotransmission, in addition to reduced hypothalamic serotonergic neurotransmission. The second hypothalamic mechanism involved in the emotional part of attack is, on the

contrary, linked to low arousal i.e., unemotional/proactive aggression. This showed an over-activated lateral hypothalamus, paradoxical modifications in vasopressinergic neurotransmission and finally, a loss of serotonergic neurotransmission´s anti-aggressive effect [48].

In the aggression model related to hypoarousal, the following pathway is activated: central amygdala-lateral hypothalamus-ventral periaqueductal gray pathway, which displays a neural control like those seen in predatory attacks. The pathway showing increased activation in the hyperarousal aggression model is, on the other hand, the medial amygdala-mediobasal hypothalamus-dorsal periaqueductal pathway. Qualitatively different neural mechanisms control various behavioral and emotional types of abnormal aggression. Several qualitative and etiological factor-dependent variations in the neural background suggests that abnormal aggression does not follow from a single neurobiological path. The mediobasal hypothalamus is an area called hypothalamic attack area. It is shown to be closely involved in attacks on individuals of the same species, so-called conspecifics. The location and extent of this area is as well as the behaviors evoked upon its stimulation, species-dependent, but its role in general seems to be evolutionary maintained [48–50].

### 2.4.1 Hypothalamic neurotransmitter's involvement in aggression

Serotonin, GABA, glutamate, dopamine, acetylcholine, noradrenaline, substance P, and vasopressin are neurotransmitters utilized by neural inputs involved in hypothalamic mechanisms. These neural inputs further influence hypothalamic mechanisms linked to attack [48].

The glutamatergic neurons located in the mediobasal hypothalamus which further project to the periaqueductal grey, is believed to cause emotional type aggression (defensive rage) in cats. The lateral hypothalamus on the other hand, is related to predatory attacks and is stimulated by substance Pergic medial amygdala neurons as well as dopaminergic and noradrenergic inputs. The predatory attack related lateral hypothalamus is indirectly inhibited by mediobasal hypothalamus through GABAergic projections. In fact, neurons of lateral hypothalamus are under GABAergic projections, but the neurochemical nature of these neurons assumed to elicit predatory attacks are not clear. Acetylcholine and dopamine facilitate both mediobasal- and lateral hypothalamic areas, while serotonin inhibits them [48, 51].

In the rat, the neurochemistry of hypothalamic mechanisms leading to predatory attacks is not well known. But, both GABAergic- and glutamatergic neurons is located in mediobasal hypothalamus, which is involved in attacks on conspecifics. The results from a study where a local infusion of agonists and antagonists were injected, suggest that GABAergic neurons locally inhibit attacks while glutamatergic neurons induce it. The mediobasal hypothalamic area is influenced by several factors such as vasopressinergic inputs, and substance P projections which possibly originates from medial amygdala. The main inputs that negatively regulates neurons of this area are, as demonstrated by stimulation studies, serotonergic in nature [48, 52].

The following content of chapter 2.4.1.1-2.4.1.3 provides incomplete depth and answers to the selected neurotransmitters role in abnormal aggression but this does not diminish the importance of the results or their relevance in the development of abnormal aggression [48]. The three neurotransmitters discussed reflects those where most relevant information was found regarding hypothalamic neurotransmitters and their role in abnormal aggression.

#### *2.4.1.1 Serotonin- its role in abnormal aggression*

Haller points to the serotonin hypothesis as an essential part of aggression control. In theory, reduced serotonergic control may lead to abnormal aggression as it indirectly upregulates the function of brain mechanisms stimulating aggression. But, in abnormal aggression, hypothalamic serotonin has shown to be very complex [48].

Two separate studies, where both models expressed abnormal aggression, analyzed serotonin related changes in mediobasal hypothalamus, an area involved in rivalry attack control. Both studies showed similar results. In one study, mice were exposed to post-weaning social isolation while in another study, rats were separated from their mother. Both models expressed abnormal aggression, and the results showed that the density of different serotonin receptors and/or fiber density of serotonin in mediobasal hypothalamus was reduced. Despite certain contraindications seen in these studies, they overall revealed a reduction in hypothalamic serotonin functions which support serotonin´s anti-aggressive effect. Opposite results were however reported in other studies. For instance, in mice selectively bred for aggressiveness, the results did not reveal a definite link between aggressiveness and serotonergic neurotransmission. Some rodent studies even showed that

elevated serotonergic neurotransmission in hypothalamus is linked with certain types of abnormal aggression [48, 53–55].

These findings demonstrate that hypothalamic serotonin may contribute to abnormal aggression when reduced, as well as when increased. This shows that the role of hypothalamic serotonin is complex [48].

#### *2.4.1.2 Vasopressin- its role in abnormal aggression*

The neurotransmitter vasopressin also has important roles in the control of aggression. It is hypothesized that abnormal types of aggression can be triggered by its elevated neurotransmission, but the information available to support it is incomplete. In a study performed on rats where juveniles were separated from their mother, results revealed that both basal and aggression-induced vasopressin expression was elevated in lateral hypothalamus, but no change was seen in the anterior hypothalamus. Contrarily, a study on hamsters repeatedly defeated during adolescence (subjugation model), showed reduced vasopressin fiber density in addition to reduced anterior hypothalamic vasopressin content [40, 48, 56].

#### *2.4.1.3 Substance P- its role in abnormal aggression*

The effect of substance P, a neurotransmitter mediated by neurokinin 1 ($NK_1$), was studied in the hypoarousal model only. Results showed that neurons of the mediobasal hypothalamus expressing $NK_1$ receptors were, by aggressive confrontations, clearly over-activated. Thus, in this specific model, these neurons seem to be especially involved in abnormal aggression [57].

### 2.4.2 Hyperactivated hypothalamic structures and their role in abnormal aggression

As Haller state in page 102 of his 2013 article, the hyperactivation theory refers to the hypothesis that “hypothalamic structures involved in attack were overactivated in abnormal aggression” [48]. As mentioned earlier, the mediobasal hypothalamus is referred to as the hypothalamic attack area which is involved in rivalry attacks [50]. The lateral hypothalamus on the other hand, is involved in predatory attacks [51]. The reviewed findings below reveal both supporting and non-supporting data.

In studies where rodents were exposed to social isolation post-weaning, results revealed elevated aggression-induced c-Fos action in mediobasal hypothalamus. Studies on rats with low anxiety as well as those performed on the hypoarousal model, did however reveal elevated activation in the lateral hypothalamus. In mice selected for increased aggression, the hypoarousal model showed no difference in mediobasal hypothalamic activation. Similar results were seen in rats selected for high anxiety, despite their abnormal attack levels. As for lateral hypothalamic activation, no elevation was seen in high anxiety selected rats, nor in animals exposed to social isolation post weaning [48, 50, 58]

The above results suggests that an over-activated mediobasal hypothalamus is seen primarily in models with hyperarousal associated aggression, such as the social isolation post weaning model. A model characterized by heightened autonomic stress- and glucocorticoid responses. Oppositely, mediobasal hypothalamic activation did not occur in hypoarousal models which represent low reduced autonomic stress- and glucocorticoid responses [48].

In summary, the emotional aspect of abnormal aggressive behavior seems, based on the above findings, to be a contributing factor in aggression controlled by hypothalamus. The abnormal attacks in the hypoarousal model are linked to predatory-like hypothalamic activation pattern while hyperarousal model is linked to rivalry-like hypothalamic activation pattern. Hyperarousal associated aggression seems to be linked to elevated activation of mediobasal hypothalamus with normal lateral hypothalamus, while hypoarousal associated aggression with elevated activation of lateral hypothalamus is not linked with elevated activation of mediobasal hypothalamus [48–50].

# 3. Hypothalamic dysfunction and anxiety

## 3.1 Anxiety

Anxiety is an emotion experienced when faced with potential or uncertain danger or threats. It can be because of a new situation or context, or because of a previously present danger or threat that is no longer present [59]. Anxiety seems to be affected by environmental factors such as early-life experiences as well as predisposing genetic factors and is a prolonged emotion with focus on the future without necessarily involving a specific object of threat [60].

Terlevic et al. describes anxiety and anxiety disorders in page 390 of their 2013 article the following way: "Anxiety is a general term describing a range of related and commonly experienced subjective mental states which normally arise in response to a wide range of external and internal stressors. If this response occurs at inappropriate times or to an inappropriate degree and is disruptive to the individual it then constitutes an anxiety disorder." [24].

As previously mentioned, hypothalamus can be seen as the key intersection point between the nervous- and the endocrine system [3]. The HPA axis, with hypothalamus as its central component, is responsible for neuroendocrine responses to stress and anxiety. There is also evidence suggesting that HPA axis dysfunction may accompany generalized anxiety disorders (GAD) [24].

Increased susceptibility to mood- and anxiety disorders has been linked to environmental stress. Additionally, observations of HPA axis hyperactivity were often seen in patients with these disorders [61]. Stress may, due to glucocorticoids or other factors, cause long-term effects on behavior. Such effects may not present itself immediately but can potentially occur a long time after the initial stress exposure [62].

In situations where individuals are exposed to stress in developmental life stages, primarily during prenatal, postnatal and adolescent life phases, studies on humans have revealed that stress may affect later development and elevate the susceptibility to several mental disorders, including anxiety disorders [62].

## 3.2 Hypothalamus volumes in patients with anxiety

A human study performed by Terlevic et al. compared hypothalamus volumes in patients diagnosed with GAD with healthy control subjects to investigate the correlation between anxiety and hypothalamic volumes. 12 patients with GAD and 21 healthy subjects of the same sex, age, ethnicity and handedness were included in the study, reflecting a limited sample size. Consequently, the results can only suggest, but not conclude, a potential relationship between anxiety and hypothalamic volumes. Larger sample sizes should therefore be used to further explore this aspect. The results revealed a significantly smaller hypothalamus in GAD patients when compared to hypothalamus volumes of healthy controls. In female patients, both left and right hypothalamus volumes were reduced. The sex only significantly impacted the left hypothalamus, while the right side indicated a trend for significance [24].

The above results, which showed a negative correlation between levels of anxiety (which in this study was measured by the Hamilton Rating Scale for Anxiety (HAMA)) and hypothalamic volumes, suggests a causal link between pathological anxiety and disrupted hypothalamic morphology. This is supported by the fact that anxiety patients showed a trend for such correlation, while healthy controls did not [24].

## 3.3 Altered function of HPA axis and its role in anxiety

As mentioned in chapter 2.2, the HPA axis is an important part of the body´s physiological stress system as it plays an important part in the regulation of various adjustments to stress. Together with the sympathetic nervous system, the physiological, behavioral and metabolic responses to stress are regulated by the activated HPA axis. A cascade of multiple responses is involved in its activation, beginning with the release of CRH and AVP performed by the PVN of hypothalamus after enduring stress. These two hormones reach the pituitary where they activate the production of ACTH, which is released into the circulation [21–23].

ACTH travels with the blood and reach its effector organ, the adrenal cortex, activating the production and release of glucocorticoids. Glucocorticoids is further involved in multiple processes in the body, including inhibition of the HPA axis and modulation of its activity. MR and GR are the two receptor systems which glucocorticoids act through. They are found

in high concentrations in hypothalamus and both genomic and non-genomic actions are a result of their receptor binding. The genomic actions are a result of induced or repressed expression of genes upon activation of glucocorticoid receptors which are important for the regulation of several processes, such as inflammation, behavior and metabolism. Non-genomic actions are, on the other hand, a result of activation of membrane-bound glucocorticoid receptors which aid in encoding information related to stress in addition to promote behaviors like aggression and other stress-related adaptive behaviors [21, 24–28].

In anxiety patients, the heightened cortisol awakening response might be caused by heightened anticipatory anxiety related to the following day [63]. Findings from a separate study which, in GAD patients, showed elevated cortisol levels in saliva after being exposed to a situation of natural stress suggested, that in patients with anxiety disorder, another cause of abnormal activation of HPA axis may be cognitive post event processing [64]. Consequently, GAD patients and patients with anxiety disorders may be exposed to an elevated cumulative dose of cortisol where worrying thoughts may be responsible for its release [24].

### 3.3.1 Anxiety linked with hyperactivated and/or dysregulated HPA axis

CRH plays an important part in the regulation of the basal- and stress activated HPA axis [23]. And as mentioned earlier, CRH is released by the PVN of hypothalamus [21]. Anxiety, which is a stress related mood disorder, is in fact involved with CRH circuits that is either hyperactive and/or dysregulated [23]. And observations of HPA axis hyperactivity are consistent findings in patients with anxiety disorders [61].

### 3.3.2 Role of stressful life events and HPA axis in anxiety disorders

Dysregulation of the body´s stress-system, which leads to increased cortisol concentrations, have been linked to anxiety disorders. In fact, a dysfunctional HPA axis in addition to stressful life events has shown to be involved with the pathogenesis of anxiety disorders [65]. However, the dysregulation of the HPA axis is not specific to the different anxiety disorders. Reports about abnormal HPA axis function have been made in the majority of anxiety disorders, and stressful life events are suggested to play a part in both the onset of and in the course of GAD. GAD is characterized by exaggerated anxiety and uncontrolled worrying thoughts about different problems and situations in life on an almost daily basis, lasting for a minimum of 6 months. The risk of developing GAD may, according

to researchers, be increased in individuals exposed to single or multiple negative life events, if those events occur unexpectedly and are of significance [59].

Studies performed on animal models supports that stressful life events, particularly those occurring early in life, may cause CNS dysfunctions and alter the stress response of an individual that lasts during adulthood. Additionally, stressful life events do, according to large amounts of work on non-human primates and rodents, influence behavior of living organisms [59]. In rodents, studies have revealed that abnormal behavior correlating with anxiety disorders in humans may be provoked by early social isolation [66].

Among human patients with anxiety disorders, observations revealed that these patients had experienced increased rates of abuse during childhood. And chronic stress may in fact, when seen in situations such as extended exposure to stressful life events, cause continuous HPA system activation which in turn leads to sustained elevations in cortisol levels. Additionally, chronic stress has been suggested to increase an individual's vulnerability to stress induced diseases. Observations made by other authors revealed a hyperactive HPA axis, with elevated concentrations of cortisol in saliva at basal level, in children that had experienced various forms of parental separation such as parenteral death or permanent or long-term separation from parents. The potential development of anxiety disorders may, in these individual´s, be increased [59, 67, 68].

Regarding GAD, the onset of this anxiety disorder seems to be linked with stressful life events related to increased loss and danger [69]. In children, pressure from parents, acute life events and being overprotected are associated with childhood GAD [70]. High levels of stress may over time lead to abnormal secretion of cortisol in patients with GAD, but little research is available regarding the actual neuroendocrine changes in this anxiety disorder. However, some studies have analyzed the possible link between HPA axis and GAD [59].

Following the dexamethasone suppression test, one study found results indicating a weaker negative feedback sensitivity of the HPA axis, with non-suppression rates of 27-37%. Another study, performed on elderly patients with GAD, showed that cortisol concentrations at basal levels were elevated by 40-50% compared to controls. Additionally, other studies also reported elevated saliva and plasma cortisol concentrations at basal level [59, 71].

On the other hand, several studies have not been able to find abnormal adrenocortical activity in patients with GAD, but despite of these findings, the majority of the results indicate a link

between increased levels of cortisol and GAD, as chronic stress may result in the continuous activation of HPA axis. Consequently, a sustained elevation of cortisol levels may occur [59].

Faravelli et al. points out that available data pointing to HPA axis dysfunction caused by stressful life events and its role in anxiety disorders are limited. This is in accordance with the literature search conducted for this thesis. In summary, exposure to stress occurring in a crucial developmental phase in life can cause HPA axis dysregulation which may, together with other various factors such as anxiety sensitivity or new life events, result in the development of anxiety symptoms. The resulting neuroendocrine changes may also enhance an individual's susceptibility to stressors in the future, leading to increased susceptibility to anxiety disorders. Additionally, once there is over-activation of the HPA axis during developmental phases, the HPA axis may stay constantly overdriven, unstable, vulnerable or dysfunctional. Finally, as there is limited research available regarding the link between stressful events early in life, HPA axis dysfunction and anxiety disorders, further research may lead to a better understanding of their relationship [59, 65].

# 4. Hypothalamic dysfunction and depression

## 4.1 Depression

In page 114 of their 2011 article, Stetler and Miller describes depression as “a heterogenous illness that manifest in a variety of symptom sets, for a variety of reasons, at various points in life” and “lasts for  a varying amount of time” [72]. Depressive disorder is among the mental disorders most frequently diagnosed in children, adolescents and adults [26], and one of the most common psychiatric diseases is MDD [73]. Worldwide, MDD affects approximately 120 million people [74].

Following stress, hypothalamus secrete CRH, which in turn leads to secretion of ACTH by the pituitary gland. ACTH then reach the adrenal cortex, via blood, where glucocorticoid synthesis and secretion occurs [74]. In fact, prior to depressive episodes, exposure to stressors has occurred in more than half of the cases [75] and prior to clinical depression, both patients and physicians have described situations provoking stress [73]. In patients suffering from major depression, a substantial part of the patients had enlarged pituitary and adrenal glands, elevated cortisol levels, and excessive cortisol response to ACTH [75].

Dysfunction of the HPA axis has been linked to major depression for a long time [74], and HPA axis hyperactivity during depression has, as stated in page 114 of Stetler and Miller´s 2011 article, “been called one of the most reliable findings in all of biological psychiatry” [72]. Stetler and Miller further points out that hyperactivity of the HPA axis manifest itself in various form in approximately 20-80% of people with depression [72]. The hypothesis that patients suffering from depression have an HPA axis dysfunction which cause altered cortisol concentrations are one of the best known. Studies on animals have supported this hypothesis while human studies have been less supportive as only around half of patients with MDD show high levels of cortisol [73].

In situations where individuals are exposed to stress in developmental life stages, primarily during prenatal, postnatal and adolescent life phases, studies on humans have revealed that stress may affect later development and elevate the susceptibility to several mental disorders, including major depression [62].

## 4.2 Altered function of HPA axis and its role in depression

As mentioned in chapter 2.2 and 3.3, the HPA axis is an important part of the body´s physiological stress system as it plays an important part in the regulation of various adjustments to stress. Together with the sympathetic nervous system, the physiological, behavioral and metabolic responses to stress are regulated by the activated HPA axis. A cascade of multiple responses is involved in its activation, beginning with the release of CRH and AVP performed by the PVN of hypothalamus after enduring stress. These two hormones reach the pituitary where they activate the production of ACTH, which is released into the circulation [21–23].

ACTH travels with the blood and reach its effector organ, the adrenal cortex, activating the production and release of glucocorticoids. Glucocorticoids is further involved in multiple processes in the body, including inhibition of the HPA axis and modulation of its activity. MR and GR are the two receptor systems which glucocorticoids act through. They are found in high concentrations in hypothalamus and both genomic and non-genomic actions are a result of their receptor binding. The genomic actions are a result of induced or repressed expression of genes upon activation of glucocorticoid receptors which are important for the regulation of several processes, such as inflammation, behavior and metabolism. Non-genomic actions are, on the other hand, a result of activation of membrane-bound glucocorticoid receptors which aid in encoding information related to stress in addition to promote behaviors like aggression and other stress-related adaptive behaviors [21, 24–28].

In depressed individuals, HPA axis hyperactivity has been demonstrated by multiple studies. The HPA axis dysregulation has also been hypothesized by some authors, to be a potential factor occurring caused by early-life events such as stressful experiences. Additionally, in depressive disorder linked to chronic stress, HPA axis hyperactivity has been implied to play an important role [26].

### 4.2.1 Hypothalamic inflammation, HPA axis dysregulation and depression

Cernackova et al. hypothesize that hypothalamic inflammation caused by exposure to stress alter the activity of the HPA axis and therefore influence depressive disorders development. Hypothalamic inflammation may be caused by multiple factors such as peripheral inflammation or by ingesting elevated amounts of saturated fatty acids. As a consequence, the homeostatic regulation by hypothalamus may be disrupted. In fact,

depressive disorder and exposure to stress has in recent studies been suggested to be linked with inflammation of the hypothalamus [26, 76].

Several factors may contribute to inflammation of the hypothalamus linked to stress, but as there are high levels of GR and MR located in the hypothalamus that regulate the activity of HPA axis, the majority of studies on stress and inflammation of hypothalamus focus on glucocorticoid effects in the neuroinflammatory process development. Glucocorticoid resistance may, in prolonged exposure to stress, develop in CRH neurons of the PVN located in the hypothalamus. The glucocorticoid resistance can disturb the negative feedback mechanism that regulates the HPA axis activity, and potentially cause continuous stimulation of HPA axis that may lead to hypercorticoidism [77–79].

Additionally, inflammatory markers, such as IL-1β, have shown to be elevated in the brain following stress. IL-1β activate CRH secretions from PVN of the hypothalamus which further leads to the activation of the HPA axis. Mice studies revealed that in animals exposed to mild chronic stress, IL-1β in the brain may serve as a moderator of depressive symptoms through the HPA axis activation. In combination with other studies that under different stressful circumstances report IL-1β expressions in hypothalamus, these findings propose the important role that chronic stress may have in the cause and development of depressive disorder. Additionally, in depressive disorder linked to chronic stress, HPA axis hyperactivity has been implied to play an important role [26, 80, 81].

Following prolonged increased concentrations of glucocorticoids in hypothalamus, glucocorticoids may activate microglia which shift into a prime state instead of producing inflammatory factors straight away. Cell surface receptors of primed microglia are increased in number, resulting in activated microglia more susceptible to further stimulation [26]. A two-hit depression hypothesis suggest that stress exposure during early life- or postnatal periods may prime microglia. It further suggests that stressful incidents occurring later in life, such as during adolescence or early adulthood, may activate those previously primed microglia which consequently induce the production of inflammatory factors, potentially resulting in hyperactivity of HPA axis and glucocorticoid resistance [82].

In depressed individuals, HPA axis hyperactivity has been demonstrated by multiple studies. Certain authors believe that stressful experiences early in life or even postnatal stress, in addition to other factors, may cause HPA axis dysregulation which may further result in

elevated susceptibility to depressive disorders. This coincides with the above mentioned two-hit hypothesis [82–86].

In summary, these findings show that inflammation of hypothalamus may regulate HPA axis activity, cause glucocorticoid resistance and lead to depressive symptoms in certain patients [26].

### 4.2.2 Cortisol levels, HPA axis dysfunction and major depressive disorder

Dysfunction of the HPA axis has been linked to major depression for a long time, and in MDD the abnormal GR signaling is linked to the continuous hypersecretion of CRH from CRH neurons located in the hypothalamus. As a result of this, the HPA axis activity is believed to shift toward higher and higher levels which may lead to constantly heightened HPA axis activity as seen in some patients suffering from MDD [74].

There is a complex link between MDD and cortisol in humans as it seems to depend on several factors including the phase of the illness, its severity, and the type of challenges faced. In patients with chronic MDD for instance, the HPA axis responsiveness doesn't seem to be affected, as studies showed no differences in serum and salivary cortisol concentrations in patients with MDD and healthy controls after the dexamethasone suppression test [74].

Several studies revealed that there is a correlation between the level of cortisol and how severe the depressive symptoms are. The atypical MDD, which is a less severe form of MDD, displayed cortisol responses which is closer to the healthy control patients. Also, dysregulation of cortisol in response to stress seems to be linked with acute and severe forms of MDD, while chronic-, atypical- and other less severe forms of depression does not seem to have such clear links. In patients with MDD, the variability in HPA axis response induced by stress represents a stronger link than the absolute cortisol levels. Only severe subtypes of MDD show increased basal cortisol concentrations, while in chronic and atypical depression, no such increase have been found [74].

### 4.2.3 Early-life stress, HPA axis dysfunction and depression

Being exposed to various traumatic experiences early in life, such as during childhood or adolescence, may have consequences in adulthood [75] as negative early life experiences during postnatal development may increase the risk of depression in adulthood [87]. Evidence suggests that the stress response ability of the HPA axis during adulthood

may suffer constant changes in individuals who has been exposed to stress during early developmental phases, and consequently increase their susceptibility to depression. The abnormalities involved seems to be associated with changes in glucocorticoids ability to perform negative feedback on the HPA axis hormone secretions via MR and GR binding. Prior to depressive episodes, exposure to stressors, in particular psychosocial stressors, has occurred in more than half of the cases [75].

As stated in page 153 of Juruena´s 2014 article, the following five subdivided childhood maltreatment are:

1. "Physical abuse: physical aggression by someone older, with the risk of or result of injury.
2. Emotional abuse: verbal aggression that affects the welfare or morale of the child or any conduct that humiliates, embarrasses, or threatens the child.
3. Sexual abuse: any type of sexual contact or conduct between a child and someone older.
4. Emotional neglect: failure of caretakers to provide for basic emotional and psychological needs such as love, motivation and support.
5. Physical neglect: failure of caretakers to provide for basic physical needs such as feeding, a home, security, supervision, and health" [75].

Children exposed to maltreatment have an elevated risk of experiencing depression during adolescence and adulthood. Additionally, depressed patients with a history of childhood abuse have, in recent studies, shown an increased likelihood to display HPA axis hyperactivity, while baseline as well as stress-induced activation of the HPA axis have been reported to be elevated or reduced after childhood maltreatment. The pattern and degree of the potential HPA axis disturbance have shown to be influenced by several factors such as parent´s responsiveness, the child´s age at the time of maltreatment, exposure to future stressors and maltreatment type [75].

As mentioned above, negative early life experiences during postnatal development may increase the risk of depression in adulthood. Several animal studies using an early life stress model in rodents showed that exposure to daily repeated maternal separation could regulate HPA axis and further alter subsequent functions in the brain, as well as adulthood behavior. Specifically, the HPA axis responsiveness may be worsened if exposed to maternal

separation, and findings have shown that maternal separation in rodents may cause HPA axis hyperactivity for the remaining part of their life [87].

In summary, both animal and human studies imply that persistent changes in the stress response ability of the HPA axis in adulthood may be induced in individuals exposed to stress during early developmental phases, which consequently increase their susceptibility to depression. In fact, neurochemical and molecular modifications caused by stressful events and depression has, based on evidence, been suggested to trigger HPA axis changes [75].

## 4.3 Hypothalamus volumes in patients with major depression

Schindler et al. performed a human study to examine whether the hypothalamus volume in patients with mood disorders is reduced. The study included 20 unmedicated (MDDu) patients with MDD, 20 medicated patients with MDD, 21 patients with bipolar disorder (BD), and 23 healthy control subjects. All 20 MDDu patients were matched with a healthy control group with people of the same gender, the same age, and matching handedness [88].

Schindler et al. expected to find reduced hypothalamus volumes in MDD and BD. However, their findings indicated the opposite. The results revealed that patients with MDD and BD, independent of medication status, had a left hypothalamus which was larger than those of healthy control subjects. On average, it was in fact 4.9% larger than the left hypothalamus of healthy controls. At the trend level, the right hypothalamus was larger than the left when comparing the total sample of both patients and controls. Regarding the volume differences found when comparing left and right hypothalamus, MDDu and BD patients revealed the largest difference. The authors further points to a possible structural correlation between volume increase in the hypothalamus, as seen in MDD and BP, and hyperactivity in hypothalamus with respect to HPA axis regulating peptides. A study performed on mice revealed that in chronically stressed mice there is an association between stress susceptibility and increased hypothalamic volumes which thereby support the assumption that increased volumes of hypothalamus may be associated with hyperactivity of the HPA axis [88].

# 5. Conclusion

Based on the literature review conducted for this thesis, most of the research results point to various roles of hypothalamic dysfunction in relation to the selected neuropsychiatric disorders aggression, anxiety and depression.

A link between HPA axis reactivity and aggression has been documented in several rodent and monkey studies, where aggression was associated with both high and low HPA axis reactivity following restraint stress or exposure to various stress in early stages of life. However, some rodent studies also found conflicting results. Further, the emotional aspect of abnormal aggressive behavior seems to be a contributing factor in aggression controlled by hypothalamus. Different hypothalamic mechanisms have also been shown to play a part in aggression, more specifically in various forms of attack.

In respect of hypothalamic dysfunction and anxiety the relationship with altered function of the HPA axis is also documented. Exposure to stress occurring in a crucial developmental phase in life can cause HPA axis dysregulation which may, together with other various factors such as anxiety sensitivity or new life events, result in the development of anxiety symptoms. Chronic stress may cause continuous HPA system activation which in turn leads to sustained elevations in cortisol levels. Anxiety is also involved with CRH circuits that is either hyperactive and/or dysregulated, and HPA axis hyperactivity are consistent findings in patients with anxiety disorders. Hypothalamic volume changes were also shown in patients with anxiety disorders, suggesting a causal link between pathological anxiety and disrupted hypothalamic morphology. It should however be noted that available data pointing to HPA axis dysfunction caused by stressful life events and its role in anxiety disorders are limited.

Dysfunction of the HPA axis has been linked to major depression for a long time, and HPA axis hyperactivity is found in many individuals suffering from depression. In depressive disorder linked to chronic stress, HPA axis hyperactivity has been implied to play an important role. Both animal and human studies imply that persistent changes in the stress response ability of the HPA axis in adulthood may be induced in individuals exposed to stress during early developmental phases, which consequently increase their susceptibility to depression. Several studies also revealed that there is a correlation between the level of cortisol and how severe the depressive symptoms are. Studies on changes in hypothalamic

volumes in MDD patients revealed that the left hypothalamus was larger than those of healthy controls. In addition, studies on mice showed an association between stress susceptibility and increased hypothalamic volumes. Finally, it has also been shown that inflammation of hypothalamus may regulate HPA axis activity, cause glucocorticoid resistance and lead to depressive symptoms in certain patients.

In this thesis, the aim was to shed light on the role of hypothalamic dysfunction in relation to selected neuropsychiatric disorders. While the literature points to several links between hypothalamic dysfunction and the selected neuropsychiatric disorders aggression, anxiety, and depression, contradictions were also found. Consequently, it is difficult to draw specific and final conclusions despite of the documented connections. Therefore, further studies and research should be conducted to gain more insight.

# 6. Summary

This thesis, on the role of hypothalamic dysfunction in relation to selected neuropsychiatric disorders, has briefly reviewed the endocrine system, the nervous system, the hypothalamus, hypothalamic dysfunction, neuropsychiatric, and hypothalamic dysfunction and mood and behavioral disorders. Thereafter, the findings from a literature review conducted in respect of hypothalamic dysfunction in relation to aggression, anxiety and depression has been presented.

Hypothalamus plays an important role in our health and wellbeing through its link between the nervous- and endocrine system, and its main function is to maintain the homeostasis of the body. It manages several important physiologic functions including behavioral and emotional responses, and how the body responds to stress. In hypothalamic dysfunctions, endocrine and neurological disturbances such as mood- and behavioral disorders are often found. Neuropsychiatric disorders are complex conditions, and their symptoms seem to impact an individual's emotions, mood, and brain function. Among the common neuropsychiatric disorders are depression, anxiety, and uncontrolled anger.

In respect of the relationship between hypothalamic dysfunction and aggression, the altered function of the HPA axis and its role in aggression was presented and the findings from several studies was summarized. In addition, developmental stress and its consequences for aggression was addressed, with particular focus on prenatal-, early postnatal-, peripubertal- and adolescent stress. Finally, hypothalamic mechanisms involved in aggression, including hypothalamic neurotransmitters and hyperactivated hypothalamic structures was presented.

The relationship between hypothalamic dysfunction and anxiety was also discussed in relation to the altered function of the HPA axis, with particular focus on the role of stressful life events. Hyperactivated and/or dysregulated HPA axis was also touched upon. In addition, changes in hypothalamus volumes in patients with anxiety was presented.

Finally, the altered function of the HPA axis as well as hypothalamus volumes were also discussed in respect of the relationship between hypothalamic dysfunction and depression. In relation to the altered function of the HPA axis and depression, the main topics were hypothalamic inflammation, cortisol levels and early-life stress.

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# Acknowledgements

I would like to start by thanking the head of department of Physiology and Biochemistry of Veterinary Medicine of Budapest, Prof. Tibor Bartha, DVM, PhD. Thank you for providing me with the opportunity to write my thesis on such an interesting topic. I would also like to thank my supervisor, Dávid Sándor Kiss, PhD. Thank you for your guidance and support during my thesis writing. To my family, thank you for your endless support and encouragement, and for always believing in me. Thank you to my mother: Bente Solberg and to my sister: Emilie Solberg Gresslien. Finally, a special acknowledgement and thank you to my father: Terje Gresslien, for always going the extra mile to support, and help me in times when I need it the most.

Thank you!

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