CHAPTER 1

GENERAL INTRODUCTION
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“When pain persists and feels like it is ruining your life, it is difficult to see how it can be serving any useful purpose. But even when pain is chronic and nasty, it hurts because the brain has somehow concluded, for some reason or another, often completely subconsciously, that you are threatened and in danger – the trick is finding out why the brain has come to this conclusion.”

Source: Book “Explain Pain” by Butler and Moseley, 2003, p. 11.

Chronic pain

Chronic pain is a complex sensory and emotional experience that varies widely between people depending on the context and meaning of the pain and the psychological state of the person[1]. ‘Nociception’ is the biological response to tissue damage or prior tissue damage[2]. The International Association for the Study of Pain (IASP) defined pain as: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. Chronic pain has most frequently been defined as ‘pain lasting longer than 3 months’[3]. It often presents at multiple body locations, typically of the musculoskeletal system. On the list of global burden of disease, musculoskeletal problems hold a top ten position[4] and are the most common cause of severe pain and long-term physical disability[5]. Moreover, chronic multi-site musculoskeletal pain has been associated with decreased quality of life[6], and with comorbidities such as depression, anxiety[7] and sleep disorders[8].

Prevalence rates of chronic multi-site musculoskeletal pain among the general population have been estimated at approximately 10% in Western countries[9] and 18% in the Netherlands[10]. However, reported prevalence rates differ between studies, mainly due to differences in pain definitions, methodologies and groups studied. Despite these differences, it is clear that chronic pain is frequently experienced among people worldwide. Women and older persons are more often affected by chronic pain than men and younger persons[9,11]. One survey among over 40,000 Europeans and Israelis demonstrated that of all people suffering from chronic pain, 60% was female, and had an average age of 51 years old[12]. Given the high prevalence and impact of chronic pain, there is an urgent need to examine the underlying mechanisms of this condition.

Although the etiology of chronic pain is not fully understood, it is hypothesized to be the consequence of central sensitization, a process of hypersensitivity of neural nociceptive pathways within the central nervous system[3]. In case of acute pain, often caused by damaged tissues, several stress response systems become active to be able to cope with the threatening situation[13]. However, in case of central sensitization, these adaptive changes no longer have their intended function and can contribute to the development and persistence of chronic multi-site pain, which
may even occur without any peripheral tissue damage[14]. There is usually no way to distinguish this pain experience from that due to tissue damage[15]. However, it appears that the perceived pain cannot be fully explained on the basis of peripheral processes and is likely due to alterations in pain transmission or descending pain modulatory pathways[15]. Central sensitization is characterized by hyperalgesia (increased pain intensity evoked by a stimulus which is normally painful) and allodynia (pain evoked by a stimulus which is normally not perceived as painful)[16].

Both biological and psychosocial factors may contribute to central sensitization, and thus to the etiology and persistence of chronic pain[15,17]. Therefore, this dissertation aims at understanding the role of biological factors, by themselves or in combination with psychosocial factors, in relation to the onset and persistence of chronic pain.

**Biological stress systems and chronic pain**

Three major biological stress systems are the hypothalamic-pituitary adrenal axis (HPA axis), the immune system (IMS) and the autonomic nervous system (ANS). These response systems regulate several bodily processes in response to stress for maintenance of homeostasis. Dysfunction of these biological stress systems are thought to play a role in central sensitization, subsequently contributing to chronic pain[18].

The HPA axis is the main neuroendocrine stress response system and activates the secretion of cortisol, a ‘stress chemical’ that under normal circumstances protects the body against challenges. A successful adaptive response upon stress exposure is activation of the HPA axis followed by its termination after the stressor has passed. The hypothalamus releases corticotropin-releasing hormone (CRH), which in turn stimulates the secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland. Subsequently, ACTH stimulates the release of cortisol from the adrenal cortex into the systemic circulation. The HPA axis has a negative feedback loop, so that cortisol in turn can inhibit the further release of CRH and ACTH. Cortisol, among other functions, diverts energy to the brain, muscles and heart, makes oxygen available, and suppresses the immune system[13]. Cortisol follows a diurnal rhythm, with a cortisol peak in the morning and a gradual decrease during the day, with lowest levels in the evening. Cortisol levels start to rise approximately 2-3 hours after sleep onset and continue to rise into the early morning and early waking hours[19]. In case of chronic pain, the HPA axis may have become hypoactive, as indicated by lower levels of cortisol and a blunted cortisol response to a variety of stressors and dynamic tests[18,20-22].

The immune system (IMS) aims to protect the body against stress or illness by activation or suppression of several cytokines (immune molecules) in the blood. Immune reactions can be divided into reactions of innate and adaptive immunity. Innate immunity refers to natural immunity, which
function is to efficiently recognize pathogenic molecules (usually within hours) independently of any prior exposure[23]. Adaptive immunity is a longer-term process and refers to molecules which are normally silent but adapt in response to illness or infection. Evidence suggests that mainly the innate immune system has become hyperactive in chronic pain. In particular, chronic pain subjects have shown increased levels of basal cytokines and increased levels of cytokines after stimulation, an indicator of disturbed innate immunity[24-26].

The autonomic nervous system (ANS) is another important biological stress system that might play a role in chronic pain. The sympathetic nervous system ('fight and flight') liberates adrenaline and is activated in response to stress. The parasympathetic nervous system ('rest and digest') usually conserves energy, and helps digestion and storing of energy[13]. Previous studies mainly found increased sympathetic and decreased parasympathetic activity in chronic pain patients[27-29], suggesting a state of hyperarousal of the ANS.

**Biological stress systems, psychosocial stress and chronic pain**

A prominent hypothesis (see Figure 1) suggests that dysfunction of biological stress systems –the HPA axis, IMS and ANS- induces and perpetuates central sensitization, ultimately resulting in the development and persistence of chronic pain[18]. Thus, dysfunction of the HPA axis (i.e. hypocortisolemia and a blunted diurnal cortisol slope), dysfunction of the IMS (i.e. increased innate immunity) and dysfunction of the ANS (i.e. increased sympathetic and decreased parasympathetic activity) are hypothesized to contribute to central sensitization. This hypothesis further suggests that psychosocial stress, i.e. adverse life events, trigger central sensitization and aggravate the impact of HPA-as, IMS and ANS functioning on chronic pain[18].

![Figure 1. Hypothetical framework suggesting that alterations in biological stress systems induce central sensitization, ultimately resulting in the onset and persistence of chronic pain, an effect which is aggravated by adverse life events[18].](image-url)
Previous findings on the association between psychosocial stress and chronic pain seem rather consistent, with higher reports of adverse life events and childhood trauma in subjects with chronic pain compared to controls\cite{30,31}. Also, several large-scale longitudinal studies confirmed that recent life events and childhood trauma increase the risk of future development of chronic pain\cite{32,33}.

With respect to dysfunction of biological stress systems in chronic pain, the available evidence comes mostly from cross-sectional studies with small sample sizes (N<500) and results have been inconsistent\cite{18,21,34,35}. These inconsistencies might to some degree be explained by a lack of measuring all relevant covariates such as lifestyle factors and depression, which might influence the association between biological stress systems and pain\cite{34,36}. The paucity of longitudinal data makes any conclusion regarding causal directions speculative. An exception is one prospective study which examined whether HPA axis dysfunction, in response to adverse life events, was associated with the onset of chronic pain over 15 months. This study (n=241) showed that HPA axis dysfunction, indicated by a blunted cortisol diurnal rhythm and a failure of the HPA axis to suppress cortisol, was associated with the onset of chronic widespread pain\cite{37}. Thus, although longitudinal evidence is limited, dysfunction of biological stress systems, in combination with adverse life events, has been hypothesized as a risk factor for developing chronic pain.

This thesis will examine the cross-sectional associations of the biological stress systems with the presence and severity of chronic pain. This will not include ANS, as this was already investigated in a previous NESDA study\cite{1}. Then, following the hypothesis by Maletic and Raison, we prospectively examine whether dysfunction of the biological stress systems (HPA axis, IMS and ANS), in combination with adverse life events, is a risk factor for the onset and persistence of chronic pain.

1 One previous NESDA study examined function of the autonomic nervous system in relation to chronic pain\cite{38}. In that study, no associations were found with the presence of chronic pain, although lower heart rate variability did appear associated with increased pain intensity among chronic pain subjects.

**Brain-derived neurotrophic factor, psychosocial stress and chronic pain**

The brain-derived neurotrophic factor (BDNF) is another biological factor that has also been associated with chronic pain. BDNF is a primary neurotransmitter in descending pain facilitation\cite{18}. BDNF positively regulates neuronal growth, recovery and development\cite{18,39}. BDNF may contribute to central sensitization\cite{40} and central and peripheral neuroplastic changes\cite{41,42}. Neuroplastic changes may occur rapidly in response to injury causing adaptive changes that, under normal circumstances, help to protect the injured structures and aid in the healing process\cite{12}. Several lines of evidence suggest that the BDNF pathway (BDNF genotype, gene expression and protein levels)
may play a role in chronic pain[18,43]. Chronic pain patients have previously shown increased BDNF levels in blood serum and plasma[44-46]. Other studies proposed that BDNF genotype and gene expression might also play a role in chronic pain[47-49]. However, the few previous studies on the role of BDNF were limited in sample size (n<155) and showed inconsistent results. Moreover, studies examining the complete BDNF pathway —genotype, gene expression and protein levels— in chronic pain are currently lacking.

Life stress may also aggravate the impact of the BDNF pathway on chronic pain, suggesting that a combination of BDNF alterations and life stress is a risk factor for chronic pain. Life stress may also have different impact depending on a person’s genetic risk. Most evidence for this hypothesis comes from psychiatric studies[50-52]. One previous study on depression showed that the impact of childhood trauma on BDNF serum levels was dependent on variation on the BDNF val66met polymorphism, a common single-nucleotide polymorphism (SNP) on the BDNF gene[53]. Evidence suggests that a combination of stress and the BDNF-pathway as etiological factors may also apply to chronic pain, especially because chronic pain and depression seem to share similar pathophysiological mechanisms[18]. Therefore, this thesis examines whether the BDNF pathway, recent life stress (recent adverse life events) and early life stress (childhood trauma), or a combination of BDNF and life stress are associated with chronic pain.

Sleep disturbances, depressive symptoms and chronic pain

Over 50% of subjects with chronic pain also report sleep problems[54]. Disturbed sleep might be an important etiological factor of chronic pain. People who suffer from sleep disturbances seem to consistently show an increased risk of developing chronic pain[32,55-60]. Disturbed sleep might decrease pain thresholds and contribute to central sensitization[61]. Sleep disturbances can manifest themselves in multiple ways. Disturbed sleep can refer to poor sleep quality, also referred to as insomnia. Also, persons can have a deviant duration of their sleep. Duration of sleep can either be shortened or prolonged, and both might contribute to health problems[62]. Evidence suggests that depressive symptoms might mediate the association between disturbed sleep and the development of chronic pain[63,64]. Depressive symptoms may contribute to the onset of chronic pain[65,66], possibly through mechanisms of increased physiologic or cognitive arousal and decreased physical activity[64]. However, the temporal relationships of sleep, depressive symptoms and chronic pain remain unclear. There is a lack of longitudinal studies examining whether sleep induces chronic pain beyond the influence of depressive symptoms. Also, whereas most previous studies examined either insomnia or sleep duration[63], this thesis focuses on both these potential etiological factors of chronic pain onset.
The NESDA study

All studies described in this dissertation used data of the Netherlands Study of Depression and Anxiety (NESDA). For this thesis, we used data from the baseline measurement, and the 2 year, 4 year and 6 year follow-up. The NESDA study (www.nesda.nl) is an ongoing longitudinal cohort study (n=2981, 18-65 years at baseline) aimed at investigating the long-term course and consequences of depressive and anxiety disorders[67]. Participants were recruited from the community (19%), from primary care (54%), and from specialized mental health care (27%). With this strategy, the NESDA study was able to include subjects with a great variation in symptoms, with or without (current or remitted) depressive or anxiety disorders, which resulted also in the inclusion of sufficient subjects both with and without chronic pain.

A few advantages of the NESDA study are the large sample size (n=2981), the longitudinal design and the inclusion of a vulnerable population at baseline. Of all persons in NESDA with baseline data on pain available (n=2980), 767 persons (26%) suffered from chronic pain at baseline. Of these 767 subjects, 28% still suffered from chronic pain after 6 years follow up (13% was lost to follow up). From all subjects without chronic pain at baseline (n=2213), 21% developed chronic pain over 6 years follow-up (8% was lost to follow-up). The NESDA study provided detailed assessment of a wide range of demographic, clinical, genetic, biological and psychosocial measures. Therefore, risk factors of chronic pain could be examined while also taking into account the influence of psychopathology. The large sample size of the NESDA study enables to test for interactions, stratify our analyses and examine potential mediation by covariates such as depression.

Biological measures at baseline examined in this thesis include function of biological stress systems and the brain-derived neurotrophic factor pathway. A range of HPA axis measures was assessed by collecting salivary cortisol samples during one day. The cortisol awakening response reflects the natural response of the HPA axis to awakening. Cortisol at awakening and cortisol in the evening reflect basal levels. The cortisol suppression ratio after dexamethasone intake reflects function of the negative feedback system of the HPA axis. When post-dexamethasone cortisol levels are suppressed, the feedback system functions adequately. Also blood samples were collected from participants of the NESDA study. Levels of basal immune molecules (including cytokines such as interleukin-6) and lipopolysaccharide-stimulated cytokines (a measure of the innate immune response) were assessed. For functioning of the autonomic nervous system, we assessed measures of the sympathetic and parasympathetic nervous system (using the VU University Ambulatory Monitoring System). Also, the BDNF val66met genotype, BDNF gene expression and serum levels were determined at baseline. Psychosocial stress measures examined in this thesis include recent life events and childhood trauma. Recent adverse life events were assessed in the year prior to baseline
using the List of Threatening Events Questionnaire. Childhood trauma before the age of 16 was assessed by calculating a childhood trauma index using the Childhood Trauma Interview. Sleep disturbances, including insomnia (≤9 score on the Women’s Health Initiative Insomnia Rating Scale) and sleep duration, were measured in the month prior to baseline. Depressive symptoms were assessed at baseline, and at 2 year, 4 year and 6 year follow-up (using the Inventory of Depressive Symptoms with a 1 week recency).

In this thesis, chronic pain is defined as pain in the prior 6 months in the extremities, the back, and the neck (also called: ‘chronic multi-site musculoskeletal pain’). Pain was assessed at baseline, and at 2 year, 4 year and 6 year follow-up using the Chronic Pain Grade (CPG)[68], a valid and reliable self-report questionnaire to measure the presence and severity of chronic pain[69,70]. In our cross-sectional studies, we examine the presence and severity (intensity and disability) of chronic pain as our outcome variables. The presence of chronic pain is defined as meeting the criteria of chronic pain at baseline. A pain intensity score is calculated from 3 questions of the CPG regarding (1) pain intensity at this moment, (2) worst pain in the prior 6 months, and (3) average pain in the prior 6 months. A pain disability score is calculated from 3 questions of the CPG regarding (1) disability in daily activities, (2) disability in spare time, social life and family activities, and (3) disability in work. In our longitudinal studies, we examine the onset and remission of chronic pain. The onset of chronic pain is examined in pain-free individuals at baseline (n=2213), and defined as meeting the criteria for chronic pain at one of the follow-up time points (2, 4 or 6 years). The remission of chronic pain (as the opposite of persistence) is examined in chronic pain subjects at baseline (n=767), and defined as not meeting the criteria for chronic pain at one of the follow-up time points (2, 4 or 6 years).

**Aims and outline of this thesis**

This thesis examines biological factors (biological stress systems and BDNF), by themselves and in interaction with psychosocial factors (life events/childhood trauma), in relation to chronic pain. In addition, we examine the role of disturbed sleep and depressive symptoms in chronic pain. First, cross-sectional examinations are performed of the HPA axis and the IMS in relation to the presence and severity of chronic pain. Second, we longitudinally examine whether baseline function of biological stress systems was associated with the onset and remission of chronic pain over 6 years, and whether recent adverse life events increased the impact of biological stress systems on chronic pain. Third, we examine whether the BDNF pathway (genotype, gene expression and serum level) was cross-sectionally associated with the presence and severity of chronic pain, and whether life events/childhood trauma increased the impact of BDNF on chronic pain. Fourth, we longitudinally
examine the association between baseline sleep disturbances (insomnia, sleep duration) and the onset of chronic pain over 6 years, and whether this association is mediated by depressive symptoms.

The main objectives of this thesis are:

1. To examine whether function of the hypothalamic-pituitary-adrenal axis and the immune system are cross-sectionally associated with the presence and severity of chronic pain at baseline (HPA axis: chapter 2; IMS: chapter 3).

2. To examine whether baseline HPA axis, IMS and ANS function, recent adverse life events, or a combination are longitudinally associated with the onset (chapter 4) and the remission (chapter 5) of chronic pain over 6 years [see Figure 1].

3. To examine whether the brain-derived neurotrophic factor (genotype, gene expression and serum level), life stress (life events/trauma), or a combination are cross-sectionally associated with the presence and severity of chronic pain at baseline (chapter 6).

4. To examine whether baseline sleep disturbances (insomnia and sleep duration) are longitudinally associated with the onset of chronic pain over 6 years, and whether this association is mediated by depressive symptoms (chapter 7).