CHAPTER 1
INTRODUCTION

CHAPTER CONTENTS:

A. LITERATURE REVIEW

1. General background

1.1. Definition

Fibromyalgia (FM) and similar conditions have been reported for centuries. Despite years of research, there still remains great disagreement on the nature of the disease and on several of the aspects involved in the disease progression. Clinicians are confronted with a physical condition marked by multiple subjective complaints in the absence of obvious local inflammation. Even in the early days of fibromyalgia research, the part psychogenic factors played in this illness were not ignored, yet clinicians and researchers could not decide whether the symptoms arose peripherally or as the consequence of psychoneurosis (1).

Right from the beginning many clinicians contributed to the search for criteria that would establish fibromyalgia as a distinct nosologic entity. During this search the concepts relating to the disorder underwent ample reformations as far as its definition and diagnostic criteria were concerned (2). Guillaume de Baillou made the first attempt to find the appropriate word to describe the phenomenon of unexplainable pain in the late 16th century (3). He used the term 'rheumatism' to describe muscular pain as well as acute rheumatic fever. In 1815 Balfour proposed that the pain was caused by inflammation in connective tissue, therefore he named it 'muscular rheumatism'. Subsequently, the disorder was termed 'neuralgia' (shooting pain in regions away from location palpitated) in 1841, 'myalgia' (radiating pain originating from nerve roots) in 1858 and 'chronic myitis' in 1876. Other terms published from early in the 20th century were nodular fibromyositis, myofascitis, neuro-fibrositis, allergic toxaemia, idiopathic myalgia, psychogenic rheumatism, psychosomatic rheumatism and myodysneuria. In 1904 the word 'fribrositis' was used for the first time, a term that would resurface time and again until 'fibromyalgia' was used from the 1980's onwards (2-4).

Fibromyalgia is a disorder marked by great controversy as far as diagnosis, absolute etiology and even definition is concerned. Although a functional term has been established for the disorder, clinicians and researchers are faced with the same obstacles as the early precursors in pain research and consequently, due to a lack of verifiable pathogenic mechanisms involved in this syndrome, as well as other inconsistencies in literature, it

remains difficult to provide a comprehensive definition for fibromyalgia that will be accepted by all researchers and physicians in the field.

Some authors portray fibromyalgia as an age-related, non-inflammatory disease accompanied by neurovegetative symptoms (5). Littlejohn, amongst others, defines it as a pain amplification disorder marked by tenderness at multiple anatomical sites without the presence of any tissue damage (6). Fibromyalgia is also described as a non-deforming rheumatic disorder (2,7). Although all of these definitions hold some truth, none of them is fully inclusive. At this stage it is safe to describe fibromyalgia as a chronic musculoskeletal pain syndrome marked by pain and stiffness in the muscles and joints that is either diffuse of has multiple trigger points (8).

1.2. Symptom presentation

The primary complaint of fibromyalgia patients is chronic musculoskeletal pain (5). Additionally, it is associated with numerous neurovegetative symptoms affecting various organ systems (examples of these symptoms are listed in Table 1.2.).

Table 1.2. *The symptomatology of fibromyalgia*

Most frequent symptoms	Bloating
Chronic musculoskeletal pain	Gastric ulcers
Tenderness at multiple	Anxiety
anatomical sites	Chilliness
Fatigue	Headaches
Sleep disturbances	Cognitive dysfunctions
Depression	Stiffness of muscles and joints
Cold extremities	Swelling of hands and feet
Muscle twitching	Numbness and tingling (paresthesias)
Balance problems	Frequent infections
Less frequent symptoms	Dry mouth
Dizziness	Sore throat
Constipation	Functional disability

Table compiled from (3,5,6,9).

To summarise, it can be said that the symptomatology predominantly exemplifying fibromyalgia involves the following three systems: the musculoskeletal system, the neuroendocrine system, and the neuropsychiatric system (5).

'Distress' is a term often used to describe the combination of somatic symptoms and the neuropsychiatric symptoms of anxiety and depression observed in fibromyalgia. The level of distress is generally associated with the number of anatomical sites where tenderness is experienced upon palpitation (7). This symptom complex (specifically multifocal pain, fatigue, memory difficulties and mood disturbances) has been termed chronic multi-symptom illness (CMI) by the Centres of Disease Control and Prevention in the United States of America (10). A common feature of CMI in fibromyalgia is the fluctuating nature of these symptoms, usually varying in severity within monthly cycles. Symptoms fluctuate according to weather change (environmental temperatures and humidity), emotional distress and physical activity (6).

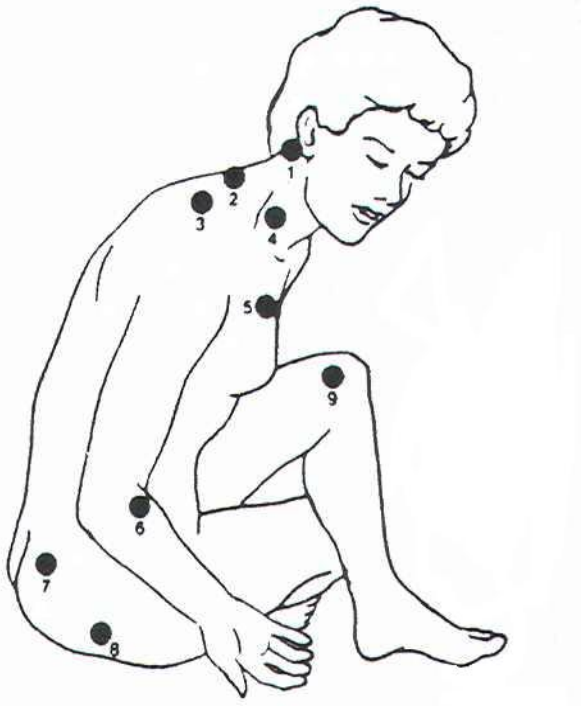
Sections 1.2.1. – 1.2.10. elaborate on some of the major symptoms fibromyalgia patients present with, and provide short descriptions on the possible causes of the symptoms.

1.2.1. Pain

Musculoskeletal pain, in all four limbs as well as the upper and lower back, is the primary symptom in fibromyalgia. Two thirds of fibromyalgia patients report that they 'hurt all over'. Ang and Wilke (1999) described the pain experienced by these patients as being continuous, deep and aching, with diffuse radiation (11). Other spontaneous descriptions for the pain experienced by patients include shooting, pressing, pricking, and nagging pain (3).

The clinical terminology used to describe the pain in fibromyalgia is allodynia, pain caused by non-nociceptive stimuli like touch, and hyperalgesia, a decreased threshold to nociceptive stimuli like heat, cold, and pressure (12). Primary hyperalgesia is usually associated with inflammatory tissue changes, not detectable in all fibromyalgia sufferers. Therefore, secondary hyperalgesia, depending on central mechanisms, are proposed as the cause of peripheral pain complaints in fibromyalgia (13).

Pain in fibromyalgia is mainly experienced in specific localized spots, named 'tender-points'. The term tender-points can be defined as areas in the body that is more sensitive to gentle palpation than surrounding regions (6). Typical examples of these areas are presented in Figure 1.2.1.



1. Nuchal muscle insertion at occiput
2. Midpoint of upper border of trapezius
3. Muscle attachments to upper medial border of scapula
4. Anterior aspects of C5-C7 intertransverse spaces
5. Second costochondral junctions, just lateral to junctions on upper surfaces
6. Muscle attachments to lateral epicondyle
7. Upper outer quadrants of gluteal muscles
8. Muscle attachments just posterior to trochanteric prominence
9. Medial fat pad of knee proximal to joint line

Figure 1.2.1. The tender points associated with fibromyalgia. Figure taken from *Wolfe,F./ Arthritis & Rheumatism 1990;33:160-172 (14).*

It is important to note that the tender-point region is histologically normal, as the problem originates from the unusual sensitivity of pain nerves in that area (6). The diffuse lowered pain threshold is inversely related to the number of tender-points found upon palpation. Additionally, tender-points appear to vary directly with the degree of distress in the patient (14). Besides the degree of distress in the patient, the other factors that often influence fibromyalgia patient symptom status (cold or humid weather, anxiety or stress, and poor sleep) is likely to specifically affect the degree of pain experienced (3).

There is clinical consensus that fibromyalgia is not primarily a musculoskeletal problem (2), even though chronic musculoskeletal pain is the major complaint in this syndrome. Because the pain associated with fibromyalgia is probably central in nature (7,15), it is unresponsive to analgesic or anti-inflammatory drugs (16).

1.2.2. Fatigue

Aside from pain, fatigue is one of the symptoms most frequently associated with fibromyalgia (moderate to severe fatigue is present in 85% of patients). For this reason, fibromyalgia and chronic fatigue syndrome (CFS) often coexist in patients. Fatigue in fibromyalgia is variously described as exhaustion, tiredness, or generalized weakness (3). Patients often describe the feeling of fatigue to be similar to having flu, i.e., a total drain of energy and an overwhelming desire to rest. Early in the day fatigue is usually the consequence of disturbed sleep, but it generally persists to, or recur in the afternoon. Fatigue is especially aggravated by physical activities (9). Together with pain, fatigue is the most debilitating symptom, leading to marked functional disability due to an inability to maintain a full day's work (17). Like pain, it is primarily of central origin and may be connected with poor sleep, physical deconditioning, as well as psychological factors (3)

1.2.3. Sleep disturbances

90% of fibromyalgia sufferers presents with sleeping problems. These problems include difficulty falling asleep, waking up several times through the night, tossing all night without any sleep, waking up early in the morning without being able to go back to sleep, or insomnia without the ability to fall asleep at all (3,9).

Some patients do sleep through the night but do not obtain restful sleep because they never enter the deep restorative sleep stage (stage four of non-rapid eye movement (non-REM) sleep) (18). Electroencephalogram studies in sleep laboratories have shown that fibromyalgia patients' sleep is often disrupted by sudden bursts of brain activity similar to alpha-wave activity seen when humans are awake. Stage two of non-REM sleep is associated with the appearance of alpha-like, 10-14 Hz, 50μV waves (called 'sleep spindles'). Accordingly patients that do fall asleep at night, generally do not enter stage four sleep but seem to be fixed in stage two sleep, constantly being disturbed by the sudden bursts/ sleep spindles (9,17).

In a study assessing autonomic nervous system (ANS) function in fibromyalgia patients, frequent awakenings during the night was associated with sympathetic hyperactivity during the supine bodily position. This derangement of the ANS is discussed in greater detail in section 3.3. Some researchers suggests that the sleep problems are the origin of the muscle

pain experienced by these patients, because the muscles do not enter the regenerative rest period during the night (9).

1.2.4. Depression

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a major depressive episode, symptoms commonly associated with depression are feelings of sadness and emptiness, a marked loss of interest in things that previously were enjoyable (anhedonia), significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or an overall loss of energy, diminished ability to think or concentrate and recurrent thoughts of death and suicide (19). In fibromyalgia feelings of hopelessness, restlessness, guilt and worthlessness have also been reported (20).

Because only 30% of fibromyalgia sufferers have depression, and since depression often comes after the onset of fibromyalgia, it has been suggested that the depression is the consequence of the chronic pain and disability (6,17), and not the cause of fibromyalgia. Thus, the depression in fibromyalgia is not a clinical depression but a reaction to the condition, or to 'the loss of health'. This explanation for depression among fibromyalgia sufferers is called the 'linear causality model' (21). Therefore it is reasoned that the fact that antidepressant medication improves mood and sleeping difficulties in these patients is no indication that depression is the cause of fibromyalgia (22). Many other reasons from a psychoneuroimmunological point of view (not to be discussed) would substantiate the argument. However, latest research into the neural pathways of pain indicates a possibility that the pathways are the same for depression, encoded by corticolimbic systems (15). For instance, it has been shown that the brain areas involved in the generation of emotion (e.g. the medial prefrontal, insular, and anterior temporal cortex, hypothalamus, and amygdala) send several projections to brainstem structures involved in pain modulation (the periaqueductal gray and rostral-ventromedial medulla) (15). It has also been shown that negative anticipation (as seen in depression) causes key brain regions to activate, causing subjects to focus, attend to, and rate pain stimuli as more severe (15). This hypothesis is called the 'mediation model', suggesting that depression lowers the pain threshold, causing debilitating pain. Facts opposing the mediation model of depression and pain is that it has been determined that patients who feel that they could continue to function despite their pain and felt that they could maintain some control over their pain, were less likely to develop depression (21).

1.2.5. Anxiety

In fibromyalgia, anxiety is characterised by excessive worry or apprehensive expectation, restlessness, irritability and muscle tension. In chronic pain disorders, anxiety intensifies when the patient's condition changes and when the person believes that increasing pain points towards a worsening of the disorder (21).

There is a high co-morbidity of pain and anxiety. One of the explanations for this co-morbidity is described by the 'pain-anxiety-muscle tension hypothesis' (21). Apparently, the anxious individual creates a cycle whereby his chronic anticipation leads to increased muscle tension, causing muscle tightening, which eventually becomes a source of pain leading to additional anxiety, reinforcing the cycle (21). Naturally, anxiety also elicits autonomic and hypothalamic-pituitary-adrenal axis activity, aggravating both the emotional (feeling nervous/tense) and the physical component (tachycardia, tension headaches, diarrhea and tachyphea) of anxiety (23).

1.2.6. Headaches

Studies have shown that about 40% of fibromyalgia patients suffer from headaches on a daily basis. Many of these cases suffer from severe headaches. These headaches can be migraine headaches, but is usually tension related, preceded by strain or tightness in the upper neck (9). Musculoskeletal head and neck pain in fibromyalgia is now referred to as 'cervical myofascial pain and headache' (24). This term describes how the pain experienced derives from myofascial trigger points (small, highly sensitive areas in muscle). These trigger points are characterised by 'hypersensitive, palpable taut bands of muscle that are painful to palpation, reproduce the patient's symptoms, causing referred pain'(24).

1.2.7. Cognitive dysfunctions

25% of fibromyalgia sufferers have fluctuating concentration and memory problems in the form of memory lapses, inability to concentrate, dyslexic episodes, inability to recall simple words, difficulty completing a project, and trouble reading (9). Through neurological research done on these patients' brains, it is now known that the cognitive abnormalities experienced by fibromyalgia patients may be the result of reduced blood perfusion and energy metabolism in key sites of the brain (22).

1.2.8. Joint pain

The occurrence of pain in the hands, elbows, neck, wrists, feet, ankles, knees, hips, and the chest wall are common in fibromyalgia patients. These pains are often experienced as joint pain, but the pain is in point of fact not associated with the joint but rather with the area surrounding the joint e.g. where the tendon attaches to the bone (9). Ignorance regarding the origin of the pain gave way for the incorrect term 'rheumatoid arthritis' for fibromyalgia.

1.2.9. Paresthesia

This is a neurological symptom in the limbs of 33% of fibromyalgia patients. Paresthesia usually involves all the fingers or an extremity. Patients describe the sensation as tingling, pins and needles or numbness. It is hypothesised that the pathophysiological mechanism behind this symptom is related to pain and autonomic dysfunction. It has been established that this symptom does not correlate with the psychological status of the patient (3).

1.2.10. Candida (yeast overgrowth)

It is said that at least 90% of fibromyalgia patients suffer from chronic yeast infections. Since it is known that the regular use of steroid medications and antibiotics can lead to the spread of yeast (usually controlled by natural bacteria in the intestinal tract) to the body in general and specifically the genital organs, it is postulated that the yeast overgrowth in fibromyalgia is the consequence of recurrent antibiotic use and not of a certain pathophysiological mechanism involved in the pathogenesis of fibromyalgia. It is, however, true that the chronic yeast infections in fibromyalgia, especially *Candida albicans* infections (known for causing thrush), could be the very cause of some of the symptoms experienced by patients (22).

Candida is dangerous because of its ability to turn from a simple yeast into an aggressive mycelial fungus which puts down 'rootlets' into the mucus membrane of the intestinal tract, releasing undesirable toxins, which moves to the bloodstream. These toxins have the ability to elicit allergic and toxic reactions. Examples of these reactions are a range of digestive symptoms (bloating, diarrhea, constipation), urinary tract infections, menstrual disturbances, fatigue, muscle aches, emotional disturbances, cognitive dysfunction and skin problems (22). Many of these symptoms are seen in a portion of fibromyalgia sufferers.

1.3. Diagnosis

Basically, two types of musculoskeletal pain syndromes can be distinguished: those that involve pain generation and those involving pain amplification. Fibromyalgia is an example of the latter. Other pain disorders in the pain amplification class is regional pain syndrome, complex regional pain syndrome and chronic widespread pain (6).

In 1990 the American College of Rheumatology (ACR) set out criteria by which a person can be diagnosed with fibromyalgia. When an individual has a history of chronic widespread pain, together with a minimum of 11 out of 18 tender-points on examination, he is, according to the ACR, suffering from fibromyalgia. The pain must be present for at least 3 months and must involve the left, as well as the right side of the body, be present below and above the waist, as well as in the axial skeleton (14). A patient diagnosed with fibromyalgia can either suffer from simple or complex fibromyalgia. A patient diagnosed with simple fibromyalgia has mild to moderate symptoms, an identifiable trigger, good family and emotional support and reasonably good coping skills. According to statistics, 80% of fibromyalgia sufferers have simple fibromyalgia. Complex fibromyalgia is associated with persisting stress, significant psychological trauma, poor coping skills and a lack of understanding of the nature of the problem. Onset after injury is common in these cases and reflects previous situations. Patients with complex fibromyalgia have a poor prognosis, especially in the short-term (6).

Fibromyalgia is further classified as regional, primary, secondary and concomitant (3). Table 1.3. provides the definitions for each of these classifications:

Table 1.3. *Classification criteria for fibromyalgia*

Regional FM:	Pain symptoms and tender points are restricted to a few anatomical sites. Also called 'localised FM' and 'myofacial pain syndrome'.
Primary FM:	Widespread musculoskeletal aching and tender points at multiple locations in the absence of an underlying or concomitant condition that could explain musculoskeletal symptoms.
Secondary FM:	FM is caused by an underlying condition e.g. hypothyroidism, active rheumatoid arthritis.
Concomitant FM:	Patient presents with the features of primary FM as well as signs of a concomitant condition.

Table adapted from *Yunus, M.B./ Myofacial pain and fibromyalgia. 1 st ed. Missouri: Mosby; 1994. p. 3-30 (3).*

Even after a diagnosis of fibromyalgia has been confirmed by conforming to the ACR diagnostic requirements, it may be necessary to perform certain laboratory tests to ensure the absence of an occult underlying problem. These tests include a full blood examination, erythrocyte sedimentation rate, liver function and routine biochemistry assessment, thyroid function evaluation, and the assessment of calcium concentration, creatinine kinase levels, antinuclear antibody and rheumatoid factor levels (6).

Using the ACR ctiteria, the prevalence of fibromyalgia ranges from 0.5 to 4% in the population (25). However, throughout literature, there is a debate ranging on the validity of the present diagnostic criteria for fibromyalgia. Population based studies in the United Kingdom and the United States of America have shown that the prevalence of chronic widespread pain and regional pain is around 10 – 11% and 20 – 25%, respectively. Furthermore, woman are 10 times more likely to develop fibromyalgia than men, in contrast to the 1.5 times likelihood in chronic widespread pain. For children the gender distribution is equal (2,5,7).

According to Clauw and Crofford (2003), the difference in prevalence between chronic widespread pain, regional pain and fibromyalgia; as well as the difference in gender distribution between these three syndromes, is solely the result of the minimum requirement of 11/18 tender points for fibromyalgia (being more common in woman than in men) (25). These authors are of the opinion that the disbandment of the 11/18 tender point-requirement will lead to an entirely different disorder that affects more men, and a patient group presenting a lower level of distress (7).

The above is only a single example of how the diagnostic criteria for fibromyalgia may fail to distinguish it from other similar syndromes. Other findings confirming the speculation, is the fact that chronic widespread pain is also associated with tender points and distress and that these patients present with somatic symptoms like fatigue and memory difficulties as well (2,7). It is therefore possible that fibromyalgia is not a distinct disorder but a subgroup of a more general chronic pain syndrome. Another possibility is that fibromyalgia is in fact a nosologic entity, but with overlapping features with other distinct disorders (27).

1.4. Overlapping syndromes

Fibromyalgia is but one of a number of overlapping syndromes marked by unexplained symptoms, lacking provable structural and biochemical aberrations (26). Actually, in the light stages, functional somatic symptoms are quite common amongst the normal population. No less than 75% of the population report at least one complaint (like fatigue, tiredness, dizziness and headaches) during a 30-day period. Even these light symptoms do not always have a pathophysiological explanation from a medical point of view (12).

It is, however, true that these minor symptoms can be aggravated to a point that it becomes intolerable and a burden for the person suffering from it, as well as for society. It is at this stage that the symptoms reach 'syndrome' status and health care services are sought. What is interesting is that depending on the medical specialty consulted, patients are given diverse diagnosis for their unexplained symptoms (27). If the patient were to visit the rheumatologist, he would probably get a diagnosis of fibromyalgia. The gastroenterologist will probably provide a diagnosis of irritable bowel syndrome. From a neurological approach, the patient is most likely to be diagnosed with chronic fatigue syndrome, whereas the gynaecologist will have the opinion that the female patient is suffering from premenstrual or post-menopausal syndrome, depending on the age of the patient seeking medical help.

Similarities among these syndromes usually include the presence of symptoms included in the CMI symptom complex (refer to section 1.3.). These syndromes (Table 1.4.) can either be 'systemic' or 'regional' in nature. Examples of systemic syndromes are fibromyalgia (FM), chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), exposure syndromes (Gulf War Illnesses), somatoform disorders and the myofascial pain syndrome (MPS). Irritable bowel syndrome (IBS), temporomandibular disorder (TMD), migraine and tension headaches, are better describe as regional syndromes (7).

Table 1.4. *Overlapping syndromes*

Conditions marked by 'unexplained symptoms'

- Chronic myofascial pain syndrome – involves numerous active myofascial trigger points and painful trigger point repercussions
- Multiple chemical sensitivity – presence of symptoms in multiple organ systems in response to multiple environmental stimuli
- Chronic fatigue syndrome – severe fatigue accompanied by 'minor' symptoms: sore throat, tender nodes, myalgias, headaches, cognitive problems, sleep disorders and post – exertional malaise
- Gulf War illness – is diagnosed only if the patients has had exposure, not by the symptoms
- Somatoform disorder – marked by multiple unexplained physical symptoms with no organic findings
- Hypotension – neurally mediated low blood pressure
- Restless legs syndrome – patient unable to keep arms and legs still during sleep
- Periodic limp movement during sleep – described as the startling response when limps are flinged to regain balance after discovering a unexpected step down
- Post-traumatic stress disorder – anxiety disorder caused by exposure to an intensely traumatic event
- Irritable bowel syndrome – chronic noninflamatory disease characterised by abdominal pain, diarrhea and constipation. It has a psychophysiological basis.
- Premenstrual syndrome – symptoms of anxiety, depression, anger, bloating, headache and fatigue occurring in the period between ovulation and menstruation
- Functional dyspepsia – impairment of power or function of digestion
- Epidemic fatigue, burnout, a variety of intoxications, radiation, postviral syndrome, vital exhaustion, irritable bladder syndrome

Table is compiled from (2,6,7,12).

Often the conditions mentioned above are present concurrently with each other within the same patient (Figure 1.4.) (12). For instance: chronic fatigue syndrome and fibromyalgia overlap in patients by as much as 75%, and multiple chemical sensitivity is present in 50% of chronic fatigue syndrome and fibromyalgia patients respectively (1,28). A study investigating the overlapping features of 13 different syndromes marked by CMI, have shown that fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and non-ulcer dyspepsia all tend to occur together (27). Apart from the co-morbid nature of these

syndromes, studies have shown that individuals with one of these conditions are much more likely to develop another of these conditions over a period of time (7).

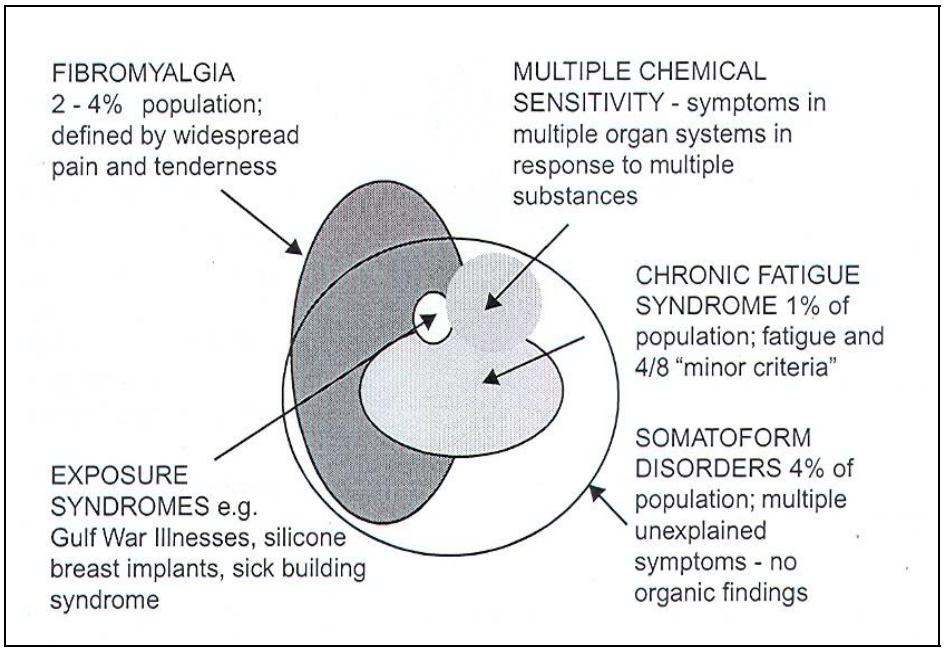


Figure 1.4. Examples of overlapping syndromes characterised by 'unexplained symptoms'. Figure taken from *Clauw, D.J./ Best Practice & Clinical Rheumatology 2003;17:685-701(7).*

These findings point in one direction. Despite the claim that these syndromes are all unique diagnostic entities with their own characteristics, the possibility that we are dealing with the same disorder is undeniable. This possibility have been recognised by some clinicians who have noted that patients often have complaints outside the symptom complex associated with the syndrome they are diagnosed with. These clinicians also identified related pathophysiological mechanisms in these syndromes (27).

For this reason researchers have been trying to develop a comprehensive term that could describe the co-aggregation of these conditions. A couple of suggestions have been made like 'Dysregulation Spectrum Syndrome', 'Affective Spectrum Disorder' and 'Central Sensitivity Syndrome'. The most prospective proposal is derived from a dualistic approach, not trying to classify the condition as being either psychological or physical of nature. Ursin & Eriksen suggested the term 'Subjective Health Complaints' in an effort to capture both the psychological and the physiological aberrations of the condition (12).

2. The pathogenesis of fibromyalgia

2.1. Triggers often preceding fibromyalgia symptoms

It has been proposed that fibromyalgia complaints could appear when a person who is genetically predisposed to symptoms in the chronic multi-system illness (CMI) complex is exposed to certain environmental stimuli. Evidence for the role genetics play in the pathogenesis of fibromyalgia comes from studies exploring the prevalence of 'unexplained symptoms' among family members. Family members of fibromyalgia sufferers display a high rate of either fibromyalgia itself, or a number of conditions related to fibromyalgia like irritable bowel syndrome, migraine headaches and mood disorders (29). Although the role genetics play in disease vulnerability should not be ignored, it is beyond the scope of this dissertation.

Examples of triggers shown to precede fibromyalgia symptoms are physical and emotional trauma (like a motorcar accident), infections (e.g. hepatitis C, Epstein-Barr virus, parvovirus, Lyme disease), acute or chronic emotional distress (as experienced in abusive relationships), endocrine disorders like hypothyroidism, immune stimulation, surgery and exposure to chemical agents or drugs (6,29,30). These triggers have a demanding impact on the body, and are therefore, for the purpose on this dissertation, referred to as 'stressors'.

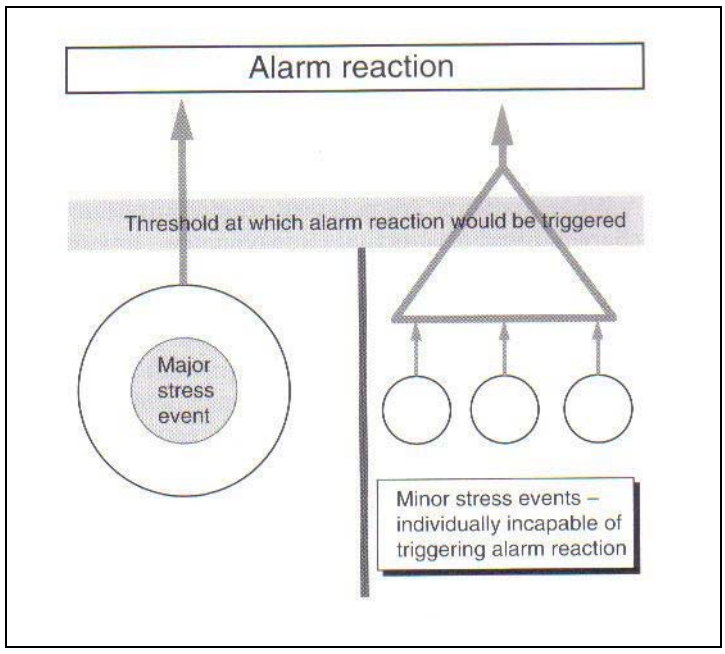


Figure 2.1. The cumulative effect of stressors. A combination of minor stressors, each incapable of triggering and alarm reaction in the general adaptation response alone, can produce sufficient adaptive demand when it is combined or sustained. Figure taken from *Chaitow, L./ Fibromyalgia syndrome – a practitioners guide to treatment. 2 nd ed. London: Churchill Livingstone; 2003. p. 21-39 (30).*

Generally, it is not one single stressor that causes fibromyalgia, but a number of different stressors occurring over a relatively short period of time, eliciting a physiological alarm reaction in the body. In fibromyalgia, any combination of biochemical, biomechanical or psychosocial stressors can work together to produce a combined stressor that exceeds the threshold at which the alarm reaction will be triggered (30).

2.2. Theories of causation

Ample research attempts have been made to discover the precise pathological mechanism underlying fibromyalgia. Among popular suggestions are the chronobiological, genetic, immune dysfunction, neurosomatic, nociceptive, retention and thyroid dysfunction hypotheses (31). Other proposals suggest the notion that the underlying cause of fibromyalgia is actually some of the symptoms characteristic of the disorder like sleep disturbances, anxiety and depression (30).

All of these theories hold some truth. The main problem with any proposed pathological mechanism in psychosomatic diseases is the impossibility to narrow the cause of a 'multi-symptom illness' down to one single causative factor. Most of the recent theories do account for multiple influences in symptom progression and have elaborated explanations on how no factor happens in isolation, but creates a cascade of happenings in the body, all attempting to restore homeostasis. However, these hypotheses fail to explain how these influences converge into a 'trigger', setting the whole process off. In contrast with these theories, one hypothesis, the 'Stress model', offers a comprehensive description of the disturbed homeostasis in fibromyalgia and the process the body engage in to re-establish balance between affected bodily systems (12).

2.3. The stress model

In terms of the stress model, fibromyalgia will develop in an individual during and after a period of sustained or overwhelming physical and emotional stress. This model explains the psychological and physiological response elicited in the healthy and afflicted individual (as seen in fibromyalgia and other disorders marked by multiple subjective complaints) during stress (29).

A modification of the model is referred to as the cognitive arousal theory of stress (CATS) (12). The word 'cognitive' implies that the alarm response in the individual is dependent

on the individual's cognitive evaluation of a particular situation. If the individual expect his strategies (and resources) available to solve the problem on hand to be sufficient, and the outcome of the situation to be positive, his stress response is likely to be dampened. Conversely, if the individual's psychological defence mechanisms fail to refute threats and produce positive outcome expectancy, a state referred to as 'hopelessness' may step in, impeding the individual to cope with the situation (12).

In neurophysiology, the stress model is explained within the framework of the arousal and activation theory. The stereotypic response of the body to endogenous or exogenous stressors is referred to as the 'general adaptation syndrome' (32). The general adaptation response is characterised by central as well as peripheral adaptation. Central adaptation leads to arousal, alertness, vigilance, enhanced cognition, focused attention, aggression, and the inhibition of the pathways that modulate vegetative functions; whereas peripheral adaptation mobilises the central nervous system by providing energy through gluconeogenesis, lipolyses, and the inhibition of growth and reproduction. Increased heart rate, blood pressure, and respiratory rate enhance the delivery of nutrients and oxygen to the muscles, enabling it to act in what is perceived to be dangerous situations (33).

These effects are exerted on the body through the body's two main stress axes: The sympathetic-adrenomedullary (SAM) and hypothalamic-pituitary-adrenal (HPA) system (34). Generally, in the early stages of the stress response, activation of the SAM-axis is associated with an active defence response, where the challenged individual remains in control of the stressful situation. Conversely, as the threats continue, HPA-axis activity is associated with passive coping where CRH – ACTH – cortisol levels increase and feelings of hopelessness arise (35). The hypothalamus and the brain stem house the central control stations of the stress system. A third component of the stress response, often neglected in literature when the stress response is reviewed, is the parasympathetic nervous system (PNS), mediating the gut responses to stress through vagal and sacral efferents. The parasympathetic nervous system is also responsible for the augmentation of the sympathetic nervous system effects during the recovery phase of the general adaptation syndrome (32,36).

Efficient and flexible physiological stress responses help the body to cope with, and adjust to changing environmental stimuli or circumstances (35). Increased vigilance and alertness,

enhanced cognition and focused attention, and even aggression is thus beneficial to the body and essential for survival. Therefore the stress response is merely an alarm reaction, prompting the individual to abolish the source of alarm by searching for solutions for the particular problem and in the process restoring homeostasis (12).

A question that comes to mind is why certain individuals will develop fibromyalgia or 'unexplained symptoms' following stressful events and others not. For instance: An epidemic of Gulf War illnesses occurred in troops deployed to the Persian Gulf in 1990-1991. 45% of deployed veterans developed symptoms in the CMI complex spectrum as opposed to 15% of non-deployed veterans (37). It seems that certain individuals have a vulnerability to these triggers accompanied by an inability to handle stress.

The first suggestion to answer the question lies in the concept of 'allostasis'. The allostatic load hypothesis proposes that prolonged, chronic stress can cause pathophysiology in the brain and body if it is not efficiently regulated (12). Dysregulation of the stress response is evident when there is an inability to adjust to recurring stress, failure to terminate the stress response in an efficient manner, or when the stressor is of insufficient magnitude to elicit an adaptive response (as explained by figure 2.1.) (34). The hopelessness that arises from these situations affects mood and eventually health (12).

Unfortunately, the answer to the question asking why some individuals are prone to develop subjective health complaints in response to stress is more complex than that. Throughout the years, numerous studies were conducted exploring and describing the relationship between early life experiences and the development of the pain circuits, the autonomic nervous system, and neuroendocrine system (38-40). These studies give insight on how past experiences shapes present experience and direct future actions and behaviour. The mechanism by which past experiences is able to modulate actions and behaviour goes further than a cognitive scheme in the mind of the individual prompting him to behave and think in a certain manner. A person's stress response is actually imbedded in neural pathways, sculpted by early life experiences and sensitised by prolonged, overwhelming stress (see Figure 2.3.) (29).

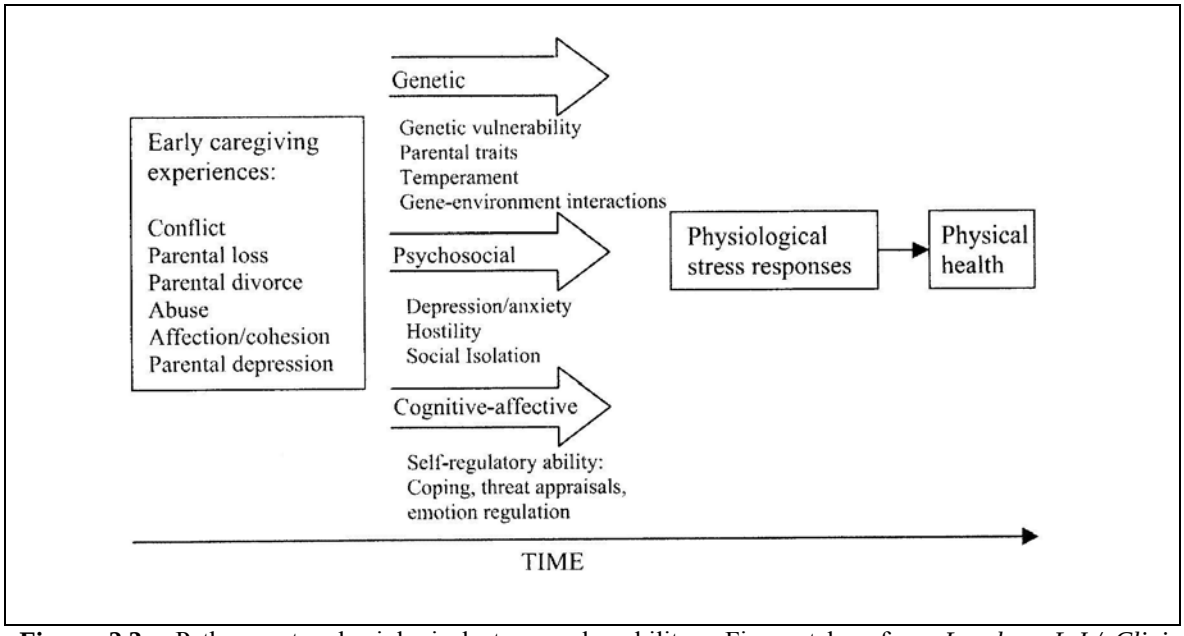


Figure 2.3. Pathways to physiological stress vulnerability. Figure taken from *Leucken, L.J./ Clinical Psychology Review 2004;24:171-191 (34).*

Figure 2.3. explains the pathways in the development of the physiological stress response and sustainable physical health. According to this scheme, an individual that is genetically predisposed to a certain physiological set-up and personality features, will be influenced by early care giving experiences like parental loss and abuse, to develop cognitive-affective schemes incapable of coping with life stresses. The consequence is an impaired physiological stress response (in both the HPA- and SAM-axes) and impaired physical health (34).

2.4. Sensitisation

The previous section explained that early life stressors could have lasting and profound effects on the physiological stress response of an individual because of the plasticity of the nervous system (29). This holds true for the effects of chronic prolonged stress during adult life as well (12). There are two types of changes in synaptic efficiency that can occur in the midst of repeated use over extensive periods of time. A decreased efficiency of a synapse due to repeated use is called habituation (e.g. the repeated exposure to olfactory stimuli). Sensitisation is an increased efficiency of the synapse because of repeated use (8). The mechanism by which sustained arousal (during infancy and adulthood) is able to predispose to fibromyalgia or any other disorder in the CMI spectrum, is by sensitising key neural pathways (12). Therefore, in a sense, the theory of sensitisation is actually an elaboration

of the stress model, serving as a further explanation why some individuals develop more subjective complaints in response to stress than others.

The sensitisation theory is especially relevant to fibromyalgia because of the high incidence of verbal, physical, and sexual abuse in the histories of these patients (41). A study done by Arnow *et al.* (2000) compared two groups of psychologically distressed patients who made high use of medical services (38). The first group comprised of patients who reported a history of sexual childhood abuse, the second group had a history of sexual as well as physical abuse. Compared to group one, group two reported significantly more severe sexual abuse with completed intercourse, emotional abuse, emotional neglect and psychological distress. This group also had a significantly higher number of emergency room visits, accompanied by significantly more frequent chronic and acute pain complaints (38).

In the light of evidence provided by studies like the one mentioned above, it has been proposed that the underlying pathogenetic process responsible for pain in fibromyalgia is peripheral and central sensitisation. Figure 2.4. explains how pain pathways are sensitised in response to sustained stress (15). During normal pain processing, the sensory (discriminatory) aspect of pain ascends with the spinothalamic pathway to terminate within the ventroposterior and ventrobasal thalamus, from where neurons project to the somatosensory cortex to be discriminated in terms of temporal encoding. The cognitive (affective) aspect of pain ascends through the spinoparabrachial pathway to project to the hypothalamus, amygdala and the insular and anterior cingulate cortices (15).

Usually peripheral sensitisation (primary hyperalgesia) is related to tissue damage, and the sustained activation of nociceptor complexes by cytokines, prostanoids and neuropeptides (15). In fibromyalgia, however, there is a lack of evidence for detectable tissue abnormalities (6). Despite the apparent absence of tissue damage, peripheral sensitisation still plays a major role in the maintenance of central sensitisation after the initial nociceptive stimuli (13). Peripheral pain mechanisms in fibromyalgia (lowering of the thresholds of nociceptors) are probably related to the increased levels of substance P in the afferent nerve fibres of fibromyalgia muscle tissue, as well as the feed-forward effect from the sympathetic nerves to the area (through the release of calcitonin gene-related peptide or ATP) (12). Triggering events, like trauma and infections, result in the spinal neuronal

activation of the second order neurons of the dorsal horn of the spinal cord by means of neurotransmitters like *N*-methyl-*D*-aspartate, protein kinase C, nitric oxide and prostaglandins. Prolonged or strong activity of these neurons can lead to central sensitisation marked by increased neuronal activity and the spreading of hyperalgesia to several spinal segments (13,15).

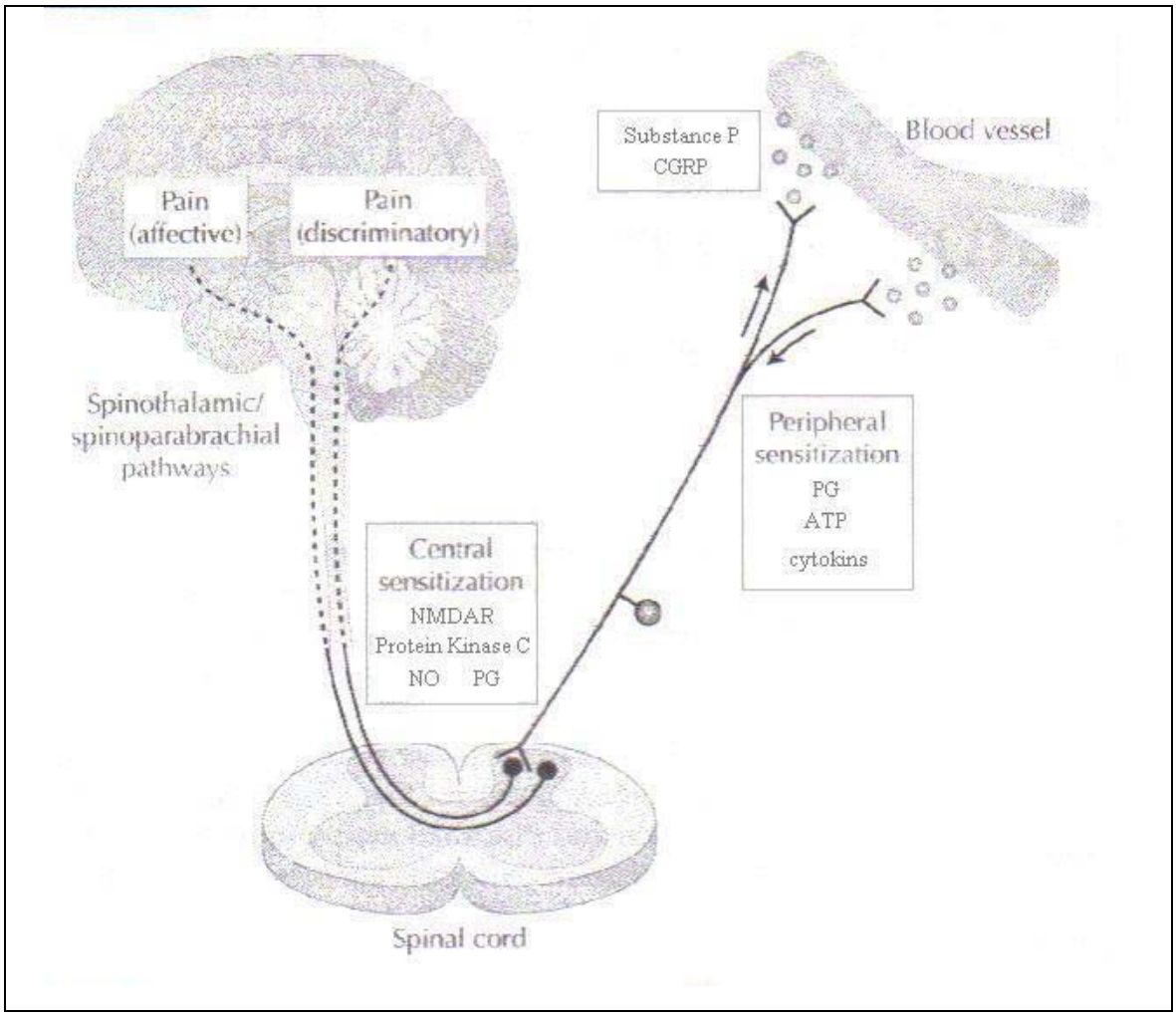


Figure 2.4. Sensitisation within the pain pathways. **Abreviations**: NMDAR, *N*-methyl-*D*-aspartate receptor; NO, nitrite oxide; PG, prostaglandins; CGRP, calcitonin gene-related peptide; ATP, adenosine triphosphate. Figure adapted from *Blackburn-Munro,G./ Current Pain and Headache Reports 2004; 8:116-124 (15).*

The sensitisation theory is also proposed as the pathological mechanism underlying co-morbid disorders (like depression and anxiety), as well as the aberrations in the autonomic nervous system and the hypothalamic-pituitary-adrenal system in fibromyalgia (42). These sensitisations involved in the pathogenesis of fibromyalgia are discussed in greater detail in Section 3.

3. The systems involved in the pathogenesis and continuation of fibromyalgia

3.1. Psychological and behavioural aspects

The influence that early life experiences has on health in adulthood has already been touched upon in the preceding section. It seems fundamental in the study of early life experiences to have a degree of familiarity with the well-known attachment theory of John Bowlby (1907 – 1990), a British physician and psychoanalyst (43). Another reason for this discussion is that attachment style assessments form part of this study. In the sections to follow, an overview is therefore given on the origin of the attachment theory, how infant-parent bonding relates to adult attachment, and how this attachment-behavioural system is embedded in an individual's brain through psychoneurological development.

3.1.1. Background: Bowlby's theory of attachment

Bowlby developed the theory of attachment in an attempt to understand the distress experienced by infants during separation from their parents (43). Bowlby observed that infants would go to great lengths to prevent separation from their parents, or to re-establish propinquity to a missing parent (44). Bowlby's theories were not met with enthusiasm though. Psychoanalytic writers of that time explained this infant behaviour as manifestations of immature defence mechanisms, attempting to repress emotional pain and anxiety. In contrast with these speculations, Bowlby hypothesized that since such expressions are common to a wide range of mammalian species, it may serve an evolutionary function (43).

Because human infants cannot feed or protect themselves, they are dependent on adult humans for protection and care. For this reason human infants, like other mammalian species, have to develop attachment behaviours like crying, clinging and sometimes hysterically searching, to evoke caring behaviour from the parents (or primary caregiver) (45). According to Bowlby, the infants who are able to establish and maintain propinquity to their primary caregiver are more likely to survive to a reproductive age (46). A motivational-control system, that Bowlby called the 'attachment behavioural system', was then gradually formed during evolution by a process of natural selection (47,48).

The attachment behaviour system is an important concept in attachment theory as it provides the link between ethological models of human development and modern theories

on emotion regulation and personality (49). Because proximity seeking protects the infant from harm, the attachment system is highly responsive to indications of danger (44). Bowlby explains the function of this system as follows: The behaviour system observes the environment to determine whether the attachment figure is close by, accessible, and attentive to his needs. If the child feels that the caregiver does fulfil in his needs, he will have a sense of love and security. This will evolve in a feeling of confidence causing the child to explore the environment and to engage in social interactions with others. However, if the child experiences the caregiver to be unapproachable or neglectful, he will feel anxious and exhibit attachment behaviours like visual searching or even active following and vocal signalling to the caregiver. The child will continue this behaviour until proximity is re-established. During long-lasting separation or permanent loss, the child is likely to give up on finding the caregiver and he will not show any attachment behaviour. As a consequence, Bowlby believed that the child will feel helpless and may experience depression (46,47).

At this stage it is important to note that the concepts of attachment should not be confused with 'bonding'. The latter was introduced to describe the emotional bonds that mothers form with their children through the process of birth and delivery. In contrast, attachment theory describes the process by which infants and young children develop confidence in their parents' protection (45).

3.1.2. Individual differences in infant attachment patterns

Mary Ainsworth, a professor of developmental psychology and a colleague of Bowlby, was interested in developing a research measure that would be a quantifiable instrument capable of evaluating the security of attachment (50). She developed a 25-minute laboratory paradigm for studying infant-parent attachment called the 'strange situation', during which infants were systematically separated from their mothers for short periods of time and then reunited again (44). She was then able to study the infant's behaviour at separation and reunion. Through this structured sequence, she was able to distinguish three different patterns of infant attachment behaviours. This work of Ainsworth was particularly significant because it provided the empirical demonstrations for Bowlby's theories (45).

The 'strange situation' technique was performed on 12-month-old infants and their parents. 60% of the children behaved in a way analogous with Bowlby's 'normative' theory: They

became upset when the parent left the room, but upon the return of the parent, actively sought and accepted the parent and his comfort. This behaviour pattern is indicative of a 'secure' attachment style. 20% of the children were uncomfortable initially, and when separated from the parent, became exceptionally distressed. When these children were reunited with the parent, they showed conflicting behaviours, ranging from the desire to be comforted to the desire to punish the parent for leaving them. Ainsworth described these children as being 'anxious-resistant'. Ainsworth also documented a third pattern: 'avoidant' attachment. These children (20%) did not appear to be distressed by the separation, but actively avoided the parent upon his return (50).

Ainsworth demonstrated that these individual differences could be associated with infant-parent interactions at home during the first year of life. For example: Children who appeared secure in the strange situation, tend to have had loving parents who were attentive to their needs (44). In later childhood, these children spent more time with their peers, are more self-assured and less dependent (35). In contrast, insecure children (anxious-resistant and avoidant) often had insensitive, inconsistent or neglectful parents (44). They tend to either live in fear or rejection or to be compulsively self-reliant (35).

3.1.3. Adult attachment

Bowlby was of the opinion that the nature of the infant-caregiver relationship persisted from 'the cradle to the grave' (49). Hazan and Shaver (1987) were the first researchers to explore the possibility that the attachment process may play out in adulthood in romantic relationships (51). They supposed that the emotional bond that develops between adult romantic partners is a function of the motivational system formed in infant-parent interaction during childhood. Hazan and Shaver distinguished the following similarities between the infant-parent relationships and adult romantic relationships (51):

- Individuals feel safe when the other is close by and approachable.
- Close, intimate, bodily contact forms part of both relationships.
- A feeling of insecurity manifests whenever the other is unavailable.
- Both relationships are marked by the discovery of one another.
- Both play with one another's facial features and show a mutual fascination and preoccupation with one another.
- Individuals engage in "baby talk" (51).

On these grounds Havan and Shaver argued that adult romantic relationships are also attachments, and that romantic love is a feature of the attachment behavioural system developing from the motivational system formed during infancy (51).

It was therefore postulated that, because adult romantic relationships are a function of the infant-parent/caregiver attachment, the adult's romantic relationships would be a partial reflection of the attachment experiences in early childhood (52). According to Bowlby (48), the child utilises early experiences to develop a 'working model' (mental representation of expectations and beliefs) regarding behaviour and thinking in relationships. Once a child has developed such expectations, he will tend to seek out relational experiences that are consistent with those outlooks and perceive others in a way that is coloured by those beliefs. Because this processes is not solely psychological of nature, but are based on neurobiological developments, attachment subtypes tend to persist over an individual's lifespan (53). (The neurobiological development during attachment will be discussed in greater detail later in this chapter.) It is however possible that, should the child continuously be confronted with experiences that are inconsistent with his working model, this attachment style could change (52). This suggests that an insecurely attached individual have the potential to move to a more secure state of mind with respect to attachment, should he be exposed to new (positive) relationship experiences (44).

If adult romantic relationships are attachment relationships, the same individual differences observed by Ainsworth in infancy, should manifest in adulthood (52). Some adults are secure: they are confident that their partner will be available in times of need and they are comfortable being depended on and depending on their partners themselves. These adults have trust in others and a sense that one has the power to affect the world (35). Other adults are insecure in their relationships, probably because of their attachment behavioural system formed from past experiences. These individuals may be anxious-resistant, constantly worrying that their partners do not really love them. These individuals experience a lot of frustration and anger when their needs are not met. The avoidant adults prefer autonomy to dependence and being dependent upon. They appear not to be too concerned about close relationships (44,52).

3.1.4. The neurobiological development of attachment

In summary it can be said that interpersonal experiences directly influence how reality is mentally constructed by shaping the structures that create representation of experience and allow a coherent view of the world. This shaping process is most crucial during the early years of childhood, but occurs throughout life (52). The patterns of relationships and emotional communication (referred to as attachment style) formed through life experiences, directly affect the neurobiological development of the brain (44). To explain the process in an oversimplified way: During infancy, experiences are able to influence brain development mainly through a process of parcellation, because of the vulnerability of the young brain (42). In later life (and adulthood), neurobiological alterations mainly occur in the nervous system through the process of sensitisation. In the paragraphs to follow, an elaboration will be given of the effects of early experiences (and trauma) on the infant brain (sensitisation has already been discussed in Section 2.4.).

At birth, the infant's brain is underdeveloped, unable to regulate its emotions or bodily reactions to emotions. The immature infant brain constitutes incompletely connected grey matter, dependent on a substantial amount of stimulation to mature (54). During the first months, infant brain maturation involves an overabundant production of synapses, forming rough cortical networks. Experience, especially that of early life with the primary caregiver, alters the activity and structure of the connections between neurons, subsequently shaping the circuits responsible for processes such as memory, emotion and self-awareness (55). This process, called 'parcellation', is better described as 'the activity-dependent fine-tuning of connections and loss of surplus circuitry' (42).

Since environmental stimuli are primarily presented through the mother (or primary caregiver), a baby is dependent on its mother for its emotional regulation. In other words, the mother is the 'external regulator' of the neurochemistry of the infant's developing brain, modulating the infant's physiological arousal (56). With responsive parenting, growth and myelinisation of the connections between the cortical (responsible for control) and limbic (responsible for emotion) structures of the infant brain can take place, developing emotional self-regulation (57). The maturation of the right orbitofrontal cortex is of particular importance here, since it regulates the responsivity of the stress axes and autonomic nervous system, which is essential for emotional self-regulation for the rest of an individual's life (42). This brain structure dominates the sympathetic and parasympathetic

limbic systems, mediating a balance between these two branches of the autonomic nervous system (this balance is vital for emotional expression) (54). The primary caregiver's ability to regulate the infant's emotions thus determines the development of the infant's long-term stress response and the infant's ability to regulate its own emotions in later life (42,56).

If the infant is exposed to overwhelming environmental stressors during the critical periods of maturation (first 18 months), dysregulated levels of stress hormones in the brain will lead to pathomorphogenesis, marked by abnormal seizure-like activity. This 'kindling', better described as a 'time-dependent sensitisation of limbic neurons', has a hyperactivating influence (42). Nonetheless, the subconvulsive kindling of the limbic structures, and the subsequent cortical inability to control emotions and behaviour, may explain why some individuals are more sensitive to certain environmental stimuli than others (12,56), as seen in fibromyalgia.

3.2. Hemisphere dominance

Hemispheric dominance is said to play a significant role in an individual's susceptibility to different pathologies (42). It appears that left-dominant individuals tend to develop physical illness, caused by their suppression of emotions, while right-dominant individuals become mentally ill, because of their inability to intellectualise feelings (58). A paper describing associations between psychological profiles and disease, hypothesized that fibromyalgia patients may be left hemisphere dominant, suppressing emotions like anger and unhappiness (42). Research exploring the hemispheric dominance of fibromyalgia patients with reliable instrumentation and methods is extremely limited, though.

In this study, the Herrmann Brain Dominance Instrument (HBDI) was used to assess laterisation in the patient group. Although Ned Herrmann, the founder of the instrument, claims to have based it on physiology, there are some concerns pertaining to the instrument's division of the brain in limbic and cerebral (cortical) structures as well as the accuracy in the way lateralised brain function is described. For instance, according to the HBDI, a person who tends to be emotional and seems to be people-orientated probably shows 'right limbic thinking'. In neurological terms this is inaccurate, since the limbic structures cannot 'think' but only influence decision making in the frontal cerebral structures. In other words, in what the HBDI refers to as 'limbic thinking' actually implies that the person is more attentive to feelings than reason in decision making or 'thinking'.

Moreover, it is important to recognise that though referred to as hemispheric dominance (laterisation), the HBDI in fact describes an individual's preferred way of thinking or 'thinking style'. Despite the criticism towards the HBDI, several doctoral degrees were done using the instrument. Due to a lack of alternative affordable methods (and other reasons mentioned in Chapter 2) the instrument was included in the study with the understanding that it was developed from a psychological point of view.

This section aims to describe brain laterisation further than the simplified suggestion that whereas the left-brain specialises in verbal analytical tasks, operating in a sequential manner; the right-brain is involved in unconscious, non-verbal, synthetic, holistic functions controlled by emotion. The tendency of individuals to differ in the extent to which they rely upon left versus right hemisphere processing will also be explored. Keep in mind that the subject matters involved in laterisation is described using HBDI terminology.

3.2.1. The organisation of the brain

Brain division in terms of function actually goes further than the left - and right hemisphere. Basically, the brain can be divided into the 'reptile brain'; comprising of the brainstem, mid-brain, the basal ganglia and the reticular activating system, operating in an instinctive manner. The limbic system, also called the 'primitive brain', is able to register rewards and punishments, control emotion, and modulate the autonomic nervous system. Over the limbic structures lies the neocortex, referred to as the specialised grey matter of the brain, controlling higher thought processes (59).

All of these brain structures are anatomically divided into a right as well as a left hemisphere. Different brain structures and hemispheres communicate with each other through interconnecting fibres. The corpus callosum connects the cerebral hemispheres of the neocortex. The detached halves of the limbic system are linked through the hippocampal commissure. The physical location of the limbic system is between the brain stem and the cerebral hemispheres. It is physiologically connected to the cerebral hemisphere and brain stem through highly developed interconnections, enabling it to mediate brain activity occurring both above and below it (59).

Therefore, according to the HBDI, the brain is actually divided in four quadrants: the cerebral left, cerebral right, limbic left and the limbic right quadrant (Figure 3.2.1.).

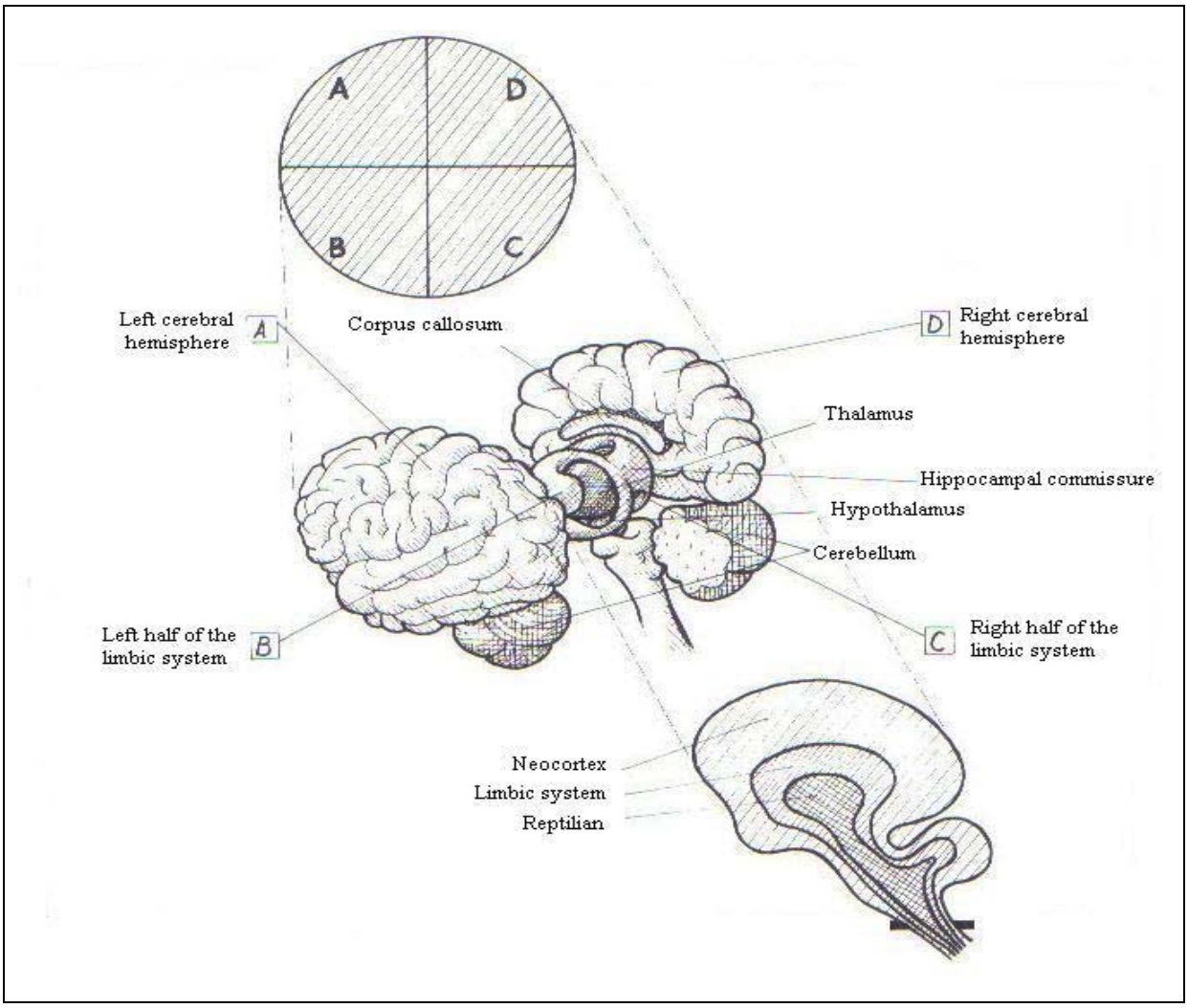


Figure 3.2.1. The interconnecting fibres linking the four quadrants of the brain. Figure taken from *Herrmann,N. The creative brain. 2 nd ed. Tennessee: Quebecor Printing Book Group; 1994. p. 43-72 (60).*

3.2.2. Specialisation of the different quadrants

Each one of the four quadrants is distinct in the thinking process it engages in during problem solving. For instance: The cerebral left quadrant uses logical, analytical thinking based on principles and formulas to solve problems. It focuses on facts and quantity measures when a situation has to be evaluated or handled. This quadrant is used when an issue needs to be dissected, enabling the brain to perceive, verbalise and express facts precisely (61).

Holistic, integrating and synthesising thoughts originates from the cerebral right quadrant. This quadrant is responsible for intuition about future events. Thoughts are communicated by the cerebral right quadrant in the form of metaphors. Other functions of this quadrant

are creativity, originality, imagination and all the processes needed to be artistic. This quadrant values experience above understanding (61).

The limbic left quadrant has some similarities with the cerebral left quadrant. It also uses a linear approach in problem solving, excluding emotion and intuition. The limbic left quadrant strives to control events and procedures. It enables an individual to be efficient when tasks have to be performed. Encoded in the left limbic structures are memories of what approaches have worked or failed in the past. These memories are used in the planning and implementing of projects. This quadrant is also involved in the testing of hypotheses and ideas that originated in the right cerebral quadrant. It is focussed on how tasks can be completed according to plan and in the correct time schedule (61).

The right limbic quadrant is responsible for interpersonal relationships and the regulation of emotions. This quadrant is focussed on the individual's own feelings as well as the feelings of the individuals it has interactions with. An important function of this quadrant is to be intuitive about other people's intensions and mood. This quadrant also enables the individual to respond to other people in a sensitive manner and to express the individual's own thoughts and feelings. Musical talent is embedded in this structure. It is kinaesthetic of nature: it allows perception and communication to be experienced as a free-flowing sequence of body sensing and movement (61). Table 3.2.2. summarises the main functions of each one of the quadrants.

Table 3.2.2. *The four quadrants and their main functions (61)*

Cerebral left	Cerebral right	Limbic left	Limbic right
Working solo	Visualising	Punctuality	Customer issues
Applying formulas	Providing vision	Establishing order	Communication
Analysing data	Having variety	Being in control	Expressing ideas
Mechanical aspects	Taking risks	Paperwork tasks	Building relationships
Financial aspects	Holistic thinking	Planning	Teaching
Solving problems	Developing new things	Stabilising	Listening and talking
Accomplishing	Designing	Attention to detail	Working with people
Diagnosing	Playing around	Structured tasks	Persuading people
Feasibility issues	Integrating ideas	Administrating	Intuition
Logical processing	Inventing solutions	Scheduling	Being part of a team
Numeral functions	Experimenting	Safety	Helping people

3.2.3. The development of dominance

Recent psychobiological models view the organisation of brain systems as a product of the interaction between genetically coded programs for the formation of structures and connections among these structures, and environmental influences (62). Influences from the social environment are imprinted into the anatomical structures that are maturing during the early brain growth spurt (starting in the last trimester, continues to about 18-24 months of age) (63). DNA production in the cortex increases considerably over the course of the first year of life (64). Both the diversity of the RNA and the amount of proteins expressed, are dependent on the early social environment (65)

Hemispheric brain growth has a cyclic nature (Figure 3.2.3) (66). This asymmetrical development continues throughout childhood with the right hemisphere in a growth spurt for the first year-and-a half (67). In actual fact, the right hemisphere is dominant for the first three years of life (68).

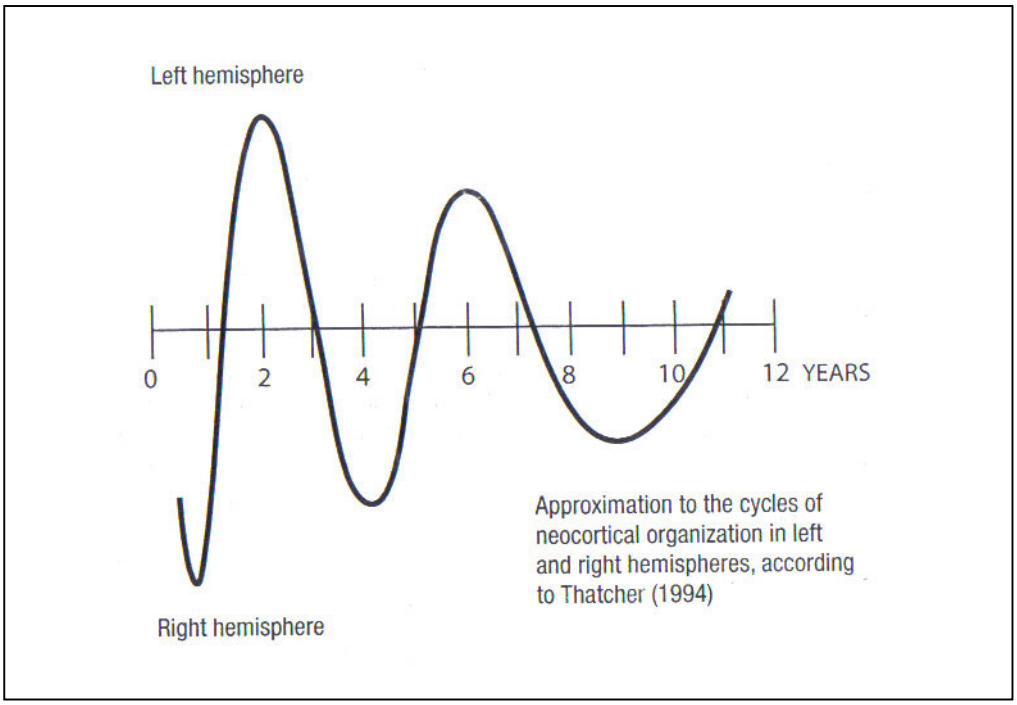


Figure 3.2.3. Asymmetrically hemispheric brain growth cycles in childhood. Figure adapted from *Thatcher, R.W. Cyclic cortical reorganization: origins of human cognitive development. In: Thatcher, R.W./ Human behavior and the developing brain. New York: Guilford Press; 1994. p. 232-266 (67).*

Since the organisation of the brain structures is dependent on stimulation from the social environment (66); and since this development occurs in cycles, varying from maturation of the right hemisphere to maturation from the left (and visa versa) (67); it could be that

isolation (under-stimulation) or high environmental stressors (over-stimulation) will affect the dominant hemisphere, currently maturing (or being modified by the environment). In other words, should the one-year-old child be exposed to adverse environmental stressors, the development of his right hemisphere is likely to be impaired, with the consequence that he will be unable to process, express, and regulate his emotions in later life (56). On the other hand, should a child be isolated from the social environment from the age of five to seven, his left hemisphere development could be inhibited (67), causing the child to avoid left-brain thinking, compulsively relying on the right hemisphere in decision making.

However, it is natural that every person will develop dominance to a specific hemisphere (or in HBDI terms, one of the four brain quadrants), just like every person has a dominant hand, eye or leg. From a philosophical point of view, this dominance has an essential role in normal functioning. Herrmann (1994) offered the following reasons for the expected dominance development: Firstly he postulates that dominance gives the individual an automatic lead response in every situation (especially dangerous situations were immediate action is needed). Thus, dominance enhances quick reaction by eliminating the decision-making step. Another advantage of dominance is that it causes higher skill levels since the brain structure that is favoured is used twice as much as the other brain structure, increasing the strength and skill of the dominant structure (69).

Herrmann also confirmed the influence of genes and environmental factors on the development of hemisphere dominance. He states that the first influence on dominance development is the genetic predisposition a person inherits to be good with certain tasks pertaining to a specific hemisphere (69). Usually the person will develop preference for this hemisphere because the repetitive use of that specific thinking processes are encouraged by performance and praise. This performance-praise-preference feedback loop can turn a small difference in hemispheric specialisation into a strong preference towards a certain hemisphere (69). Secondly, Herrmann is also of the opinion that the child will develop the cognitive preference that is focussed on in his family environment and that his parents resort to in handling situations (69).

3.2.4 The importance of integration

There seems to be constant competition between the two hemispheres within the same individual when it comes to thinking style preferences (69). As mentioned in the previous

section, it is completely normal to prefer one mode of thinking to another. This is called directional asymmetry; the one side (structure) differs consistently from the other. However, in fluctuating asymmetry, the differences between the two sides are random (non-directional) (70). In this case the individual do not endorse 'whole-brain thinking' and repeatedly chose the same mode of thinking for every situation he is confronted with. Apart from the fact that this individual limits his own performance (not using all the resources his brain has to offer), it could also have health implications (69). For example, previous research has shown that greater relative right frontal EEG activation in adults may be a marker for negative affect, dysphoric mood state, and depression (71).

It has been shown that fluctuating or unhealthy asymmetry results from the perturbation of processes in development as early as *in utero*. Evidence have been provided that this perturbations results from maternal stress (55). According to Weinstock (2001) the degree of asymmetry is positively correlated with the magnitude of the environmental stressor that the foetal was indirectly (through the mother) exposed to (72). One study showed how newborns with greater right frontal EEG activity had mothers with lower vagal tone, lower prenatal and postnatal serotonin and higher postnatal cortisol levels. These mothers also exhibited greater relative right EEG activity upon evaluation. In turn, the newborns born to these mothers had elevated cortisol levels, signs of depression and sleeping abnormalities. In this study, a discriminant function analysis classified 67% of the newborns' EEGs by prenatal maternal variables (71).

Greater right frontal EEG activity has also been noted in infants and young children with behaviours marked by fearfulness (71). A study on the children born to 'war-stress mothers' indicated that the abnormal social interaction reported in these children could be due to prenatal interference in the development of the prefrontal cortex and its relationship with the amygdala (73). This suggestion was confirmed by a study exploring the structural and functional interrelationships between cortical and limbic structures in chronically fearful or anxious monkeys (the monkeys had exaggerated fear-related defence responses) (70). In these monkeys, increased stimulation of the amygdala (critical for the mediation of fear, anxiety and mood regulation) by inputs from the right prefrontal cortex resulted in increased negative mood states (70).

Apparently, brain asymmetry can also influence the immune responses (74). Geschwind & Behan (1982) was the first to suggest an association between left-handedness and the prevalence of immune disorders (75). Increased left-handedness has also been reported in samples of patients with chemical intolerance (CI). These patients also reported a higher incidence of allergies, migraine headaches, and autoimmune disorders (76). Bardos *et al.* (1981) showed how that lesioning of the left neocortex in mice caused NK activity to decline (77). In addition, Renoux *et al.* (1983) published data suggesting that T cell functions were also controlled by the left neocortex. Yet another study on the effect of brain lesions on the immune response concluded that there appear to be a general decline in peripheral immune functions after lesioning the left cortex, whereas lesioning of the right caused an increase in immune functions (78). Finally, extreme laterisation has been shown to be a risk factor for greater sensitisation (sensitisation has been proposed as a possible pathogenetic factor in fibromyalgia in previous sections) (76). These findings are additional evidence that an abnormal high preference for a certain brain hemisphere could impair health.

In summary it can be said that development of dominance towards a certain hemisphere is a natural process, essential for normal functioning. The key, however, lies in the ability of the individual to integrate the activity in the two hemispheres. It is important to note that integration does not just involve the combination of information processing in the left and the right hemisphere, but also the ability of the cortical structures to regulate input from the limbic structures. Failure to integrate may occur when the individual has abnormal brain asymmetry (and insufficient connections between brain structures), probably caused by prenatal and postnatal stress. In cases like these, psychological and physical abnormalities are prone to develop. Therefore, as Panzer & Viljoen puts it, “optimal health ensues with integration of reason and emotion” (42, p.78).

3.3. Autonomic Nervous System (ANS) functioning

There also seems to be a link between early life experiences and autonomic nervous system functioning. At birth, the limbic sympathetic branch of the autonomic nervous system dominates. The excitatory ventral tegmental system, by which the orbitofrontal cortex modulates the sympathetic nuclei of the hypothalamus, originates in the A10 dopaminergic neurons in the midbrain, and mainly maturates from 10-12 to 14-16 months of age (64). The inhibitory lateral tegmental limbic circuit, responsible for the activation of

parasympathetic nuclei, only maturates from 14-18 months. During this period, medullary noradrenaline (A2) neurons from the lower brainstem medullar reticular formation innervate the orbitofrontal cortex. With positive, stimulating early experiences, these two limbic systems become reciprocally coupled, a condition essential for optimal health. However, with exposure to adverse environmental stressors or isolation (under stimulation), aberrations can develop in sympathetic-parasympathetic balance (56).

Latest research has shown that dysautonomia could be characteristic of fibromyalgia. In actual fact, many authors propose that the symptomology observed in fibromyalgia is the consequence of aberrant autonomic functioning (16,36,79), and that fibromyalgia is actually caused by a deranged autonomic nervous system. Yet, thus far, no consistent autonomic abnormality could be found in the majority of fibromyalgia patients (79). Therefore it could be possible that the identifiable abnormalities in the autonomic function are only present in a subset of fibromyalgia patients (29).

Most research studies point towards an alteration in sympathetic nervous system (SNS) function in fibromyalgia. These alterations seem to be present in both the sympathoneural as well as the adrenomedullary component of the sympathetic stress response. The first studies examining the involvement of autonomic function in fibromyalgia were done using guanethidine as a selective sympathetic blockade (79). The observation was made that baseline pain, as well as the number of tender points were significantly reduced when fibromyalgia patients were treated with sympathetic blockade. Consequently, the suggestion that increased sympathetic nerve activity could be a possible underlying mechanism in fibromyalgia was published (36,79). Another method employed to measure autonomic tone comprised the assessment of skin microcirculation. The autonomic nervous system reacts to a cold pressor test by eliciting a sympathoneural response. Fibromyalgia patients showed a diminished vasoconstrictor response in comparison to controls. This suggests that the autonomic nervous system has either an attenuated sympathetic or an exaggerated parasympathetic response (33,36). Sympathetic nerve activity in muscle does not seem to differ between fibromyalgia patients and controls in resting conditions, but after muscle sympathetic activity has been stimulated by static handgrip, contraction of the jaw muscle, or mental stress, a lack of sympathetic activity amplification, in fact a tendency towards lower activity was observed in patients (33). The alteration in this branch of the autonomic nervous system was also shown through the evaluation of neuropeptides Y

levels. The plasma neuropeptide Y is co-localized with noradrenalin in the sympathetic nervous system. It is released by high-frequency stimulation from the noradrenergic neurons (80). The concentration of this peptide has been reported to be low in fibromyalgia patients, reflecting lowered sympathetic activity during stress and thus representing either a measure of hypofunction, or depletion of the sympathetic stress axis (11).

More recent studies relied on the power spectral analysis of heart rate variability (HRV) to examine autonomic function in fibromyalgia. In these experiments dysautonomia was evaluated in terms of the sympathetic-parasympathetic balance of the autonomic nervous system. A couple of studies reported low baseline sympathetic tone and an inability to respond to stressors (29). The majority of studies, however, presented data showing increased sympathetic nervous system activity. Cohen *et al* (2000) studied HRV in woman with fibromyalgia, and found that the basal autonomic state of these patients was marked by increased sympathetic and decreased parasympathetic tones (81). When the same authors repeated the study with a study group composed only of men, they basically achieved the same results (82). When the data of the two studies were compared, it was concluded that the autonomic dysfunction in females was more severe than in males (79). Another study demonstrated a significant reduction in HRV and vagal tone in comparison to controls (81). All of the above studies supported Martínez-Lavín's (1998) findings of diminished HRV due to 'changes consistent with relentless circadian sympathetic hyperactivity'. His results were obtained during a 24-hour cardiovascular modulation and analysis of the circadian variations in heart rate in fibromyalgia patients (83). Despite the high basal sympathetic activity seen in fibromyalgia, Martínez-Lavín also reported an impaired sympathetic surge in response to orthostatic stress (hypoactivity) (84).

Other types of investigations supported the data obtained from the majority of spectral analyses of HRV. These studies used biochemical markers as a surrogate measure of autonomic function and found an impaired catecholamine response to a variety of different stressors (e.g. exercise, muscle contraction and hypoglycemia) (36).

The clinical manifestations that are related to autonomic dysfunction include orthostatic intolerance, vasomotor instability and visceral dysfunction (fatigue, sleep disturbances, irritable bowel and migraine are well known signs of dysautonomia) (29,79). Therefore the

derangement of the central sympathetic influences could very well be the origin of many of the patients' complaints (16,85).

In summary: A number of studies confirmed a state of dysautonomia in fibromyalgia patients. This dysfunction of the autonomic nervous system often manifests in response to orthostatic stress (or during tilt-table testing) and involves the inability of the sympathetic branch of the autonomic nervous system to respond to various physical stressors. In addition to hypoactivity during stress, numerous studies also reported sympathetic hyperactivity and parasympathetic hypoactivity of the autonomic nervous system during restful conditions. It is however true that for all of the findings mentioned above, opposing authors have published contradictory results. Table 3.3. is a summary of the results obtained by the studies described in this section.

Table 3.3. *Summary of ANS derangements found in fibromyalgia*

Procedure used to evaluate ANS function	**ANS derangement found**	**Ref.**
Selective sympathetic blockade	Baseline sympathetic hyperactivity	(79)
Skin microcirculation	Sympathetic hypoactivity/ parasympathetic hyperactivity during stress	(36)
Evaluation of muscle sympathetic tone	Sympathetic hypoactivity in response to stress	(33)
Evaluation of neuropeptide Y levels	Sympathetic hypoactivity during stress	(11)
Heart rate variability analysis	Baseline sympathetic hyperactivity Baseline parasympathetic hypoactivity Sympathetic hypoactivity in response to orthostatic stress Lowered heart rate variability	(82) (81) (29) (84) (83)

3.4. Hypothalamic–pituitary–adrenal (HPA) axis function

Extensive research has been done on the function of the hypothalamic–pituitary–adrenal (HPA) axis in fibromyalgia over the last decade (86). Figure 3.4. presents the normal neuroendocrine response elicited by stress in a healthy individuals:

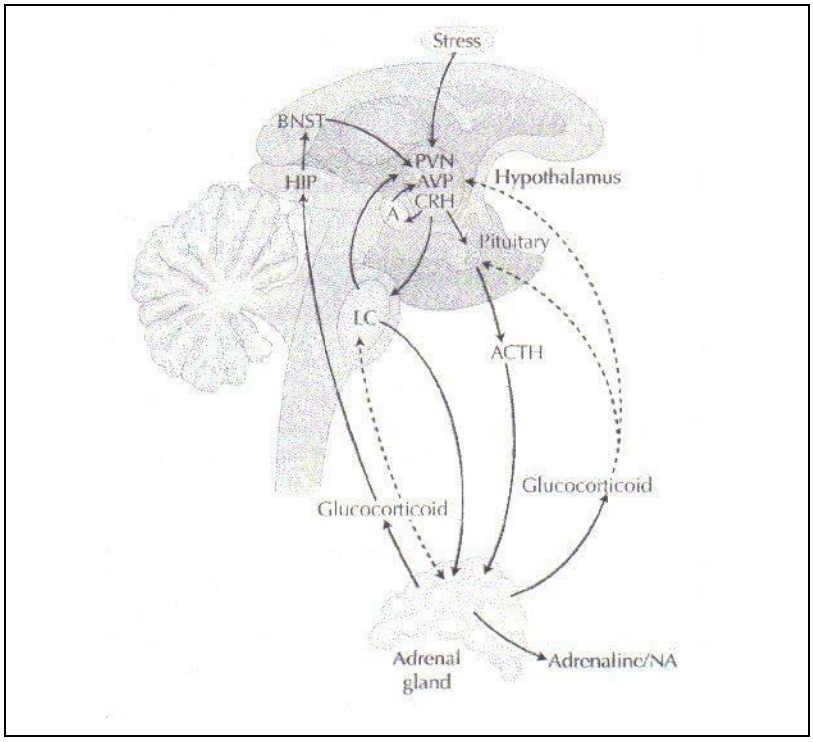


Figure 3.4. HPA axis modulation of the stress response. **Abbreviations**: A, amygdala; ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; BNTS, bed nucleus stria terminalis; CRH, corticotropin- releasing hormone; HIP, hippocampus; LC, locus coeruleus; NA, noradrenalin; PVN, paraventricular nucleus. Figure taken from *Blackburn-Munro, G./ Current Pain and Headache Reports 2004; 8:116-124 (15).*

Stress activates the parvocellular neurons within the paraventricular nucleus (PVN) of the hypothalamus to synthesize corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP). Corticotropin-releasing hormone (CRH) is the main hypothalamic mediater of the HPA axis. Arginine-vasopressin (AVP), an adjunctive secretagogue for pituitary adrenocorticotropic hormone (ACTH), becomes important in HPA-axis regulation during chronic stress or CRH deficiency. These peptides are released into the hypophyseal portal system to be transported to the anterior pituitary gland. CRH then acts on the anterior pituitary (in synergy with the weaker AVP) to stimulate ACTH secretion, which will be released into the systemic circulation. ACTH facilitates the production of glucocorticiod hormones, essential for the stress-adaptation response in the periphery (e.g. lipolysis, gluconeogenesis, immunosuppression). These hormones (like cortisol) are produced by, and released from the adrenal cortex. In addition to the stress-dependent activation of the HPA axis, it also exhibits a spontaneous circadian rhythm, which is regulated by light-dark and sleep-awake cycles (15,87,88).

An important homeostatic mechanism in the regulation of the stress response is the negative feedback inhibition of the HPA-axis. Glucocorticoids act on low-affinity glucocorticiod receptors at several levels in the HPA-axis, exerting a limiting effect on further production and secretion of glucocorticiod hormones (33). In addition to this inhibitory feedback mechanism, hippocampal 5-HT receptors also suppress the stress response, controlling CRH release by means of direct- and indirect GABA-mediated inputs to the locus coeruleus, amygdala, and the PVN of the hypothalamus. The 5-HT (serotonin) system also stimulates ACTH release at the hypothalamic and pituitary level (15,87).

At this stage it is important to bring to mind that the HPA-axis, like all brain systems, are plastic and will change in reaction to various lifetime experiences. Naturally, the variation in lifetime experiences from individual to individual, accounts for the variation in neuroendocrine responses between individuals (33). Sufficient evidence is now available on how changes induced by early life stressors ultimately affects the activity of the CRH neuron. Since the expression of CRH receptors are influenced by the reciprocal secretion of CRH, CRH receptor expression is also affected by the changed CRH neuron activity (e.g. increased CRH secretion in response to stress down-regulates CRH receptors in the anterior pituitary) (89). This altered CRH activity occurs either directly or indirectly through the inhibitory negative feedback mechanisms, and is not only present during childhood, but also detectible throughout life (33).

According to Ehlert *et al.* (2001) traumatic life events (premature birth, parental separation, childhood sexual or physical abuse) could result in a continual sensitisation or desensitisation of feedback systems of the HPA-axis. Studies have shown that both children and woman with a history of childhood sexual abuse has increased pituitary-adrenal responses to psychosocial stressors (90,91).

There is still uncertainty about HPA-axis function in fibromyalgia. Both hyperactivity and hypoactivity have been reported in patients with fibromyalgia (87). A number of standardised neuroendocrine challenge tests exist to induce HPA-axis activation. The rationale behind the different approaches in these tests is to determine the level of alteration in HPA-axis function (in the PVN, on pituitary level or at the adrenal cortex). Examples of these tests are (89):

- Insulin tolerance test (ITT) – evaluates the integrity of HPA axis (cortisol level)
- CRH stimulation test – assesses the sensitivity and integrity of the pituitary corticotrophs (ACTH level)
- ACTH stimulation test – assess the sensitivity and integrity of the adrenal cortex (cortisol level)
- Dexamethasone – inhibits the negative feedback loop by suppressing ACTH and cortisol. The combined effect of dexamethasone and CRH administration measures HPA axis function under the condition of suppressed glucocorticiod feedback
- Methyrapone – induces a cortisol production blockade, simulating an adrenalectomy (89).

Table 3.4. reviews different studies utilising the neuroendocrine tests mentioned above to determine HPA-axis function in fibromyalgia. According to the majority of review articles on the neuroendocrine abnormalities in fibromyalgia, the HPA-axis perturbations in fibromyalgia include elevated basal plasma and salivary cortisol levels, reduced 24-hour urine free cortisol and a blunted circadian change in plasma cortisol levels. Challenge tests indicate that fibromyalgia is associated with enhanced ACTH release and a blunted cortisol response (despite the exaggerated ACTH release) after exogenous CRH and induced hypoglycemia, as well as blunted HPA-axis activity to stressors (87). As far as HPA-function on the PVN level is concerned, two studies reported an diminished CRH in response to stressors. However, results opposing these findings have also been published (as seen in Table 3.4.).

Therefore it seems that, just like the research findings on the autonomic nervous system in fibromyalgia, there is lack of congruence between different studies. A possible reason for these differences in HPA-axis results could be the presence of concomitant disorders in the patient group selected. For instance, if the fibromyalgia patients in the study group have major depression, elevated cortisol levels could be part of the disease profile of depression and not fibromyalgia (92). The same could be true for the presence of chronic fatigue syndrome amongst fibromyalgia subjects (assuming that these two disorders is not the same condition). The neuroendocrinology of chronic fatigue syndrome and fibromyalgia shows remarkable similarities, but some differences as well. In chronic fatigue syndrome, for example, there do not seem to be an exaggerated ACTH response to CRH stimulation, as observed in fibromyalgia (87).

Table 3.4. *Summary of studies exploring HPA-axis function in fibromyalgia*

Authors	Procedure	Findings	Conclusions	Ref.
Calis *et al.* 2004	▪ 22 patients, 22 healthy controls ▪ ACTH (1 µg) stimulation ▪ Metyrapone (30 mg/kg) administration ▪ Adrenal size	▪ Peak cortisol level lower than controls ($p<0.05$) ▪ 11-deoxycortisol level in response to metyrapone was lower in patients ($p<0.05$) ▪ Adrenal size the same	HPA – axis is underactivated in FM	(93)
Riedel *et al.* 2002	▪ 13 patients, 13 healthy controls ▪ CRH (100 µg) administration	▪ No significant difference in increase of ACTH and cortisol ▪ Increase in plasma CRH higher in patients ($p<0.05$)	Elevated CRH in patients suggest elevated CRH-binding protein, explaining similar cortisol and ACTH levels between patients and controls	(94)
Kirnap *et al* 2001	▪ 16 patients, 16 healthy controls ▪ Insulin-tolerance test (ITT) ▪ Standard (250 µg) dose ACTH test (SDT) ▪ Low (1 µg) dose ACTH (LDT)	▪ Peak cortisol level in response to ITT, SDT, and LDT lower than controls ($p<0.0001$) ▪ Peak cortisol level (patients) in response to LDT is significantly lower than in response to ITT or SDT ($p<0.0001$)	HPA-axis is underactivated in FM Some FM patients may have subnormal adrenocortical function LDT is more sensitive than SDT and ITT in the investigation of HPA-axis function	(95)
Torpy *et al.* 2000	▪ 13 patients, 8 healthy controls ▪ Interleuken 6 (IL-6) injection	▪ Delayed ACTH response in patients ($p=0.02$) ▪ No significant difference in cortisol levels	Delayed ACTH release in FM is consistent with defected CRH function (authors believe that CRH function is deficient in FM)	(96)
Catley *et al.* 2000	▪ 21 FM patients, 18 rheumatoid arthritis (RA) patients, 22 healthy controls ▪ Baseline cortisol assessment	▪ FM and RA patients had similar mean cortisol levels, higher than controls	FM and RA are associated with elevated cortisol levels	(97)
Adler *et al. 1999*	▪ 15 patients, 13 healthy controls ▪ Performed a hypoglycemic hyperinsulinemic clamp	▪ No significant difference in baseline 24-h urinary free cortisol, diurnal ACTH and cortisol ▪ 30% reduction in ACTH in response to hypoclycemia in patients ▪ No difference in cortisol levels in response to hypoclycemia	The defect in HPA-axis function in FM is on the hypothalamic-pituitary level	(98)

Table 3.4. *Summary of studies exploring HPA-axis function in fibromyalgia – continued*

Authors	Procedure	Findings	Conclusions	Ref.
Griep *et al. 1998*	▪ 40 patients, 14 healthy controls ▪ CRH (100 µg) challenge test ▪ Dexamethasone (1mg) suppression test in conjunction with ▪ ACTH administration (0.025 or 0.1 µg ACTH/kg body weight) ▪ Basal adrenocortical assessment	▪ Elevated ACTH in response to CRH challenge ($p=0.001$) ▪ No difference in cortisol response to CRH or ACTH between groups ▪ Dexamethasone suppressed cortisol in 95% of patients ▪ 24-h urinary free cortisol lower than controls ($p=0.02$) ▪ Basal total cortisol lower than controls ($p<0.05$)	Mild hypocortisolemia Hyperactivity of pituitary ACTH release to CRH Glucocorticoid feedback resistance	(99)
Maes *et al.* 1998	▪ 14 FM patients, 10 major depressive (MD) patients, 10 post-traumatic stress disorder (PTSD) patients, 17 healthy controls ▪ 24-h urinary free cortisol assay	▪ The mean and total 24h urinary cortisol excretion were the highest for the PTSD group, followed by the MD group, then the FM group, with the lowest levels for the healthy control group ▪ The 24-h urinary cortisol level did not correlate with the duration of illness, number of tender points, or subjective assessments of pain in FM group	FM is associated with elevated baseline cortisol levels	(26)
Crofford *et al.* 1994	▪ 12 patients, 12 healthy controls ▪ 24-h urinary free cortisol assay ▪ Ovine CRH infusion (1 µg/kg)	▪ Similar morning cortisol levels in patients and controls ▪ Evening cortisol higher in patients ($p<0.04$) ▪ Mean 24-h urinary free cortisol level lower in patients ($p<0.002$) ▪ Basal cortisol level higher in patients ($p<0.02$) ▪ Peak cortisol level and ACTH in response to CRH was similar in two groups (netto change in patients is thus decreased ($p<0.02$))	Adrenal hyporesponsivity to ACTH because of chronic understimulation due to deficient CRH production	(100)
Griep *et al.* 1993	▪ 10 patients, 10 healthy controls ▪ Dexamethasone (1mg) suppression test ▪ CRH infusion (100 µg) ▪ Insulin-induced hypoglycemia (0.1 unit insulin/kg of body weight)	▪ Basal ACTH and cortisol the same in two groups ▪ ACTH levels in response to CRH significantly higher in patients ($p<0.05$) ▪ Cortisol levels in response to CRH the same in two groups ▪ The same pattern in response to hypoglycemia ▪ Increase in plasma CRH higher in patients ($p<0.05$)	Hyperactivity of CRH upon stressful situations	(101)

B. PURPOSE OF THE STUDY

A multitude of studies has been published on fibromyalgia. In most, only certain aspects of either psychological or physiological status were examined. The aim of this work was to see whether a specific psychoneurological profile could be identified for fibromyalgia by examining psychological and physiological aspects simultaneously, determining if any correlations exist.

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