THE PSYCHONEUROLOGICAL PROFILE OF FIBROMYALGIA

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ABSTRACT

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Fibromyalgia (FM) is a chronic pain syndrome of unknown etiology. It was previously suggested that patients with fibromyalgia were, in early life, often subjected to either psychological or physiological trauma. It is, in general, known that early life experiences and attachment to primary caregivers can influence physiological function in adult life, especially those functions related to stress vulnerability. Many studies have been performed on fibromyalgia patients but most of them investigated either psychological or physiological aspects. The purpose of this study was to investigate the psychological profile (attachment style, preferred way of thinking as well as prevalence of depression and anxiety) and physiological aspects (autonomic nervous system function and cortisol levels) simultaneously in an attempt to see whether a link exists between the two aspects and whether a specific psychoneurological profile could be discerned for fibromyalgia patients. Sixteen patients (14 females, 2 males) with fibromyalgia, and 15 age- and sex-matched controls (13 females, 2 males) were studied. Patients were diagnosed according to the American College of Rheumatology (ACR, 1990) criteria for fibromyalgia. The Patient Health Questionnaire gathered information on the patient's past health problems, operations, accidents and the prevalence of traumatic events. The Fibromyalgia Impact Questionnaire and Review of Current Symptoms Questionnaire were completed to assess the severity of the disorder. The Experiences in Close Relationships – Revised Questionnaire determined attachment styles. Hemisphere dominance (preferred way of thinking) was evaluated by the Herrmann Brain Dominance Instrument (HBDI), heart rate variability (HRV) by recording R-R intervals and calculating time and frequency domain parameters and salivary cortisol levels by ELISA.

Significant differences were seen between patients and controls for cortisol levels; the total number of symptoms; the number of adverse events in lifetime; anxiety and avoidance subscales of the ECR-R; FIQ total scores; and scores for scales within the FIQ. R-R spectral analysis revealed distinct lowered overall HRV in patients. An orthostatic test revealed a weakened shift towards sympathetic dominance upon standing. During a psychological stressor (filling out the ECR-R), the patients' autonomic nervous system failed to respond with lower HRV as with the controls. As far as the hemispheric dominance of the patients was concerned, the majority appeared to be right-brain orientated with thinking styles preferences strongly influenced by limbic functions. Preference for thinking styles influenced by right limbic structures increased during stress. A link existed between anxiety and depression and the severity of the fibromyalgia symptoms.

The results of individual psychological and physiological parameters found in this study are largely in concordance of that of other studies. Significant differences exist between the psychoneurological variables of fibromyalgia patients and healthy controls: The patient group in this study were characterised by a high prevalence adverse events, insecure attachment styles, high emotionality in the absence of rationality, multiple somatic symptoms, and altered stress-axes activity reflected in low HRV, an inability to mount an appropriate sympathetic response to acute stressors and elevated baseline cortisol levels. It can be concluded that fibromyalgia patients in the present study presented with a distinct psychoneurological profile.

Keywords: early life experiences, attachment style, hemisphere dominance, stress-axes, heart rate variability, autonomic balance, salivary cortisol level, psychoneurological profile

OPSOMMING

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Fibromialgie (FM) is ‘n chroniese pynsindroom met ‘n onbekende etiologie. Dit is voorgestel dat pasiënte met fibromialgie in hul kinderjare aan fisiologiese of sielkundige trauma blootgestel was. Dit is, in die algemeen, bekend dat vroeë kinderjaarervarings en gebondenheid (engels: attachment) met die primêre versorger fisiologiese funksie in volwasse lewe kan beinvloed, veral die funksies wat te doen het met streskwesbaarheid. Talle studies is al op fibromialgie gedoen, maar die meeste van hierdie studies het óf sielkundige, óf fisiologiese aspekte ondersoek. Die doel van hierdie studie was om die sielkundige profiel (gebondenheid, denkwyse van voorkeur, en die voorkoms van depressie en angs) en fisiologiese aspekte (hartspoedvariasie, outonome balans en kortisol vlakke) gelyk te bestudeer, in ‘n poging om te sien of ‘n verband tussen die twee aspekte bestaan en of ‘n spesifieke psigoneurologiese profiel vir die pasiënte met fibromialgie onderskei kan word.

Sestien pasiënte (14 vrouens, 2 mans) met fibromialgie, en 15 ouderdom- en geslag-ooreenstemmende kontroles (13 vrouens, 2 mans) is bestudeer. Die pasiënte is gediagnoseer volgens die ‘American College of Rheumatology (ACR, 1990)’ klassifikasie kriterium vir fibromialgie. Die ‘Patient Health Questionnaire (PHQ)’ het informasie gegee oor gesondheidsprobleme, operasies, ongelukke en traumatiese gebeurtenisse in die pasiënte se verlede. Die ‘Fibromyalgia Impact Questionnaire (FIQ)’ en ‘Review of Current Symptoms Questionnaire’ het die graad van die simptome ondersoek. Die ‘Experiences in Close Relationships – Revised Questionnaire (ECR-R)’ het gebondenheid bepaal. Hemisfeerdominansie (denkwyse van voorkeur) is deur die ‘Herrmann Brain Dominance Instrument (HBDI)’, hartspoedvarieerbaarheid (HRV) deur die opname van R-R intervalle en berekening van tyd en frekwensie parameters, en speeksel kortisolvlakke deur middel van ELISA bepaal.

Statisties betekenisvolle verskille het voorgekom tussen die pasiënte en die kontroles vir kortisolvlakke; die totale aantal simptome; die aantal traumatiese gebeurtenisse in leeftyd; angs- en vermydingskale op die ECR-R; FIQ totale lesings; en lesings vir subskale van die FIQ. Ontleding van die R-R spektrale intervalle het getoon dat die pasiënte verlaagde hartspoedvarieerbaarheid het. ‘n Ortostatiese toets het aangetoon dat daar ‘n suboptimale verskuiwing na simpatiese oorheersing is wanneer die pasiënte opstaan. Gedurende ‘n sielkundige stressor, het die kontroles se harspoedvarieerbaarheid afgeneem, terwyl die pasiente s’n dieselfde gebly het. Wat die hemisfeer dominansie betref, is die meeste pasiënte regter-brein georiënteerd, met denkprosesse wat sterk deur limbiese funksie beinvloed word. Die voorkeur vir denkprosesse wat deur die regter limbiese strukture beinvloed word, neem toe gedurende spanning. Daar is ‘n verband tussen angs en depressie en die graad van fibromialgie simptome.

Die resultate van die individuele sielkundige en fisiologiese parameters van hierdie studie kom grootliks ooreen met dié van ander studies. Betekenisvolle verskille bestaan tussen die psigoneurologiese veranderlikes van fibromialgie pasiënte en gesonde kontroles: Die pasiënt groep in hierdie studie was gekenmerk deur ‘n hoë voorkoms van traumatiese gebeure, onseker gebondenheid, veelvoudige somatiese simptome, hoë emosionaliteit in die afwesigheid van rasionaliteit, en gewysigde stres-as aktiwiteit soos gereflekteer in lae hartspoedvarieerbaarheid, ‘n onvermoë van die simpatiese senuweestelsel om gepas op ‘n akute stressor te reageer, en verhoogde kortisolvlakke. In samevatting kan gesê word dat die fibromialgie pasiënte in die huidige studie ‘n psigoneurologiese profiel het wat duidelik van dié van die kontroles verskil.

Sleutelwoorde: vroeë lewenservarings, gebondenheid, hemisfeerdominansie, stress-asse, hartspoedvariasie, outonome balans, speeksel kortisolvlak, psigoneurologiese profiel

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CHAPTER 1
INTRODUCTION

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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).

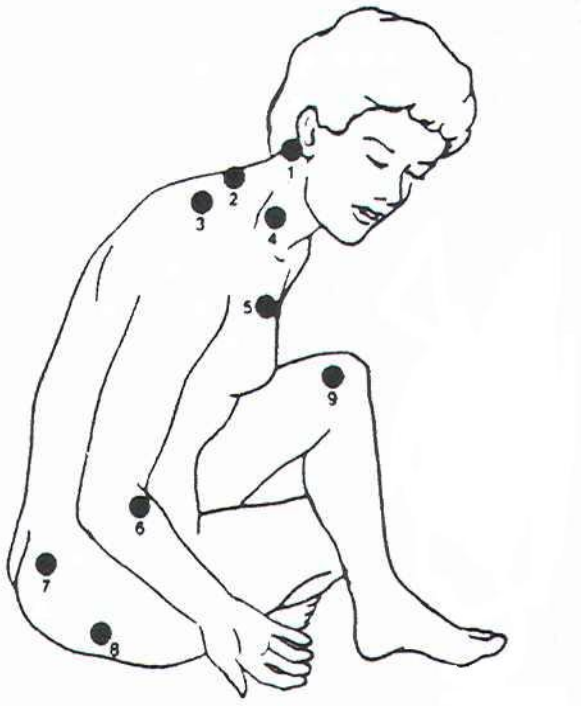
Sections 1.2.1. – 1.2.10. elaborate on some of the major symptoms fibromyalgia patients present with, and provide short descriptions on the possible causes of the symptoms.

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).

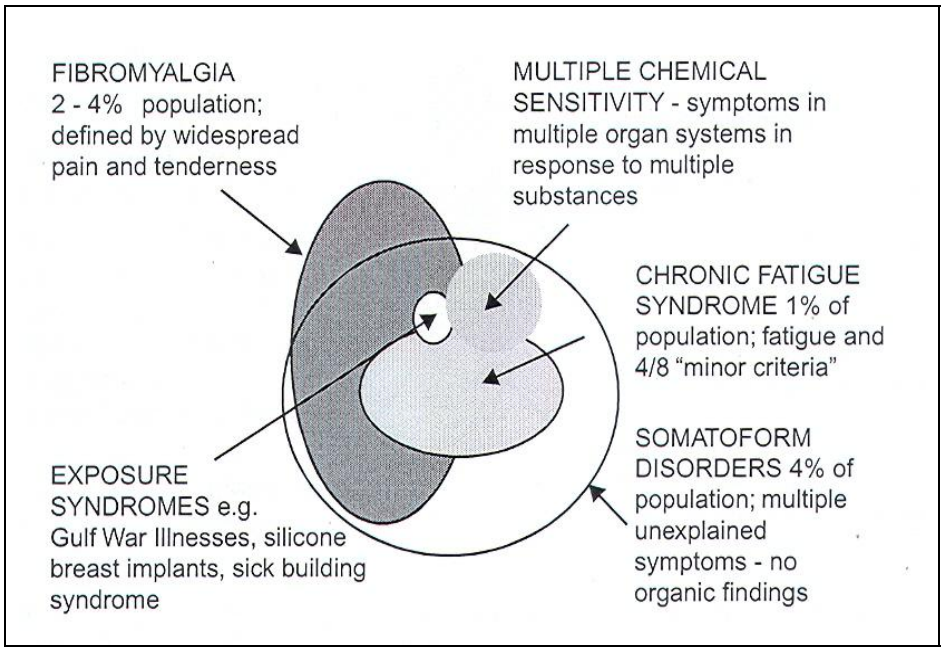


Figure 1.4. Examples of overlapping syndromes characterised by 'unexplained symptoms'. Figure taken from *Clauw, D.J./ Best Practice & Clinical Rheumatology 2003;17:685-701(7).*

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'.

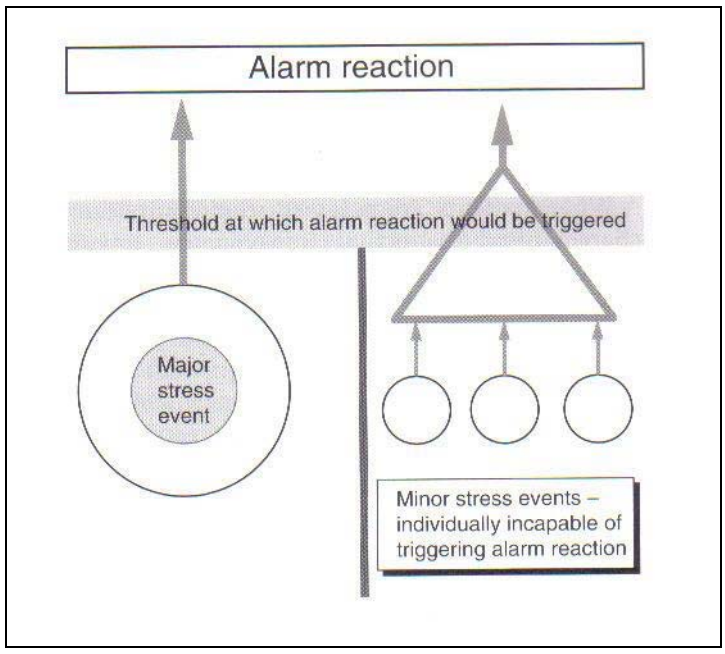


Figure 2.1. The cumulative effect of stressors. A combination of minor stressors, each incapable of triggering and alarm reaction in the general adaptation response alone, can produce sufficient adaptive demand when it is combined or sustained. Figure taken from *Chaitow, L./ Fibromyalgia syndrome – 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).

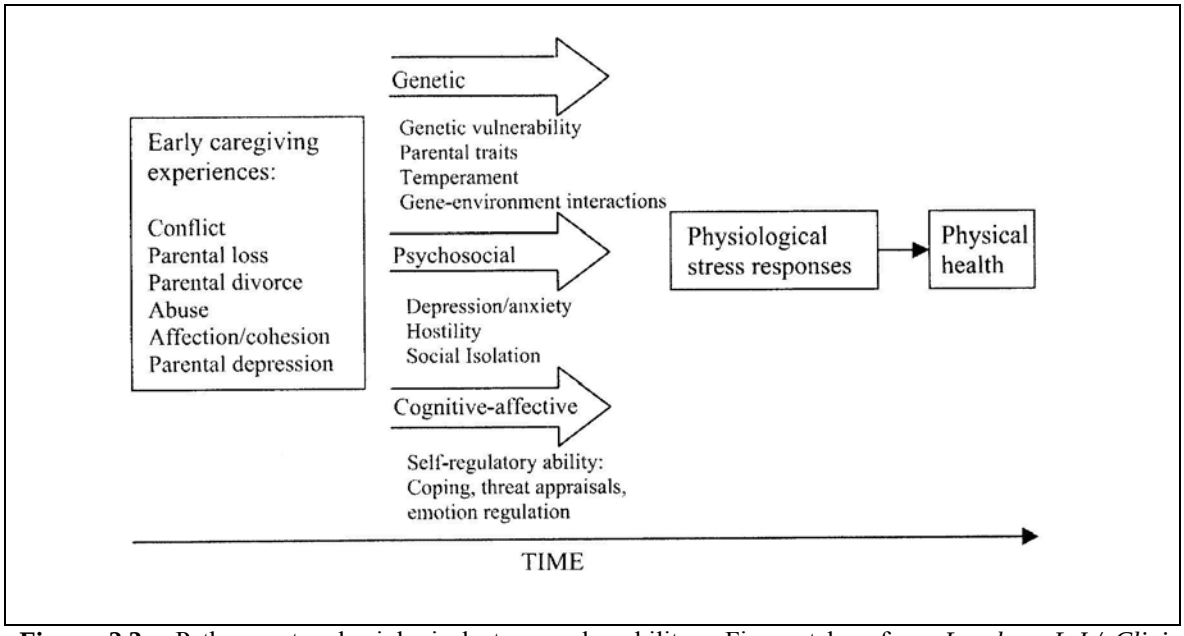


Figure 2.3. Pathways to physiological stress vulnerability. Figure taken from *Leucken, L.J./ Clinical Psychology Review 2004;24:171-191 (34).*

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).

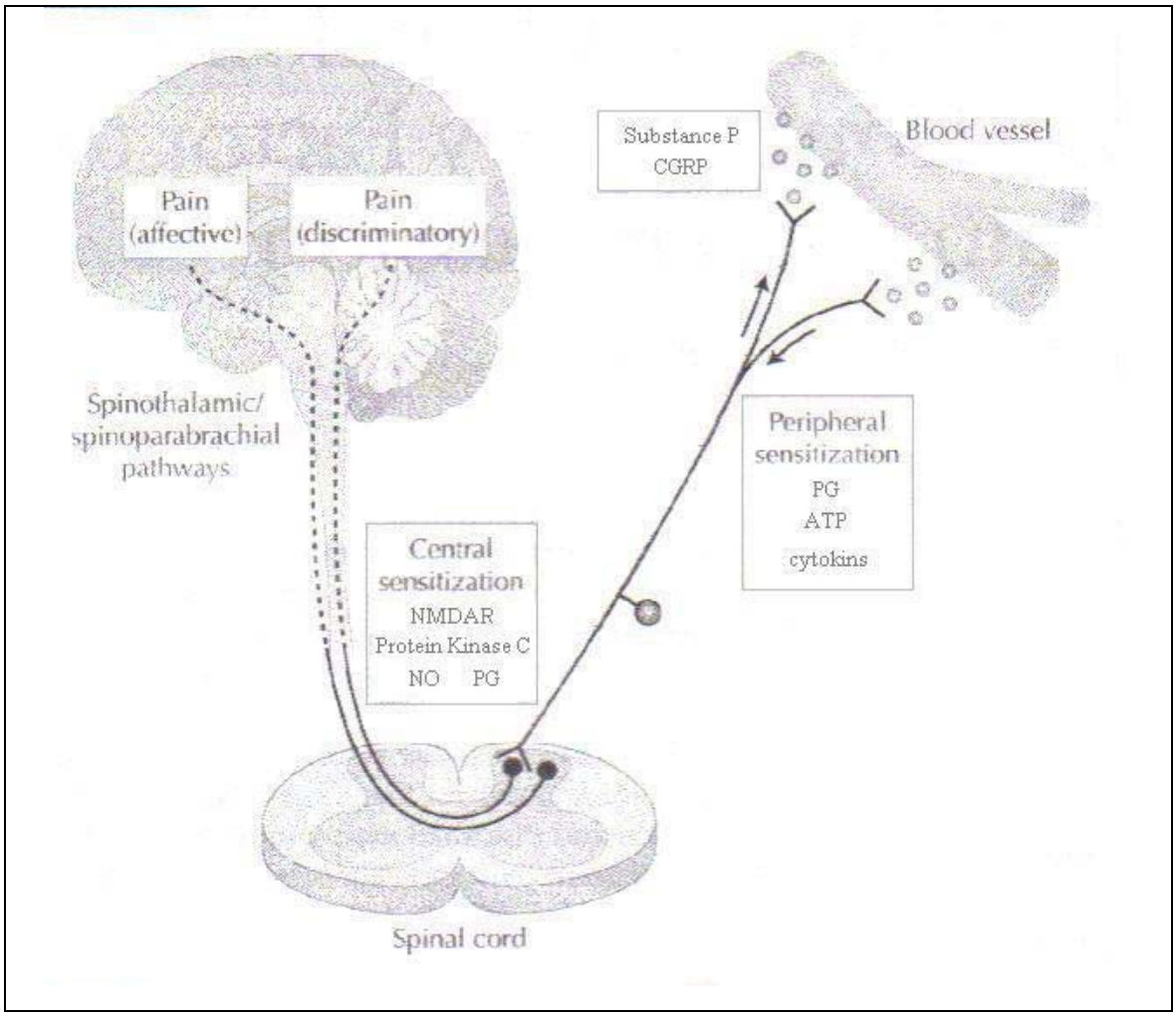


Figure 2.4. Sensitisation within the pain pathways. **Abreviations**: NMDAR, *N*-methyl-*D*-aspartate receptor; NO, nitrite oxide; PG, prostaglandins; CGRP, calcitonin gene-related peptide; ATP, adenosine triphosphate. Figure adapted from *Blackburn-Munro,G./ Current Pain and Headache Reports 2004; 8:116-124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

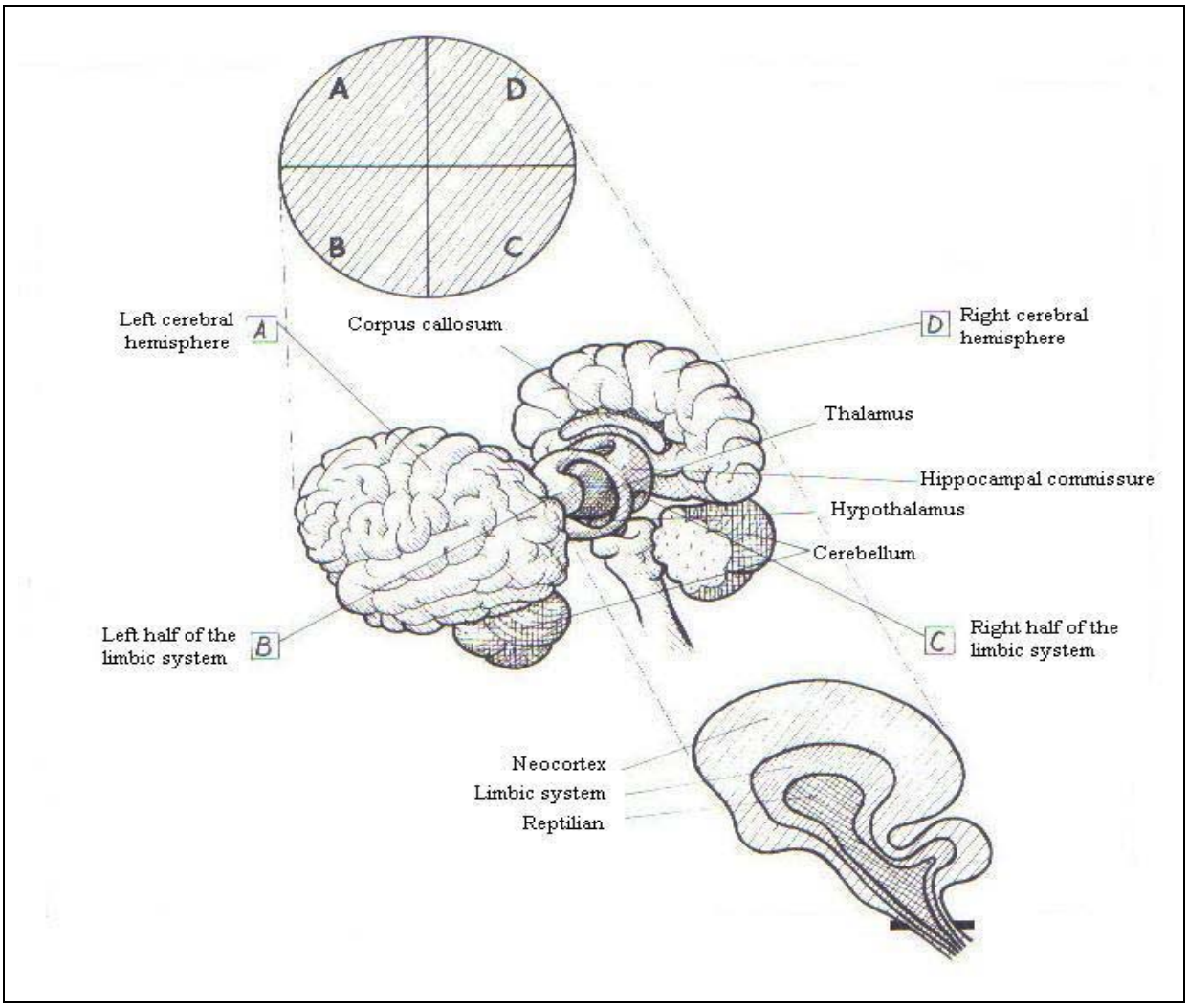


Figure 3.2.1. The interconnecting fibres linking the four quadrants of the brain. Figure taken from *Herrmann,N. The creative brain. 2 nd ed. Tennessee: Quebecor Printing Book Group; 1994. p. 43-72 (60).*

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).

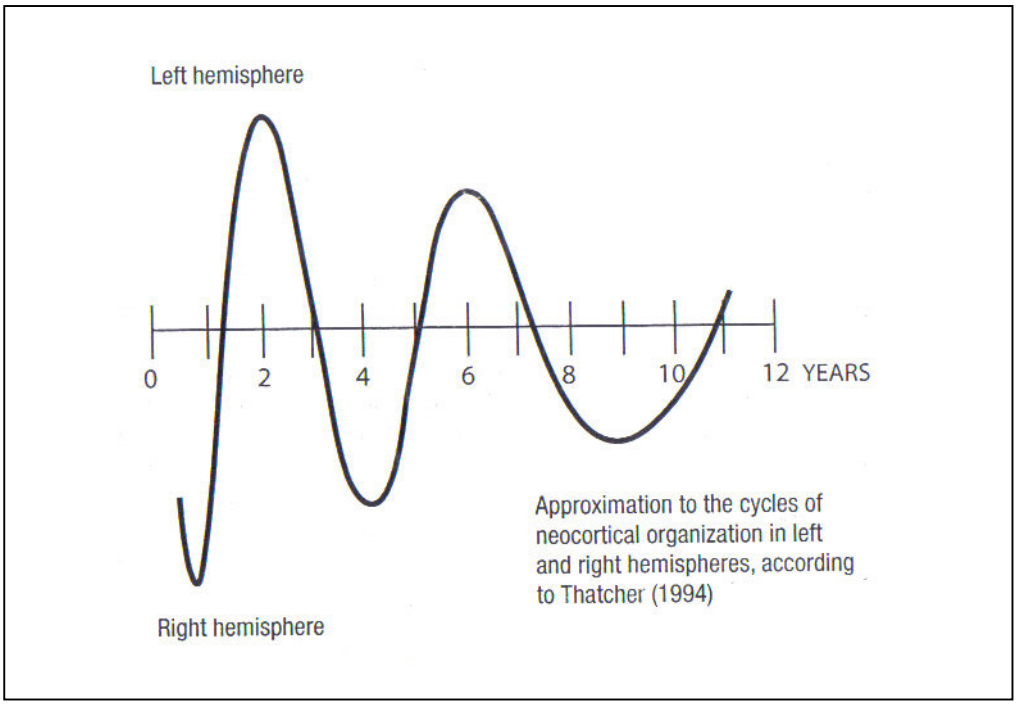


Figure 3.2.3. Asymmetrically hemispheric brain growth cycles in childhood. Figure adapted from *Thatcher, R.W. Cyclic cortical reorganization: origins of human cognitive development. In: Thatcher, R.W./ Human behavior and the developing brain. New York: Guilford Press; 1994. p. 232-266 (67).*

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:

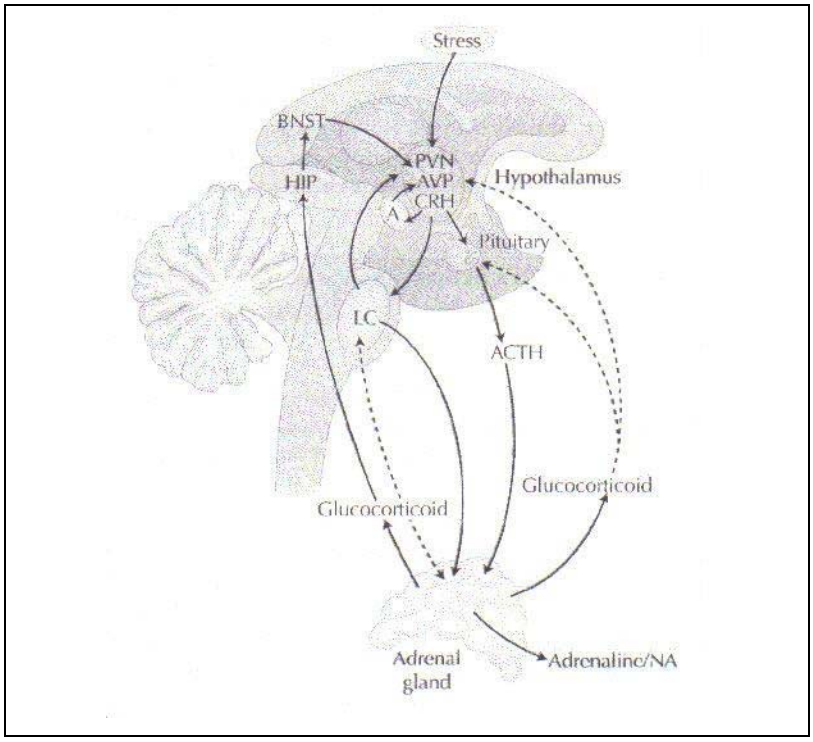


Figure 3.4. HPA axis modulation of the stress response. **Abbreviations**: A, amygdala; ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; BNTS, bed nucleus stria terminalis; CRH, corticotropin- releasing hormone; HIP, hippocampus; LC, locus coeruleus; NA, noradrenalin; PVN, paraventricular 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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CHAPTER 2
MATERIALS AND METHODS

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1. Introduction

All the methods used in the study, physiological as well as psychological, will be dealt with in this chapter. Before the onset of the study it was necessary to test the sensitivity and reliability of heart rate recordings as well as the spectral analysis of heart rate variability. The technique evaluation for this study is presented in Chapter 3. The protocol was presented to the Faculty of Health Sciences Research Ethics Committee, University of Pretoria on 21/10/2003 and accepted (ethical clearance number: S234/2003).

In this study, the psychological profile of the patients was assessed in terms of the attachment style of the patient. To achieve this objective, the Experiences in Close Relationships-questionnaire (ECR-R) was used (1). The physiological health was evaluated by means of a Patient Health Questionnaire (PHQ), gathering information on the patient's past health problems, operations and accidents. The Review of Current Symptoms-questionnaire (RCS) evaluated the patient's present health complaints. The components of health status that are believed to be most affected by fibromyalgia, (e.g. pain, fatigue and depression) were evaluated by means of the Fibromyalgia Impact Questionnaire (FIQ) (2). Neurological parameters assessed as part of the physiological profile of the patients, were hemispheric dominance and autonomic nervous system function. The Herrmann Brain Dominance Instrument (HBDI) determined whether a person prefers to think with either his left or right hemisphere, or with his cerebral versus limbic brain structures (3). Autonomic nervous system function was assessed by spectral analysis of the patient's heart rate variability. ELISA provided a way of measuring cortisol levels in the saliva (4). This gave information on the HPA-axis function of the patient.

2. Summary of tests and techniques used

I. TECHNIQUE EVALUATION (see Chapter 3)

- Technique reproducibility
- Interpersonal variation
- Intrapersonal variation
- Sensitivity and response to stressors

II. PSYCHOLOGICAL PROFILE

Experiences is Close Relationships - Revised (ECR-R)

Fibromyalgia Impact Questionnaire - depression score

Fibromyalgia Impact Questionnaire - anxiety score

III. PHYSIOLOGICAL PROFILE

Heart rate variability (HF, LF, HF/LF etc.)

Salivary cortisol level

Patient Health Questionnaire (PHQ)

Review of Current Symptoms (RCS)

Fibromyalgia Impact Questionnaire (FIQ)

Preferred mode of thinking (HBDI)

3. Experimental subjects

The study group consisted of 31 subjects:

I. Patient group: Fibromyalgia patients presently being treated. Although this could be considered a confounding factor, the purpose of this study was not to investigate the origin of the disease but the status quo, in other words, to put together a profile for fibromyalgia patients irrespective of their therapies (n=16).

II. Control group: Sex- and age-matched healthy controls (n=15).

Patients were selected and clinically evaluated by a physician from the Department of Family Medicine (University of Pretoria) who runs a fibromyalgia clinic. Fibromyalgia patients were subsequently sub-diagnosed with chronic fatigue syndrome (CFS) if they fulfilled the Fukuda diagnostic criteria for chronic fatigue syndrome (see Table 3.2.). Potential control subjects were evaluated to ensure that they did not have fibromyalgia or chronic fatigue syndrome. All subjects gave written informed consent to the experimental procedure. The inclusion and exclusion criteria are set out in Table 3.1:

Table 3.1. *The inclusion and exclusion criteria for the two study groups*

Subject group	Inclusion	Exclusion
Patient group	▪ Patient must meet the 1990 American College of Rheumatology (ACR) classification criteria for FM (see Table 3.3.) ▪ FM must have been confirmed to be present for at least 3 months	▪ Patients with any current psychiatric illnesses diagnosed in addition to FM other than mood disorders of the depressive spectrum ▪ A FIQ score less than 35
Control group	▪ Healthy persons ▪ Body mass index close to that of the patient	▪ Persons suffering from any chronic disease ▪ Persons with current psychiatric illness ▪ A FIQ score larger than 30

Table 3.2. *Fukuda diagnostic criteria for CFS*

1. Unexplained, persistent, or relapsing fatigue lasting six or more consecutive months:
   - that is of new or definite onset
   - is not substantially relieved by rest
   - is not the result of ongoing exertion
   - results in substantial reduction in previous levels of occupational educational social personal activities

2. Four or more of the following symptoms occurring concurrently:
   - impairment of short term memory or concentration
   - sore throat
   - tender cervical or axillary lymph nodes
   - muscle pain, or multijoint pain
   - headaches
   - unrefreshing sleep
   - post exertional malaise (5).

Fukuda, K./ Annals in International Medicine 1994;121:953-959 (5).

Table 3.3. *American College of Rheumatology Criteria for Classification of FM (1990)*

1. History of widespread pain (i.e., presenting at all of the following sites):
   - Right and left sides of body (including shoulders and buttocks)
   - Above and below waist
   - In axial skeleton (i.e., cervical spine or anterior chest)

2. Pain on digital palpation (performed with about 4kg of force) in 11 or more of the following 18 tender points (bilateral points at each site):
   - Occiput: at suboccipital muscle insertion
   - Low cervical: at anterior aspects of intertransverse spaces at C5-C7
   - Trapezius: at midpoint of upper border
   - Supraspinatus: at origins, above scapula spine near medial border
   - Second rib: at second costochondral junctions, just lateral to junctions on upper surfaces
   - Lateral epicondyle: 2cm distal to epicondyles
   - Gluteal: in upper outer quadrants of buttocks in anterior fold of muscle
   - Greater tronchanter: posterior to trochanteric prominence
   - Knee: at medial fat pad proximal to joint line (6).

~In this definition, low back pain is considered segment pain.

~Patient must state the palpation is painful; tenderness is not considered pain.

Ang, D./ Comprehensive therapy 1999;25:221-227 (7).

4. Psychological assessments

4.1. Experiences in close relationships (ECR-R)

4.1.1. Development and validation of questionnaire

The Experiences in close relationships questionnaire consists of 36 items reviewing the individual's 'attachment style', classifying him/her into a secure or insecure attachment group (on a scale of continuity). The questionnaire was filled out while the subject were connected to the Polar heart rate monitor (after an initial baseline recording was completed). This way the questionnaire served as a psychological stressor on the autonomic nervous system.

In early attachment research, the association between individual differences in adult attachment and people's perceptions about their relationships, and their childhood memories

about their relationships with their parents, were studied. Hazan and Shaver (1987) were the first researchers to develop an uncomplicated questionnaire to measure these individual differences (8). The simple questionnaire (based on Ainsworth observations of the 'strange situation) involved three type-descriptions that subjects had to read and indicate which paragraph describes their behaviour in close relationships best:

I. "I am somewhat uncomfortable being close to others; I find it difficult to trust them completely or to allow myself to depend on them. I am nervous when anyone gets too close, and often, others want me to be more intimate than I feel comfortable being."

II. "I find it relatively easy to get close to others and am comfortable depending on them and having them depend on me. I do not worry about being abandoned or about someone getting too close to me."

III. "I find that others are reluctant to get as close as I would like. I often worry that my partner does not really love me or won't want to stay with me. I want to get very close to my partner, and this sometimes scares people away." (8)

The work of Hazan and Shaver (1987) was useful in the study of the association between attachment styles and relationship functioning, but their questionnaire classified subjects into three attachment-style prototypes or categories. These authors did not keep track with additional work done through discriminate analysis by Ainsworth, which stated that the infant attachment types identified in her 'strange situation' should be scored on a continuous rating scale (9). Soon researchers realized that the three major attachment types could be conceptualised as regions in a two-dimensional space, the two dimensions being avoidance and anxiety. The three type-descriptions were broken up into 'agree-disagree' items, which could be factor-analysed, and then presented on continuous scales (10).

Kim Bartholomew (1991) organised these two dimensions conceptually on a two-dimensional, four-category conceptual scheme of individual differences in adult attachment and labelled the two dimensions 'model of self' and 'model of others'. The 'model of self' relates to anxiety and the 'model of others' to avoidance (11). Figure 4.1. demonstrates Bartholomew's four-category scheme:

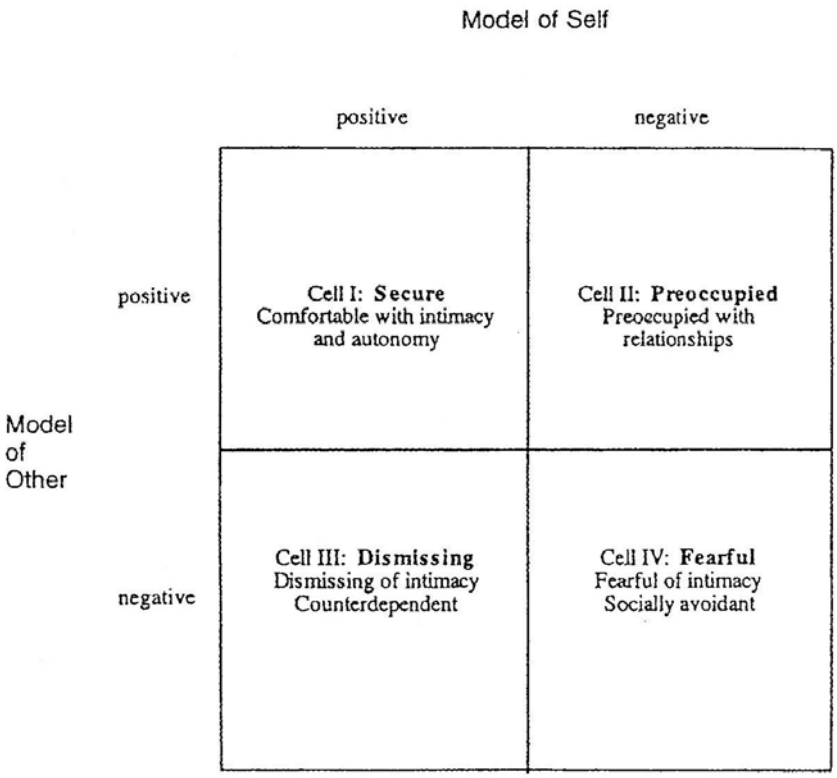

Figure 4.1.1. Bartholomew's (1990) four-category diagram. Model of self – individuals with a high score for this variable tend to be concerned about their partners' availability, attentiveness and responsiveness. A low score is associated with security in relationships. Model of other/partner – individuals on the high end of this dimension, prefer independence. Individuals on the low end tend to be more comfortable with intimacy. Figure taken from *Brennen, K.A./ Attachment theory and close relationships. New York: The Guilford Press; 1998. p. 46-76 (10).*

Brennan *et al.* conducted a large-sample study in an effort to incorporate the findings of various authors actively working on attachment into a comprehensive measuring tool. Out of a pool of 482 (extracted from attachment literature) they selected 323 items from which 60 subscales scores was computed. These subscales were factor-analysed to produce two essentially independent factors that corresponded to the 'anxiety' and 'avoidance' dimensions. After clustering subjects into four groups based on their anxiety and avoidance scores, the groups corresponded to Bartholomew's four types. These findings led to the development of a multi-item measure of adult romantic attachment called the 'Experiences in close relationships' questionnaire (10).

In this study the ECR-R was used to measure attachment as it provides continuous scores on the two dimensions, excluding true attachment typology, as there is no evidence for distinct attachment classes (1).

4.1.2. Contents of questionnaire

Table 4.1.2 includes the questions constituting the Experiences in close relationships-questionnaire (ECR-R). The fist 18 questions form the attachment-related anxiety subscale of the ECR-R (Table 4.1.2.a). Table 4.1.2.b. contains the questions forming the attachment-related avoidance subscale. During the evaluation of subjects, these two subscales are merged into a single questionnaire.

Table 4.1.2.a. *The attachment-related anxiety subscale of the ECR-R*

1. I am afraid that I will lose my partner's love.
2. I often worry that my partner will not want to stay with me.
3. I often worry that my partner doesn't really love me.
4. I worry that romantic partners won't care about me as much as I care about them.
5. I often wish that my partner's feelings for me were as strong as my feelings about them.
6. I worry a lot about my relationships
7. When my partner is out of sight, I worry that he/she might become interested in someone else.
8. When I show my feelings for romantic partners, I'm afraid they will not feel the same about me.
9. I rarely worry about my partner leaving me.
10. My romantic partner makes me doubt myself.
11. I do not often worry about being abandoned.
12. I find that my partner(s) don't want to get as close as I would like.
13. Sometimes romantic partners change their feelings about me for no apparent reason.
14. My desire to be very close sometimes scares people away.
15. I am afraid that once a romantic partner gets to know me, he/she won't like who I really am.
16. It makes me mad that I don't get the affection and support I need from my partner.
17. I worry that I won't measure up to other people.
18. My partner only seems to notice me when I am angry. (10)

Table 4.1.2.b. *The attachment-related avoidance subscale of the ECR-R*

1. I prefer not to show my partner how I feel deep down.
2. I feel comfortable sharing my private thoughts and feelings with my partner.
3. I find it difficult to allow myself to depend on romantic partners.
4. I prefer not to be too close to romantic partners.
5. I get uncomfortable when a romantic partner wants to be very close.
6. I find it relatively easy to get close to my partner.
7. It's not difficult for me to get close to my partner.
8. I usually discuss my problems and concerns with my partner.
9. It helps to turn to my romantic partner in times of need.
10. I tell my partner just about everything.
11. I talk things over with my partner.
12. I am nervous when partners get too close to me.
13. I feel comfortable depending on romantic partners.
14. I find it easy to depend on romantic partners.
15. It's easy for me to be affectionate with my partner.
16. My partner really understands me and my needs.
17. I don't feel comfortable opening up to romantic partners.
18. I am very comfortable being close to romantic partners. (10)

4.1.3. Scoring of questionnaire

The scoring criteria for the ECR-R are published in 'An item response theory analysis of self-report measures of adult attachment.' by Fraley, Waller, and Brennan (2000). The two subscales in table 4.1.a) and b) are answered on a 7-point scale where 1 = strongly agree and 7 = strongly disagree. Certain of these questions are stated in the negative, and need to be reversed before scoring. For the anxiety-related subscale the reversed questions are question 9 and 11. For the avoidance-related subscale, questions 2, 6-11, 13-16 and 18 need to be reversed. After these questions are reversed the scores (on scale ranging from 1 to 7) for each subscale are added together and divided by 18 (the number of questions in subscale). This way a mean anxiety and avoidance score is calculated for each subject. Because of the undersized study group in this study, the scores were not multiplied by the item parameter estimate as proposed when item response theory is applied in analysis (1).

5. Physiological assessments

5.1. Patient health questionnaire (PHQ)

5.1.1. Development of questionnaire

The questionnaire gathers information regarding the medical history of the patient and lists the medication presently utilised. The occurrence of a major traumatic incident, which could have been a possible trigger to the persisting symptoms, was also recorded. Various questionnaires (developed by physicians working with fibromyalgia or other diseases in the multiple subjective complaints spectrum) were combined in order to set up the PHQ. The purpose for the development and inclusion of this questionnaire in the study was to collect information regarding the demographic variables of patients.

5.1.2. Contents of questionnaire

Items on the questionnaire included the following:

- Personal information (age, weight, height, marital status, highest academic qualification, occupation)
- Current medical problems
- Past illnesses and medical problems
- Duration of fibromyalgia complaints
- Previous hospitalisations, surgeries, accidents, major psychological traumatic event with the year in which it occurred
- How fibromyalgia started. Here the patient could choose between the following responses: following an accident, operation or illness; after a time of over-exertion; gradually; without preceding provoking events; following a significant psychological stressor
- Changes in symptoms – whether it be better, more painful locations, higher pain intensity, unclear or no change at all
- Major complaint
- Description of pain
- Treatment. The patient indicated whether he/she make use of an exercise program, physiotherapy, medication, and/or non-allopathic treatment
- List of current medications
- Factors that influence symptoms. Possible factors were exercise, alcohol, stress, time of day, humidity, sleep, caffeine, season, heat, barometric pressure, certain

foods, salt, sunlight, cold. For each of these factors, the patient was expected to state whether it changes their symptoms for better or worse.

- The patient's drinking and smoking habits
- Fitness level
- Disability compensation (this item was included in the questionnaire to discern whether patients exaggerated in reporting symptoms to gain financially from disability compensation)

5.2. Review of current symptoms (RCS)

5.2.1. Development of questionnaire

The RCS-questionnaire verified which symptoms were present, as well as the extend to which patients experience these symptoms. Various internet websites were explored for clinics that treat fibromyalgia. Most of these clinics have a form available on their website that prospective patients need to complete before their treatment program begins. This way the physician can constitute a patient profile before the first appointment. All of these surveys were combined to set up a comprehensive questionnaire assessing all the possible symptoms the patients in this study could present with.

5.2.2. Contents of questionnaire

The total of 100 symptoms, commonly associated with fibromyalgia and chronic fatigue syndrome, were grouped together in categories. The 15 categories were:

- constitutional symptoms, e.g. fatigue
- skin, eyes, ears
- nose/throat
- mouth
- lymph nodes
- breasts
- respiratory symptoms
- gastrointestinal symptoms
- reproductive system function
- thyroid function and
- neuropsychiatric symptoms.

For each symptom the patient has, the patient was expected to state whether he/she experience the symptom as being mild, moderate or severe. Table 5.1 lists the 15 categories with the symptoms associated with that specific organ system:

Table 5.2.2. *The Review of current symptoms (RCS) questionnaire*

Constitutional:	**Breast:**	**Joints:**	**Thyroid:**
fatigue	lumps	ache/pain	mass or lump in neck
weight change	cystic breasts	stiff	cold or heat tolerance
fever/chills/sweats	discharge	swelling	history of x-ray to neck
appetite change	swollen		
abnormal thirst		**G.U. and Hormonal (Female):**	
difficulty sleeping	**Lungs:**		
light-headed	cough	severe menstrual cramps	**Neuropsychiatric:**
	wheezes	severe premenstrual cramps	headache (mild/ moderate)
Skin:	shortness of breath	menstrual irregularity	headache (severe)
itching	- at rest	herpes	depression/apathy
flushing	- on exertion	frequent vaginal discharge	anxiety/irritable
rashes	can't get full breath	yeast or candida infection	hyperactive
hives	hyperventilation	painful or difficult urination	learning disability
dry/rough skin	phlegm/mucus/ bronchitis	pressure/urgency/ itching	"brain fog"/difficulty concentrating
acne	chest pain on exertion	vaginal rash	mood swings
nail/hair problem	other chest pain or distress	sexual problem	suicidal
	palpitations/rapid, slow or irregular heart rate/rhythm		homicidal
Eyes:	ankle swelling	**G.U. (male):**	numbness, tingling
vision	calf pain on exercise	difficulty voiding	faints/blackouts
tearing	sore tender legs	prostate problem	seizures/convulsions
itching	high blood pressure	lump on testis	
feels heavy		sexual problem	**Gastrointestinal:**
allergic shiners	**Mouth:**	herpes	nausea
	sores/fissures		blenching, bloating, or passing gas
Ears:	herpes or frequent cold sores	**Muscles:**	heartburn or stomach pain
itching	gum/tooth problems	tight/stiff	diarrhea
hearing problem	tongue problem	ache-sore-pain	constipation
blocked ears		- neck	cramps or aches
ringing in ears	**Lymph nodes:**	- shoulder	rectal pain or itching
sensitive to sounds	swollen	- upper back	blood or black stools
dizziness/vertigo	sensitive	- low back	worms or parasites
		- extremities	
Nose/Throat:		weakness	
stuffed/runny nose			
postnasal drip			
sore throat			
tight/swollen throat			
hoarse voice			
trouble swallowing			

5.2.3. Scoring of questionnaire

For each subject, the average response to each symptom, average number of symptoms in an organ category, total number of symptoms, and the most severe symptoms, were calculated.

5.3. Fibromyalgia Impact Questionnaire (FIQ)

5.3.1. Development and validation of questionnaire

Burckhardt, Clark & Bennett (1991) developed the Fibromyalgia Impact Questionnaire (FIQ) to be utilized as an assessment and evaluation instrument, measuring fibromyalgia patient symptom status, progress and outcome (2). This brief, self-administered instrument has been designed to measure the components of health that are most affected by fibromyalgia. The FIQ is composed of 10 items, providing scores for physical impairment, well-being, work status, pain, fatigue, stiffness, sleep, anxiety and depression. The items for the questionnaire were derived from clinical interactions with patients, publications on the major characteristics of the syndrome and from existing rheumatology health status instruments like the Health Assessment Questionnaire (HAQ) and the Arthritis Impact Measurement Scales (AIMS) (12,13).

In 1991 Burckhardt *et al* published an article on the validation of the FIQ (2). The AIMS were chosen as the comparison instrument of the psychometric properties of the FIQ as it is a thorough instrument (both psychometrically and clinically) for measuring health status in rheumatic disease; and is more comprehensive than the HAQ. The objectives of the authors to determine the reliability, content validity and construct validity of the FIQ, were met in the following way:

- Reliability (which items of the AIMS yielded valuable information in patients with fibromyalgia)

  The percentage of patients signifying impairment in response to each of the physical function items in the AIMS, were calculated. A cut-off criterion of > 25% impairment responses were set to indicate a valid item.

- Content validity

  The percentage of missing data was calculated.

- Construct validity

  After evidence was gathered for the construct validity of the AIMS and FIQ respectively, correlations were done between the two instruments by associating measures of symptom severity and comparable scales. The authors also attempted to establish whether the 11 sub-items of item 1 would lead to one single factor.

The authors ascertained that the FIQ has test-retest reliability, that there are significant correlations between the items on the FIQ and the comparable scales of the AIMS (indicative of convergent construct validity), and that the content of the instrument is relevant to the syndrome (2).

5.3.2. Contents of the questionnaire

Each of the ten items has a maximum score of 10, with a higher score indicating a greater impact of the syndrome on the patient. The average fibromyalgia patient usually scores about 50, severely afflicted patients 70 plus (the maximum possible score is 100). The questions asked in the FIQ are listed in the following table:

Table 5.3.2. *The Fibromyalgia Impact Questionnaire (FIQ)*

1. Were you able to:
   - Do shopping?
   - Do laundry with a washer and dryer?
   - Prepare meals?
   - Wash dishes/cooking utensils by hand?
   - Vacuum a rug?
   - Make beds?
   - Walk several blocks?
   - Visit friends or relatives?
   - Do yard work?
   - Drive a car?
   - Climb stairs?

Patients were expected to answer these questions on a scale ranging from 0 (always) to 3 (never).

2. Of the 7 days of the week, how many days did you feel good?
3. How many days last week did you miss work, because of fibromyalgia?

For questions 2 and 3, patients had to encircle the number of days ranging from 0 – 7.

4. When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework?
5. How bad has your pain been?
6. How tired have you been?
7. How have you felt when you get up in the morning?
8. How bad have your stiffness been?
9. How nervous or anxious have you felt?
10. How depressed or blue have you felt?

Questions 4 to 10 were answered by indicating the severity of the problem on a 100mm horizontal visual analog scale ranging from 0 to 10 (2).

5.3.3. Scoring criteria

Table 5.3.3. *The scoring criteria for the FIQ*

No.	Scale	Items	Recode	Score range	Normalization
1	Physical impairment	11	No	0 – 3	Raw score * 3.33
2	Feel Good	1	Yes	0 – 7	Raw score * 1.43
3	Work Missed	1	No	0 – 7	Raw score * 1.43
4	Do Job	1	No	0 – 10	None
5	Pain	1	No	0 – 10	None
6	Fatigue	1	No	0 – 10	None
7	Rested	1	No	0 – 10	None
8	Stiffness	1	No	0 – 10	None
9	Anxiety	1	No	0 – 10	None
10	Depression	1	No	0 – 10	None (2)

The questionnaire is scored in the following manner:

I. The physical functioning scale is made up by the first 11 questions, assessing the patient's ability to perform large muscle tasks. As mentioned above, each of the 11 questions is rated on a 4-point Likert type scale: 0 – always, 1 – most, 2 – occasionally or 3 – never. These scores were then summed. Since it is possible that the patient do not do a specific task at all (not because of impairment caused by fibromyalgia), the patients were given the option to delete the questions that is not applicable. The summed score was then divided by the number of questions answered. The highest possible score for the physical functioning scale is 33. The raw score was normalized (to count out of 10) by multiplying it by 3.33 (see Table 5.3.3.).

II. The score for item two needed to be reverse so that the higher number indicated impairment. The reversed score was then multiplied by 1.43 (see Table 5.3.3.).

III. This score was also normalized by multiplying it by 1.43 (see Table 5.3.3.).

IV. The items 4 – 10 are visual analogue scales marked in 10 increments on which the patients marked the severity of their pain, fatigue, stiffness, anxiety and depression. No normalization needed to be done for these items as the scale already ranges from 0 – 10 (2).

6. Neurological assessments

6.1. Herrmann Brain Dominance Instrument

6.1.1. Background on the assessment of hemispheric dominance

The scientific techniques occasionally used to assess hemispheric dominance include electro-encephalograph measures (EEG), tachistoscope measures, eye movements, dichotic listening and self-administered questionnaires (14). A short description of each technique and the principle it relies on, is presented in Table 6.1.1. Naturally the assumption can be made that physiologically based testing would be the most reliable in hemispheric dominance assessment, but this assumption is not necessarily correct. EEG recordings probably provide the most dependable measurement tool, but could not be used due to a lack of accessibility to the EEG apparatus and expertise to perform the recordings. The other measurement instruments presently being employed have their own limitations (see Table 6.1.1.a).

The practice of assessing an individual's tendency towards right- or left-brain laterisation is common in the corporate sector (in the process of personal selection and training). The validity of these techniques for the measurement of hemispheral laterisation is not well established, though. A couple of self-administered questionnaires have been developed that seems to perform just as well as physiological measures (Table 6.1.1.b). From a financial point of view, as well as availability of instrumentation, these questionnaires offer the most feasible option for the testing of hemispheric dominance. Reviewing the self-administered questionnaires available to assess hemispheric dominance, the Herrmann Brain Dominance Intrument (HBDI) was noticeable the best alternative for reasons that will become apparent in Section 6.1.2.

Table 6.1.1.a *Different techniques for the study of laterisation*

Dichotic listening	
Description	**Principle**
Using stereo-phonic earphones, different sounds (tunes or words) are sent to either the left or the right or both ears simultaneously. The respondent then needs to perform a certain task in response to the signal (14).	Information sent to the one ear will be processed with the opposite hemisphere. For instance: Tunes sent to the left ear seems to be recognized better than tunes sent to the right ear (15). Only a limited number of studies attempted to cross-validate this technique to other measures of hemispheral dominance (14).

Table 6.1.1.a *Different techniques for the study of laterisation – continued*

Electro-encephalographic measures (EEG)	
Description EEG recordings provide a method for the psycho-physiological measurement of the electrical activity of the brain. By placing electrodes on the unopened scull, it is possible to signify variations in brain potential. In studies assessing hemisphere laterisation, electrodes are placed on the left and right frontal region, as well as on the left and right rear side of the scull (14).	**Principle** During rest, the brain exhibits alpha waves from 7 – 12 Hz, where as cognitive activity generates beta waves from 12 – 24 Hz. In the experimental setup, the subject will be asked to perform a certain task, and if the individual is relying more on the on hemisphere than on the other, it will be evident in the electrical activity of that specific brain hemisphere/quadrant. Increased beta waves in this particular hemisphere will be indicative of the individual's preference towards a specific hemisphere (14,15,15).
Tachistoscope measures	
Description A respondent is expected to fix his attention on a particular point. Information is then brought into either the left or the right visual field. Afterwards the respondent is supposed to tell what he saw (what the test material was) (14). This technique was first used by Sperry (1973) in split-brain studies (16).	**Principle** The tachistoscope relies on the principle of human vision that when an object appears in the one visual field (whether is the left or the right), the information is initially transferred to the opposite hemisphere (15). This measure is not that reliable though, because normal individuals will probably transmit the information from the one hemisphere to the other shortly after the initial exposure to the visual field (14).
Eye movements	
Description Different types of questions are asked to the respondent, and his different lateral eye-movements are then observed.	**Principle** Kinsbourne (1972) recorded that with verbal type of questions, the respondents tend to move their eyes to the right, whilst other type of questions results in left lateral eye-movements (17). The validity of this method is questionable, though.

Table 6.1.1.b *Self-administered questionnaires*

Example of questionnaire	**Reference**
▪ Richardson's verbaliser-visualiser dimensions	Richardson, 1977
▪ The Hansen-Lundsgaard lateralisation index	Hansen & Lundsgaard, 1981
▪ The Donegan test	Donegan, 1979
▪ The Herrmann brain dominance instrument (HBDI)	Herrmann, 1979

6.1.2. Development and validation of the Hermann Brain Dominance Instrument

Ned Herrmann, the father of the Herrmann brain dominance instrument, spent 30 years in active research to develop the instrument. In his search for a way to measure brain dominance, he had two main objectives. He wanted to develop an instrument that would be able to provide a scale for measuring preference in mental functioning, similar to the model used to measure handedness. In other words, he wanted the instrument to measure and express laterisation on a continuum from left to right (18).

It is important to note that Ned Herrmann defined laterisation/ hemisphere dominance in terms of the individual's preferred thinking style or his 'preferred modes of knowing' like Herrmann called it. The specific thinking style used by an individual was determined by assessing the individual's tendency to use faculties characteristic of each hemisphere (i.e. analytic thinking for the left hemisphere or holistic thinking for the right). This way, Herrmann's second objective for the model was reached: the model had to relate measures of brain dominance to specific thinking and learning styles (3).

The first step in the development of the instrument was to find some kind of measuring device to supply the data for the individual preferences in thinking styles. Herrmann started the search by performing biofeedback experiments utilizing a bimodal EEG apparatus. In these experiments different tasks were performed to see which hemisphere was activated during those tasks (18).

The success with the initial biofeedback experiments led to comprehensive EEG research, referred to as the 'Berkeley brain tests' where a 'mind mirror', providing an analogue display of the frequency states in both hemispheres at once, were also used in conjunction with the digitised autogenic EEG apparatus (14,18). The initial results were confirmed but this method still did not offer an ideal way in which individuals could be tested (for practical and financial reasons).

This was the motivation to develop the instrument in the form of a questionnaire, the items of which were validated with EEG-measures and factor-analised to determine what factors explained the correlations among different items. The instrument was cross-validated with selected psychological tests (19). In this factor-analytical study, seven factors were extracted from the 18 variables (16 factors from the psychological tests and the left and the right score from the HBDI profile). The correlations between these 16 factors and the left and right score of the HBDI were all under 0.4 except for the 'sensing-intuition' and the judging-perceiving' score of the Myers-Briggs instrument (14,19).

6.1.3. Composition of instrument

The instrument is based upon a questionnaire in which subjects:

- indicated their preferred job activities out of 60 alternatives;
- selected eight self-descriptive items among 25 possibilities;
- reported on preferred hobbies from 23 alternatives;
- had to choose among 24 self-descriptive adjective pairs;
- had to rate 20 Likert-type self-descriptive items;
- indicated their own perception of their degree of introversion vs. extroversion
- reported handedness
- had to indicate whether they have tendencies towards motion sickness (3,14).

6.1.4. Scoring of the instrument

In this study, the scoring of the instrument involved that the subject's responses to the questions above were captured with software provided by Ned Herrmann International (Africa). The data were then sent to Ned Herrmann International USA to be scored in a standardized, rather complicated manner. Only the patients' responses were scored because of insufficient funds. The patients' brain profile scores was then compared to data obtained from over 500 000 scored HBDI surveys (published in 'The Creative Brain' by Ned Herrmann).

The HBDI determined the subjects' tendency towards right versus left hemisphere, and cerebral versus limbic brain structure thinking. An individual's thinking style were described in terms of a score for each one of the following quadrants: the so-called cerebral left, cerebral right, limbic left and limbic right (each one of these quadrants is referred to as quadrant A, quadrant D, quadrant B and quadrant C respectively). In addition to the

quadrant scores, percentages for the left and right hemisphere (mode) as well as the cerebral and limbic structures were calculated by adding the scores for quadrant A and B together for a 'left mode' value; quadrant C and D together for a 'right mode' value; quadrant A and D for a cerebral structure value; and B and C for a limbic structure value. The scores for each quadrant were drawn in a figure like the one shown in Figure 6.1.4. In the figure it is suggested that a total of 27 different individual types can be distinguished based on the scores for each quadrant/dimension (3). These types of profiles are referred to as 'generic codes' or 'profile codes'.

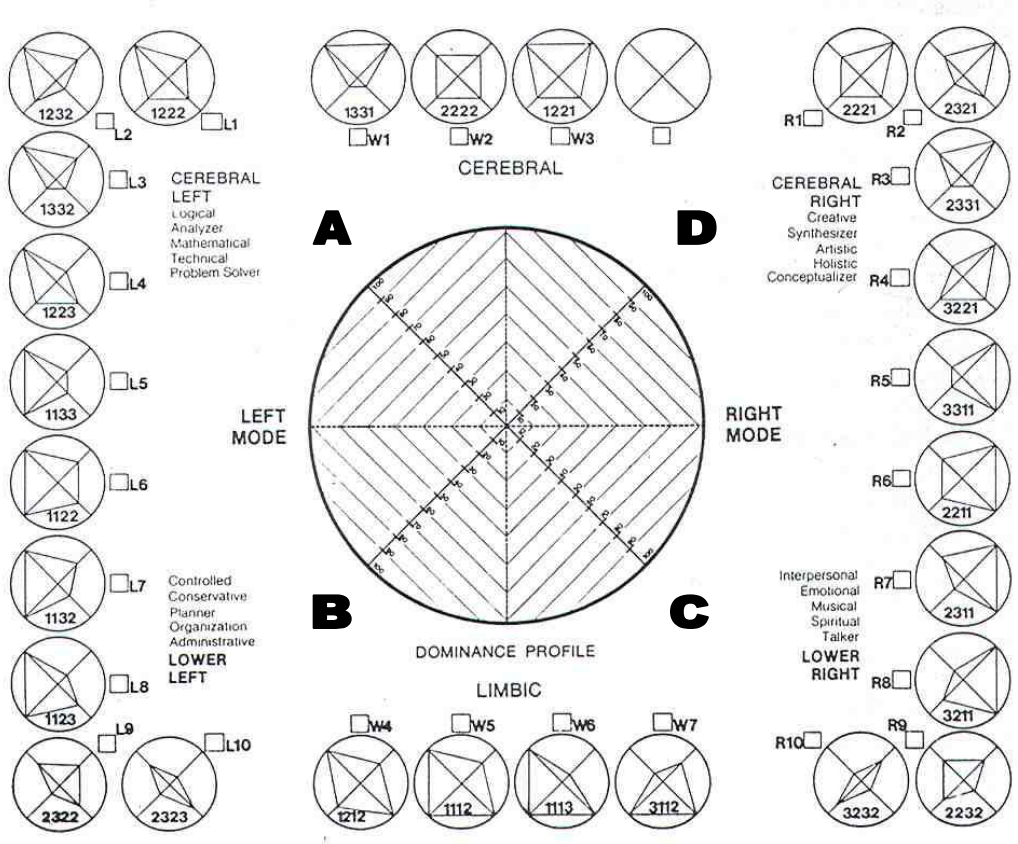

Figure 6.1.4. Scoring scheme for the Herrmann brain dominance instrument. Typical examples obtainable from the four HBDI quadrants are shown around the central scoring scheme. Abbreviations: **A**, quadrant A; **B**, quadrant B; **C**, quadrant C; **D**, quadrant D. Figure taken from *Hansen, F./ Journal of Economic Psychology 1984;5:49-70 (14).*

Generic codes are described by various combinations e.g. 2-1-3-1, 2-1-1-1 or 3-2-1-1 (as seen in Figure 6.1.4.). These combinations are representative of the four HBDI quadrants in the following arrangement: A-B-C-D ('A' referring to quadrant A, 'B' to quadrant B, 'C' to quadrant C and 'D' to quadrant D). In these combinations a '1' indicates a primary (very strong) preference, which means that the person obtained a score of 67 and higher for the specific quadrant. A '2' refers to a secondary preference (intermediate), with scores

between 34 and 66 for the particular quadrant. '3' is a tertiary (low) preference, indicative of scores less than 34. Thus, the generic code 3-2-1-1 actually means: quadrant A (low preference) – quadrant B (intermediate preference) – quadrant C (very strong preference) – quadrant D (very strong preference).

An interesting feature of the HBDI is the score calculated for what is referred to as 'adjective pairs'. This score is calculated from a range of responses on the questionnaire where the person is forced to choose between adjective pairs of self-descriptive words. In other words, the person must select the word (from the adjective pair) that he/she feels describe him/herself the best, even if the person feels that he/ she doesn't relate hundred percent to that word. Apparently this score, also expressed in terms of the four HBDI quadrants, is an indication of how a person will react or behave in stressful situations.

Before the onset of the study the MSc candidate underwent training in the administration of the HBDI as well as in the interpretation of the results obtained by the instrument.

6.2. Heart rate variability

6.2.1. Heart rate variability (HRV)

The technique evaluation for the recording and analysis of R-R intervals (heart rate variability) were completed before the onset of the fibromyalgia study. During the technique evaluation, technique reproducibility, interpersonal variation, intrapersonal variation and the technique's sensitivity in response to stressors were evaluated. The technique evaluation can be found in Chapter 3. The physiological basis as well as the mathematical analysis of heart rate variability is also discussed in that chapter.

6.2.2. The recording of R-R intervals

R-R intervals were recorded using the Polar S810 Heart Rate Monitor. The recording itself relies on a few simple steps:

- The transmitter is put around the subject's chest after a water-based gel had been applied to the electrodes.
- The wrist receiver is put around the subject's wrist.
- With the press of the OK button on the wrist receiver the subject's heart beat per minute are displayed on the screen.
- With a second press of the OK button, the stopwatch and exercise recording start.

During the first session, basal recordings were done, followed by a physical stressor (subject lied down, sat upright, and were then required to stand up). On the second study day, a basal recording was done followed by a psychological stressor (subject was required to fill out the attachment (ECR-R) questionnaire whilst connected to the monitor).

To terminate the recording, the stop button was pressed. The stopwatch and other calculations stopped. The heart rate measurement continued until the stop button is pressed a second time. The exercise data could then be downloaded to the computer by means of an interface using an infrared connection.

6.2.3. Analysis of data

The procedure followed in the analysis of the R-R interval data are set out in Chapter 3. Similar to the technique evaluation, data was analysed with advanced HRV Analysis Software 1.1, developed by The Biomedical Signal Analysis Group, University of Kuopio, Finland. Time- and frequency domain parameters were then calculated at five-minute intervals. Each 30-minute recording period were segmented into ten-minute segments, separating supine, sitting, standing and ECR-R recordings. In the frequency domain, only fast Fourier analysis was used to study the sympathetic-parasympathetic balance and the amount of variability in heart rate, since the technique evaluation proved it to be more reliable than autoregression transformation analysis.

The variables applicable to the assessment of autonomic balance and the amount of variability were:

- Time domain results:
  - mean heart rate (HR)
  - standard deviation of the mean heart rate (mean HR (STD)
- Frequency domain results:
  - low frequency (LF)
  - LF normalised units
  - high frequency (HF)
  - HF normalised units
  - LF/HF ratio
  - total power.

These parameters are described in detail in chapter 3.

7. Endocrinological assessment (salivary cortisol)

7.1. Enzyme-linked immunosorbent assay (ELISA)

7.1.1. Salivary cortisol

The cortisol level in saliva represents the concentration of biologically active free cortisol (4). As no venous puncture had to take place by drawing blood, the DRG Salivary Cortisol ELISA (purchached from AEC Amersham (PTY) LTD) provided a reliable method for the determination of free cortisol. This way the stress experienced by the subjects was minimised, and dependable values could be obtained for the level of cortisol.

7.1.2. Saliva collection

During the day, there is fluctuation in cortisol levels, with the highest level in the morning and the lowest level at night (20). For this reason, samples were taken at the same time of the day and the exact time the samples were taken was recorded to be able to take circadian rhythms into account. Each subject delivered ±10 ml of unstimulated saliva into a sterile centrifuge tube. The saliva was centrifuged at 3500 rpm for 10 min at 4 ˚C, the clear supernatant removed and stored at –70 °C until use.

7.1.3. The assay

7.1.3.1. Principle of the test

The solid phase enzyme immunoassay for cortisol is based on the competition and microplate separation principle. An unknown amount of cortisol present in the sample and a fixed amount of cortisol conjugated with horse-radish peroxidase (HRP-cortisol) compete for the bindings sites of a polyclonal cortisol-antiserum, coated onto the wells of the microstrips. An hour incubation time follows. Once the competitive immuno-reaction has occurred, the microtiterplate is washed to stop the competition reaction. After the substrate solution is added, the HRP-cortisol fraction bound to the antibody in the solid phase is converted to a blue compound. The cortisol is inversely proportional to the optical density of this compound measured at 450 nm (4).

7.1.3.2. Validity of method

AEC Amersham LTD evaluated their technique for determining salivary cortisol by means of ELISA by calculating the specificity, precision and accuracy of the test and finding a lower limit of detection (4).

-

Specificity

The specificity of the DRG Cortisol kit was assessed according to Abraham's method. The specificity of the kit for corticosterone is 29.0%, 60.0% for prednisolone, and 100.0% for cortisol.

- Precision

  The inter assay variation coefficient for a sample size of 19 is 5.88% and 4.73% for n = 21.

  The intra assay variation coefficient for a sample size of 18 is 5.14% and 3.65% for sample size of 20.

- Accuracy

  The accuracy of the assay was evaluated by recovery and dilution tests. The recovery tests proved that the kit's percentage recovery (depending on the concentration cortisol) ranges from 98.6 to 107.7%. According to the dilution test the percentage recovery ranged from 91.2 to 107.8%.

- Lower limit of detection

  The lower limit of detection is defined as the cortisol concentration given by the mean absorbance of the zero calibrator minus two standard deviations. It has been found to be approximately 1.14 ng/ml (3.14 nmol/l) (4).

7.1.3.3. Assay procedure

Table 7.1.3.3. *The ELISA procedure*

1.	Bring all reagents to room temperature.
2.	Leave sufficient strips in the strip holder to enable the running of standards, controls and samples in duplicate, plus one well for chromogen blank. Place the remaining strips and the desiccant into the transparent plastic pouch and seal it properly.
3.	Pipette 50 µl of standards and samples into the appropriate wells of the strips.
4.	Add 250 µl of HRP-cortisol conjugate to each well in sequence.
5.	Incubate for 60 minutes at room temperature without covering the plate.
6.	Washing: discard the incubation solution, rinse the wells three times with the washing solution, and remove any residual
7.	Promptly pipette 100 µl of the chromogen/substrate mixture into the rinsed wells.
8.	Incubate for 15 minutes at room temperature.
9.	Stop the reaction by pipetting 100 µl of stop solution into the wells with the same sequence adopted to dispense the chromogen/substrate mixture.
10.	Shake the microplate gently, being careful not to let the content come out from the wells and read at 450 nm within 30 minutes from stopping.

7.1.3.4. Calculation of results

The cortisol level of each sample was then obtained as followed (4):

$$B/Bo * 100 \quad \frac{A - Ac}{Ao - Ac} \quad * 100$$

- The mean absorbance of the standards and the samples (A) were calculated.
- The absorbance of the chromogen blank (Ac) was subtracted from all the means.
- Then, the corrected mean absorbance obtained was divided by the corrected mean absorbance of the zero calibrator (Ao), and multiplied by 100.
- A standard curve was constructed by plotting the average absorbance of each reference standard against its corresponding concentration. The average absorbance of each serum sample was used to determine the cortisol concentration value by simple interpolation from the standard curve. The cortisol concentration was calculated in ng/ml, and this value was then compared to the normal controls as well as normative values for the time the samples were taken.

8. Statistical calculations

Statistical calculations (descriptive and inferential) for each of the evaluations mentioned above were done in collaboration with staticians from the Department of Statistics, University of Pretoria. Descriptive statistics involved the generation of contingency tables as well as the calculation of means and standard deviations for all the respective variables. Inferential statistical estimates provided p-values for the differences between the patients and controls. Finally, Pearson coefficients (correlations) and model R-square estimations (obtained through regression analysis) were calculated to aid in setting up a psychoneurological profile for the fibromyalgia patients.

9. Schematic representation of daily procedures

Diagnosis of patient (ACR classification 'tender point' assessment)

Evaluation of control (according to inclusion criteria)

↓

Study Day 1:

- Saliva sample taken (for patient and control group)
- Explanation of protocol and informed consent to subject
- Heart rate variability recording (HRV):

  Physical stressor:
  - 10 minutes supine
  - 10 minutes sitting
  - 10 minutes standing
- Explanation of questionnaires (HBDI, PHQ, RCS, FIQ) – filled out in own time

↓

Study day 2:

- Heart rate variability recording (HRV):

  Psychological stressor:
  - 10 minutes supine
  - 10 minutes sitting
  - 15 minutes filling out ECR questionnaire
  - 10 minutes supine
- Patient hand back completed questionnaires

Patients were visited at their homes to minimize stress and discomfort.

The questionnaires were completed in the patient's own time, and collected on the final study day.

All the evaluations were done during a 07:30 to 9:00 timeslot. The precise time each determination was done, were recorded on the following sheet:

PATIENT PROTOCOL

Patient no:…….
Date:…….

Session 1

				Time allocated	Time
1. Introduction				5 min	:
2. Saliva sample				10 min	:
3. Heart Rate Variability	Supine: (10:00)	BP	Pulse		:
	Sit: (10:00)				:
	Stand: (10:00)				:
4. Questionnaires – explain each scale	Complete in own time				

Session 2

Date:…….

				Time allocated	Time
1. Introduction				5 min	:
2. Heart Rate Variability	Supine: (10:00)	BP	Pulse		:
	Sit: (10:00)				:
	ECR: (15:00)				:
	Supine: (10:00)				:
3. Review questionnaires	In own time				

(The same protocol was followed for each of the controls)

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CHAPTER 3
BACKGROUND TO HRV AND TECHNIQUE EVALUATION

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A. HEART RATE VARIABILITY

1. Introduction

1.1 The definition of heart rate variability

Blood circulation is a periodic process. The phasic nature of circulation is caused by the cyclic activity of the heart. As a heart period is the length of a heart cycle, heart rate is inversely proportional to the heart period. Instantaneous heart rate (HR) is not steady, but demonstrates continuous small fluctuations. Heart rate variability (HRV) describes the variations in the oscillations between consecutive heartbeats (RR-intervals) as well as the oscillations between consecutive instantaneous heart rates (1).

Sometimes heart rate does not change from cycle to cycle - a negative clinical sign described as a pendulum-like rhythm (2). The loss of HRV therefore serves as a prognostic marker for cardiovascular disease such as diabetic autonomic neuropathy, hypertension, myocardial infarction, and heart failure and can also be an indication of psychological illness (3).

In the first part of this chapter (section A), the physiology of HRV is discussed with regards to the mechanisms involved in the regulation of heart rate. This fundamental discussion is followed by an explanation of the origins, mathematics and different types of HRV analyses.

The second part of Chapter 3 (section B) discusses the technique evaluation of HRV analysis to be utilised in the fibromyalgia study.

2. The physiology of heart rate variability

The sinoartrial node, located at the posterior wall of the right atrium of the heart, initiates each heart beat. Spontaneous action potentials arise in the adapted myocytes in this region due to the unstable membrane potential of these cells. The physiological regulation of heart rate is complex, involving several overlapping control mechanisms, all influencing the autorhythmicity of the sinoartrial node (both directly and indirectly). The principle behind this regulation is to maintain homeostasis. That is, because various influences constantly

act on the heart, heart rate has to change in an effort to achieve and preserve stability. This ability to maintain stability through change is also referred to as allostasis (3,4).

2.1. Factors involved in the modulation of heart rate variability

Various pacemaker tissues control the intrinsic rate of cardiac contraction, which is further regulated by extrinsic factors. Examples of extrinsic influences on heart rate are changes in activity, posture, mental stress (state of arousal) and emotional stress. Intrinsic periodic factors include respiratory sinus arrhythmia, baroreceptor reflex activity, thermoregulation, neuroendocrine secretion and circadian rhythms (5). All the factors modulating the rhythm of the sinoartrial node, add variability to the heart rate signal at different frequencies (Figure 2.1)(3).

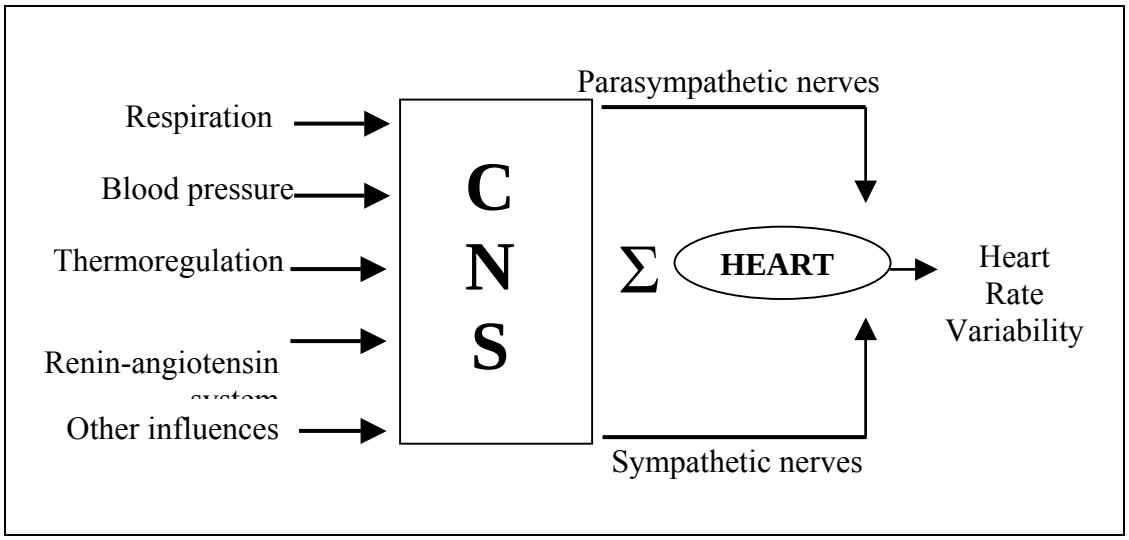


Figure 2.1. Factors affecting heart rate. **Abbreviations**: CNS, central nervous system; Σ, sum. Figure adapted from *Ori, Z./ Cardiology Clinics 1992;10:499-533 (5).*

These intrinsic and extrinsic factors are communicated to the heart mainly via the two branches of the autonomic nervous system, the sympathetic and the parasympathetic nervous system (SNS and PSN) (3). Neurohumoral regulation is especially involved in this process (6).

2.1.1. Autonomic control of the heart

The autonomic nervous system (ANS) controls the functioning of the visceral organs, blood and lymphatic vessels and smooth muscles. It interacts with the somatic nervous system and is, as illustrated in Figure 1, under the control of the central nervous system (CNS) (6).

The small fluctuations in heart rate are largely attributable to changes in autonomic input to the sinoartrial node (4), modulated by the antagonistic interaction between the SNS and PNS with each other. Both the SNS and PSN modify heart rate by altering the activity of the cyclic AMP second-messenger system in the innervated cardiac cells (7).

The two divisions of the autonomic nervous system differ with regards to their anatomic structure, functional effects and neuromediators released from the postganglionic nervous terminals. In effect, it has been suggested that the differentiation in the characteristics of sympathetically and vagally mediated heart rate fluctuations are mainly attributable to the different 'response properties of the nodal tissue to the respective neurotransmitters' (Berger, 1989) (8).

Sympathetic stimulation gives rise to increases in conductivity and contractility of the heart. These positive inotropic (force of cardiac contraction) and chronotropic (impulses increasing heart rate) effects redouble the sympathetic intensity though a process of syntaxis. It is well known that heart rate is also indirectly influenced by the sympathetic system through the release of adrenomedullary catecholamines (9). Parasympathetic stimulation results in a decreased conductivity and weaker atrial contraction (6).

2.1.1.1. Parasympathetic nervous system (PNS)

The postganglionic fibers of the PNS insert into the sinoartrial node, the atrio-ventricular node, the atrial musculature, the ventricular musculature and the coronary vessels (parasympathetic innervation of the ventricles is sparse, though) (7). Acetylcholine, released from the vagus nerve, mediates the parasympathetic influence on heart rate. Acetylcholine slows the rate of sinoartrial node depolarization and discharge by binding to muscarinic receptors, activating an inhibitory G protein that reduces activity of the cyclic AMP pathway, and in so doing, decreasing heart rate (1,6,9). Vagal stimulation is followed by a rapid response from the heart, with its maximum effect at approximately 0.5 seconds, a return to baseline within one second, followed by a slower rebound in the direction of decreasing R-R intervals (9).

2.1.1.2. Sympathetic nervous system (SNS)

The efferent nerve fibers of the SNS insert into a number of different structures within the heart e.g. the sinoartrial node, the conduction system, the atria, the ventricles and the

coronary vessels. Sympathetic influence on heart rate is mediated by the release of adrenalin and noradrenalin. Noradrenalin speeds the sinoartrial rhythm via a beta1-receptor–mediated second messenger cascade of intracellular signals (9). The result of an acceleration of the beta-adrenergic receptors is an increase in the rate of slow diastolic depolarization, accelerating heart rate (1). These impulses from the noradrenergic sympathetic nerves also inhibit the parasympathetic nervous system through the release of neuropeptide Y (a co-transmitter in the sympathetic nerve terminals) (6). Sympathetic stimulation is followed by a slower response from the heart (in comparison to parasympathetic stimulation), typified by a pure time delay of approximately one second, a maximum decrease in R-R intervals in four seconds and a return to baseline in 20 seconds (7,9).

2.1.1.3. The reciprocal action of the efferent innervation of the heart

As mentioned previously, vagal and sympathetic activity constantly interacts in the regulation of heart rate (10). In other words: at any given moment, heart rate will be determined by the balance between the inhibitory effects of the PSN and the stimulating effects of the SNS. Despite the fact that acetylcholine is rapidly hydrolysed (because of the sinus node's richness in acetylcholinesterase), and that the effect of any vagal impulse is therefore concise, vagal tone dominates and variations in heart period are, under resting conditions, largely dependent on vagal modulation (11). Parasympathetic influences most likely surpass sympathetic effects via two independent cholinergically induced mechanisms: a decrease of noradrenalin release in response to sympathetic activity, and an attenuation of the response to an adrenergic stimulus (1,6). The activity of these two branches of the ANS is coordinated by the cardiovascular control centre in the brain stem (7). It is important to note that the two branches are not always reciprocally controlled, and that they are able to vary independently, and can demonstrate coactivation and coinhibition (12).

Because the control of the heart rate is largely attributable to autonomic innervation, HRV offers a valuable tool for the assessment of autonomic nervous system function (3,13), granting information on both the sympathetic and parasympathetic nervous system as well as 'autonomic balance'.

2.1.2. Heart rate modulation by the higher control centres in the brain

The higher control centres in the brain involved in the regulation of the heart include the thalamus, the hypothalamus, the cerebral cortex, the cortical and diencephalic (innerbrain) centres, and the medulla oblongata. These centres mostly modulate heart rate, the heart rhythm and the contractility of the heart (6).

Stimulation of the thalamus results in tachycardia, which is an increase in heart rate (2). The hypothalamus is associated with the cerebral cortex and autonomic centres in the brainstem and spinal cord. It controls unconditional and conditional reflexes of vitally important functions such as breathing, circulation and metabolism. It is therefore expected that stimulation of the hypothalamus will produce variations in heart rate. Furthermore, the hypothalamus has reciprocal connections with the vasomotor centre, increasing blood pressure in response to emotions like anger (6). The paraventricular nucleus of the hypothalamus also appears to have a central role in mediating the circadian rhythm of the ANS (3). Cerebral cortex areas that have an effect on cardiac function are the anterior temporal lobe, the pre-motor and motor cortex, the cingulate gyrus, the orbital cortex, the insula and the frontal lobe. The cortical and diencephalic centers initiate cardiac reactions in response to emotional states like excitement or anxiety (6).

The vasomotor centre, comprising of the vasodilator and vasoconstrictor areas, is situated in the medulla oblongata. These areas exert their effects through the sympathetic and vagal innervation of the heart. The depressor area of the vasodilator area decreases heart rate by reducing both muscle contractility (lessening stroke volume) through vagal stimulation, and by reducing peripheral resistance (13). The vasoconstrictor area houses the pressor area, which produces a reciprocal effect to the depressor area through increased activity of the sympathetic neurons to the heart. The increased sympathetic discharge is accompanied by a decrease in the tonic activity of the vagal fibres (6).

2.1.3. Reflex control of heart rate

2.1.3.1. Respiratory sinus arrhythmia

Respiratory sinus arrhythmia (RSA) reflects the coupling between breathing and autonomic neural outflow. RSA is predominantly mediated by respiration-driven gating of parasympathetic efferent activity to the heart. Vagal efferent traffic to the sinus node occurs primarily in phase with expiration and is absent or attenuated during inspiration. The end

result is that RSA will fluctuate with the phase of respiration, e.g. cardio-acceleration during inspiration, and cardio-deceleration during expiration. Both sympathetic and parasympathetic nerve traffic fluctuate with respiration, but the time constant for changes in the sympathetic nervous system tone to affect heart rate is too long to affect heart rate at normal breathing frequencies (9). Because RSA is predominately mediated by the fluctuations in vagal nerve traffic, the respiratory frequency band, which ranges from 0.15 Hz to 0.4 Hz, can be used as an index for vagal activity (14) (the implications for HRV analysis will be discussed later).

2.1.3.2. Baroreceptor reflex

Baroreceptors are stretch receptors in the walls of the heart and the blood vessels that respond to stretching and distension. Their afferent fibres travel via the aortic and carotid sinus nerves to the medulla. The frequency at which action potentials are generated in the baroreceptor, are proportional to the changing pressure in the structure in which they are located (13). Increased baroreceptor discharge reduces the tonic discharge of the vasoconstrictor nerves and stimulates the vagal innervation of the heart, creating bradycardia (6).

In the frequency domain of power spectral analysis of HRV, baroreceptor activity is associated with the low frequency band (15). Chronic corticosterone treatment is one of the factors known to reduce baroreceptor reflex-mediated HRV (3). One can therefore perhaps expect high psychological or high physiological stress induced cortisol levels to have a similar effect.

2.1.4. Endocrine influences

Quantitative data on the time domain or frequency domain responses of heart rate to hormonal modulation is limited. However, it has been shown that thyroxine, reproductive hormones, the renin-angiotensin system, steroids and other endocrine factors have an affect on HRV (3,13). Evidence of non-autonomic control of heart rate in the time-domain or frequency domain is best surmised from HRV recordings on heart transplant patients (before sympathetic reinnervation occur). Results obtained in the time-domain on these patients suggest that hormonal heart rate control is only active at frequencies below 0.03 Hz (9). Therefore there is no need to be concerned that results obtained from HRV analysis could be biased by hormonal influences.

2.1.5. Thermoregulation

Cooling of the heart, a method used in heart surgery, causes bradycardia. Conversely, heart rate is increased by fever. Heart rate increases with 18 beats per minute per ºC increase in body temperature. Heart rate slows down in response to decreasing temperatures, until body temperatures of 15.5 ºC to 21.2 ºC are reached. At temperatures like these, the heart beats only at a few beats per minute and death as a result of hypothermia may results (6). Fluctuation in temperature is thus a significant source of changes in heart rate (3).

The effect of thermoregulation on HRV is not only achieved through ANS function. Studies have shown that both direct effects of temperature on the pacemaker activity of the sinus node, as well as indirect effects through the ANS, mediate temperature effects on HRV (3). The effects of temperature regulation on HRV should always be taken into account when the experimental set up (conditions) in which HRV experiments are to be conducted, are planned.

Applications of measures of HRV range from investigations into autonomic balance, to evaluations of cognitive development and clinical risk, to studies of fundamental links between psychological processes and physiological functions (1,16).

3. Analysis of heart rate variability data

Physicians recognized the importance of cardiac rhythms long before the emergence of modern constructs of HRV. Consequently they have been monitoring heart sounds and rhythms and noted beat-to-beat rhythms shifts related to aging, illness, and psychological states. Initially, the method for studying heart rate patterns was limited to auscultation. Yet, the technology for the quantification of the electrical activity of the heart progressed from the galvanometer, to the kymograph, to the polygraph, to electrocardiograms and now to digital signal processing systems (9).

During the last two decades researchers and clinicians started to recognise the significant relationship between alterations in autonomic nervous system activity and cardiovascular mortality. In the search for experimental data to confirm this observation, HRV analysis proved to be the most promising of all the quantitative markers for autonomic activity (1).

The R-wave in the electrocardiogram central waveform (QRS-complex) is the easiest to detect and is used to derive the HRV signal. Originally, HRV was assessed manually from calculating the mean R-R interval and its standard deviation measured over short-term (five minutes) electrocardiograms (Figure 3.a) (9). The smaller the standard deviation in R-R intervals, the lower is the HRV (16). At the present time, heart rate monitors able to record the R-wave digitally, are used (Figure 3.b).

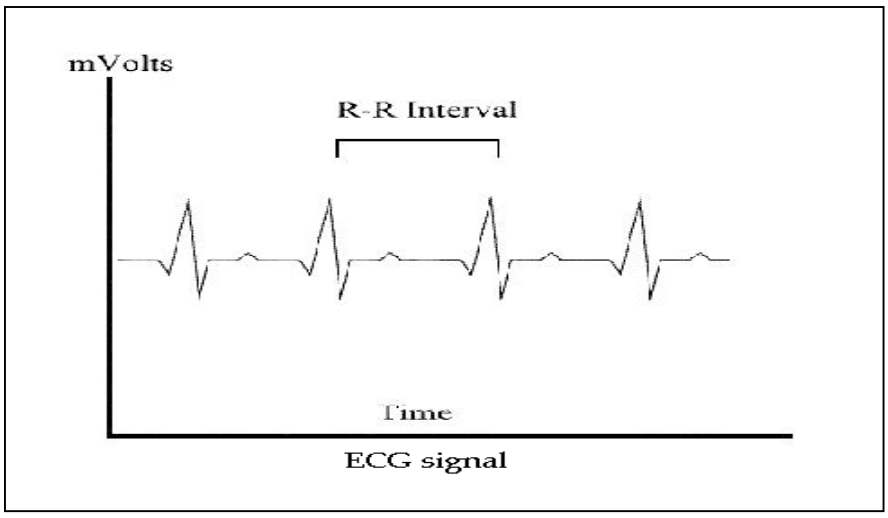


Figure 3.a. The RR-interval is derived from the electrocardiogram signal's QRS-complex

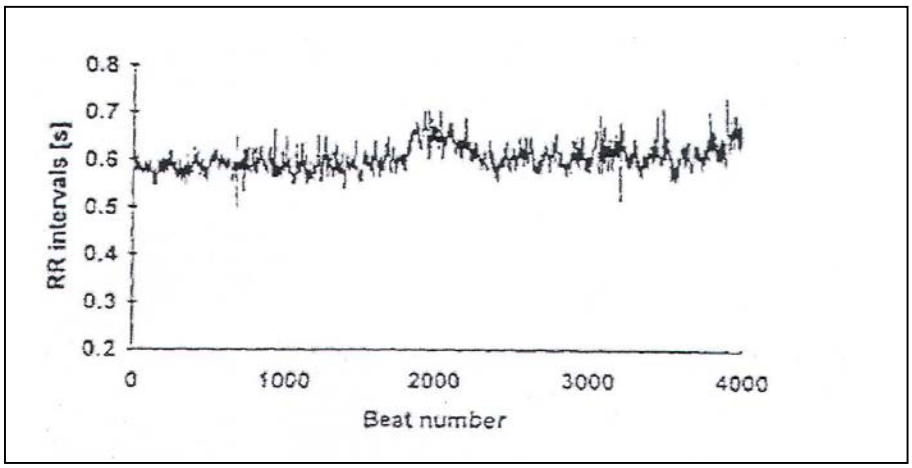


Figure 3.b. Heart rate monitors that record the RR-interval digitally produces a tachogram when the data are downloaded to a computer.

A 1996 report of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology presented a citation serving as an important step towards the standardisation of the field of HRV analysis (1). These guidelines were followed in HRV analysis in the technique evaluation and the fibromyalgia study.

3.1. Time domain analyses of heart rate variability

The time-domain parameters are the simplest of the HRV factors to calculate and includes statistical as well as geometric methods of calculation. Time-domain measures are computed from the raw R-R interval time series. In these calculations, either the heart rate at a certain point in time, or the intervals between successive normal R-R intervals are determined. Basically, this parameter measures the amount of variability. To date, over 26 different types of arithmetic manipulations of R-R intervals have been used in the literature to represent HRV (17). Table 3.1 summarises the most frequently used time domain measures.

Table 3.1. *Different time-domain measures*

Variable	Unit	Description
Statistical measures		
Mean & STD RR	s	Mean and standard deviation of the selected RR interval series (similar to SDNN)
Mean & STD HR	hr/min	Mean and standard deviation of the selected heart rate series (similar to SDANN)
RMSSD index	ms	The root-mean square of the difference of successive R-R intervals
NN50	count	Number of consecutive RR intervals that differ more than 50ms in the entire recording
pNN50	%	Percentage value of consecutive RR intervals that differ more than 50 ms
Geometric measures		
HRV triangular index		Base of the triangular area under the main peak of the R-R interval frequency distribution diagram
TINN	ms	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals
Differential index	ms	Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights
Logarithmic index		Coefficient of the negative exponential curve which is the best approximation of the histogram of absolute differences between adjacent NN intervals

Table adapted from *Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology./, Circulation 1996;93:1043-55 (1).*

Since many of the time-domain measures correlate closely with others, the Task Force of the European Society of Cardiology recommended the use the following time-domain measures:

- SDNN (standard deviation of all normal RR intervals)
  - for the estimation of overall HRV
- HRV triangular index
  - to estimate the overall HRV
- SDANN (standard deviation of the average normal RR intervals)
  - for the of the long-term components of HRV
- RMSSD (square root of the mean differences between successive RR intervals)
  - to estimate the short-term components of HRV (1,18).

3.2. Frequency Domain Analyses

The total variance in heart rate is partitioned into underlying rhythms that occur at different frequencies. In other words: HRV has a propensity to aggregate into different frequency bands, which can be associated with the different underlying intrinsic rhythms involved in the regulation of heart rate (9,13). Although HRV in the frequency domain fails to provide full information on autonomic tone, it is still able to grant valuable information regarding autonomic function. Underlying rhythms, the physiological process represented by these rhythms and the power of each of these underlying rhythms can be determined by frequency domain analyses (1,3).

The underlying rhythms in the heart rate signal are (Figure 3.2):

- High frequency bands (HF) – at respiratory frequencies (9-24 cycles/minute)/ 0.15-0.40 Hz.
- Low frequency bands (LF) – at approximately every 8-10 seconds/0.04-015 Hz.
- Very low frequency bands (VLF) – at approximately every 20 seconds to every 5-minute frequency.
- Ultra low frequency power band (ULF) – at less than every 5 minutes to once in 24 hours (10,13,14).

Figure 3.2.a. illustrates the number of oscillations for the three major rhythms of the heart and Figure 3.2.b the combined effect of these individual rhythms.

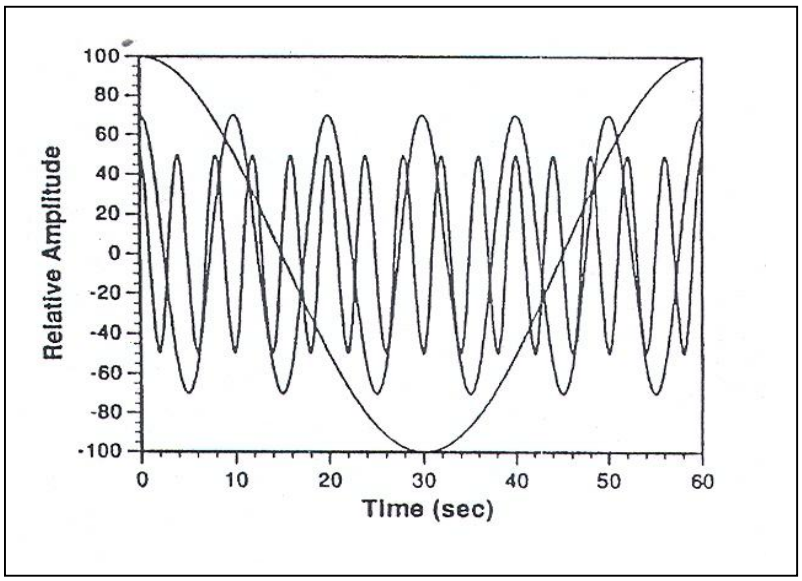


Figure 3.2.a. The number of oscillations for the three major rhythms of the heart: HF (0.25 Hz; 15 cycles/min), LF (0.1 Hz; 6 cycles/min), VLF (0.016 Hz (1cycle/min). **Abbreviations**: HF, high frequency; LF, low frequency; VLF, very low frequency; ULF, ultra low frequency. Figure taken from *Akselrod, S./ Science 1981;213:220-2 (13).*

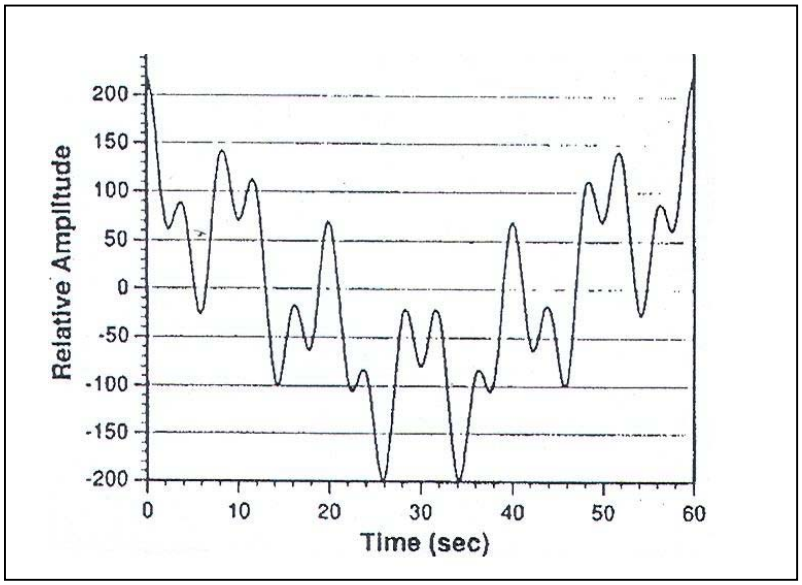


Figure 3.2.b. The combined effect of the different rhythms of the heart. Figure taken from *Akselrod, S./ Science 1981;213:220-2 (13).*

Power spectral density (PSD) is a traditional spectral practice, which provides information about power (variance) distribution as a function of frequency (1). In a PSD graph, the power of the respective spectral components is represented by the area (ms^2) under the relevant frequency curve as seen in Figure 3.2.c.

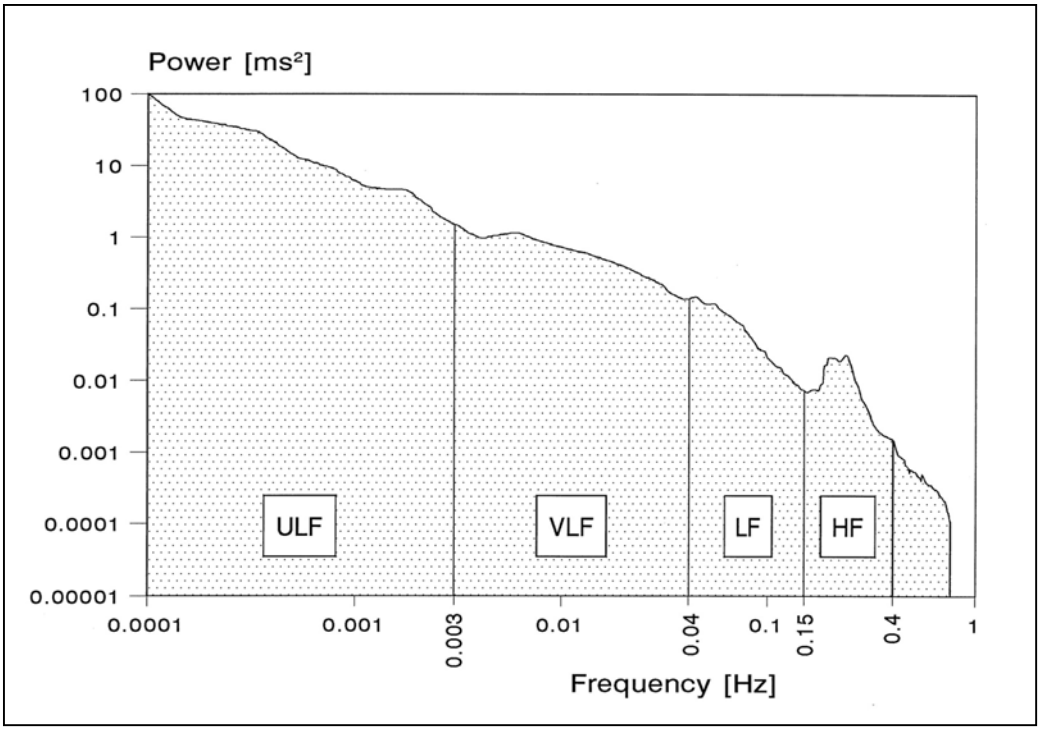


Figure 3.2.c. Power spectral density graph showing the different frequency bands. Note the frequency ranges for each frequency band: HF (0.15 - 0.4 Hz), LF (0.04 - 0.15 Hz), VLF (0.003 - 0.04 Hz), and ULF (0.0001 – 0.003 Hz). **Abbreviations**: HF, high frequency; LF, low frequency; VLF, very low frequency; ULF, ultra low frequency. Figure taken from *Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology./ Circulation 1996;93:1043-65 (1).*

Methods for PSD calculation, is non-parametric (based on fast Fourier transformations (FFT)); and parametric (based on autoregressive (AR) time series modeling) (Figure 3.2.d). The advantages and disadvantages of these methods are presented in Table 3.2.

Table 3.2. *The advantages and disadvantages of different PSD spectra*

Parametric spectrum	**Non-parametric spectrum**
Advantages Smooth spectral components Frequency bands are easy to distinguish Unproblematic post-processing Accurate PSD calculation **Disadvantage** The suitability of the chosen model order	**Advantages** Uncomplicated algorithm High processing speed (1).

needs to be verified (1).	

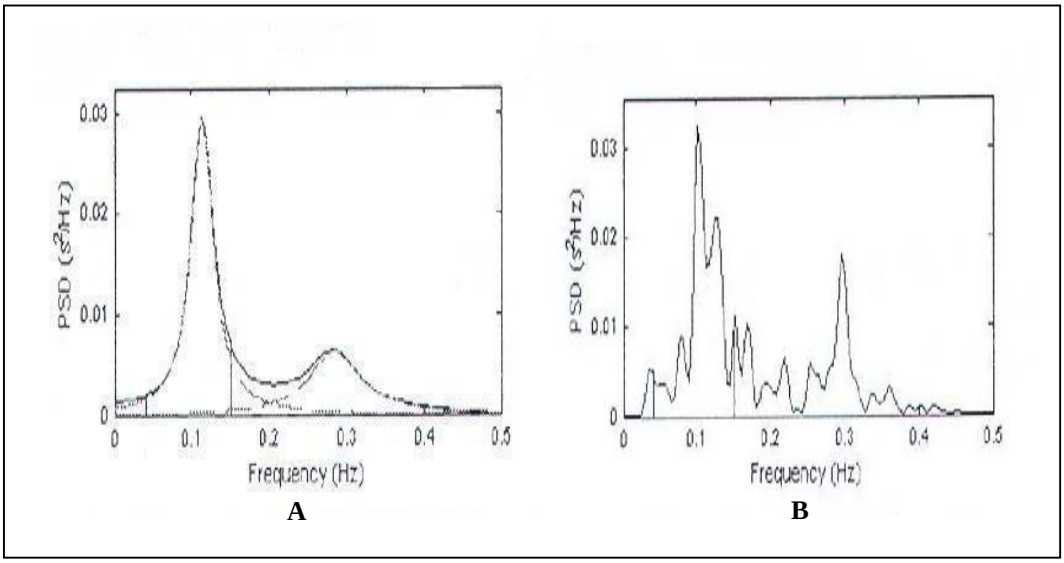


Figure 3.2.d. Power spectral density (PSD) calculated using parametric (A) and non-parametric methods (B)

3.2.1. The High Frequency Band

Spectral power in the high frequency (HF) solely reflects parasympathetic outflow (4,19) and, as mentioned before, enumerates RSA. The PNS responds over a wide frequency range, whereas the SNS only responds at frequencies below 0.1 Hz. This implies that the amount of power at high frequencies solely reflects vagal modulation of HR (amount of vagal-cardiac nerve traffic) (3).

The amount of power in the HF band is affected by the breathing rate. Figure 3.2.1. demonstrates how different breathing rates influences the maximum spectral power. Nonetheless, mean RR-intervals are nearly constant across the different breathing frequencies (refer to the right of Figure 3.2.1.). The consistency of the RR-intervals can be taken as evidence for the steadiness of vagal-cardiac traffic (20). It is thus important to note that the HF component in spectral analysis does not reflect vagal tone (3). If changes in HF power reflected changes in vagal tone, heart rate should also be affected. However, changes in HF power at different breathing rates do not affect heart rate (10). On the other hand, because HRV is derived from the electrocardiogram, it is not possible to distinguish reduced central vagal activity (in the vagal centres of the brain) from reduced peripheral activity (the contribution of the sinus node or the afferent/efferent pathways conducting the neural impulses to/from the brain) (20).

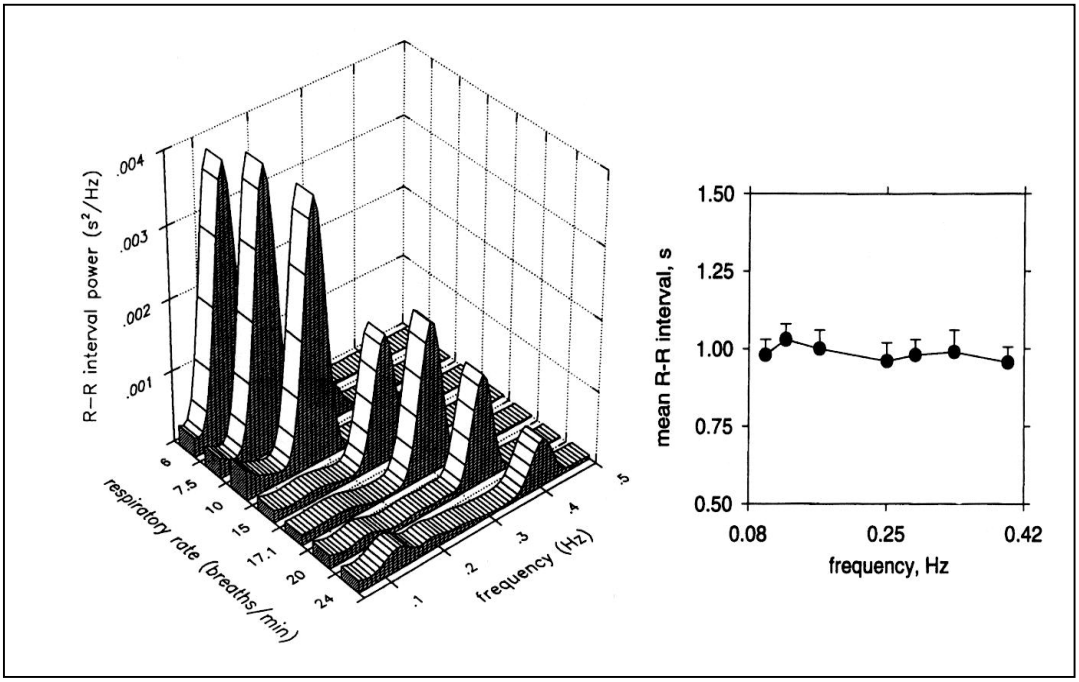


Figure 3.2.1. Average RR-interval spectral power and RR-intervals from 10 healthy supine subjects breathing at seven breathing rates. Note how the HF component changes with different breathing rates, whilst the mean R-R interval stays the same. Figure adapted from *Eckberg, D./ Circulation 1997;96:3224-32 (10).*

3.2.2. The Low Frequency band

The low frequency component (also called the mid-frequency) gives information regarding the sympathetic activity but with notable influence from the parasympathetic nervous system, baroreceptor feedback and centrally generated brainstem rhythms (3,10,13). Some researchers propose that, in order to obtain a reliable index for sympathetic activity, it is necessary to normalize the LF component (normalization are discussed in 2.2.3). They suggest that this frequency band can be used as an index of sympathetic modulation of HR with the requirement that the normalized HF power should be subtracted from the normalized LF power to exclude the parasympathetic influence from the HF component (19). However, according to the standardisation criteria set out by the Task Force of the European society of Cardiology, the LF component of HRV reflects the sympathetic activity directly (1). In this study, the LF is used as the index for sympathetic activity, like the Task Force proposed.

3.2.3. The low frequency / high frequency ratio

Since physiological intervals incite reciprocal changes in sympathetic and vagal neural outflow, it was necessary to find an index to reflect the balance between the opposing neural mechanisms. The LF/HF ratio provides a measure of sympathovagal balance, where an

increase in the LF/HF ratio reflects a predominance of sympathetic over parasympathetic activity. A decrease in LF/HF ratio would be interpreted as a shift of sympathovagal balance towards parasympathetic predominance (19). The use of this ratio as an index for sympathovagal balance remains controversial though, because of a lack of complete understanding of the low frequency component by researchers (1,10).

Power in normalized units (nu, also called relative power), is power centered at the frequency of interest (LF or HF) divided by the total power less the VLF power. Thus LF nu = LF/(LF + HF) and HF nu = HF/(LF + HF). Now, because calculations of normalized LF and HF powers involve the rearrangement of the same LF and HF terms, a change of normalized LF power must necessarily be associated with a change of normalized HF power. Sympathovagal balance (in dimensionless units) is then the ratio between the absolute LF to absolute HF power (10).

3.2.4. The very low frequency (VLF) band

VLF fluctuations are linked to changing vasomotor tone in response to localized needs (thermoregulatory or metabolic needs), activity, periodic breathing and thermogenesis. The effect of thermoregulation on the VLF HRV is already touched upon earlier in this chapter. The VL frequencies are also affected by hormonal systems, the action of the renin-angiotensin system has a dampening effect of the VLF band (3). When parasympathetic activity is blocked, VLF fades away. For this reason decreased VLF can be used as an indicator for parasympathetic abnormalities (13).

3.2.5. Ultra Low Frequency Band (ULF)

Circadian rhythms, reflected by ULF band oscillations, are significantly influenced by the ANS (21). A decrease in ULF is a strong predictor of mortality (9). The VLF and ULF rhythms of heart rate may have clinical applications and psychophysiological correlates, but these mechanisms are ambiguous (22).

3.3. Correlations and dissimilarities between time and frequency domain parameters

There are strong correlations between several time and frequency domain variables when RR-intervals are recorded over a 24-hour period (1). Although the recordings in the technique evaluation and the fibromyalgia study are rather short (30 min recordings divided

into 5 min intervals), the strong similarities in long-term recordings grant information on the mathematical and physiological interpretation of these variables. The next table (Table 3.3) compares some of these variables.

Table 3.3. *Correlations between time and frequency domain variables*

Time domain variable	**Appropriate frequency variable**
HRV triangular index	Total power
TINN	Total power
RMSSD	HF
NN50 count	HF
pNN50	HF
Differential index	HF
Logarithmic index	HF (1)

3.4. Non-linear Analyses

Poincaré plots are the simplest technique to describe non-linear components of HRV. Non-linear measures, also called 'return maps', quantify complexity and self-similarity by describing the relationship between successive samples of a time series. This relationship is described by graphing each R-R interval against the next R-R interval. The transversal axis of the poincaré plot is an indicator of the short-term variability (SD1) as the vagal induced RR-interval develops faster than those sympathetically. The longitudinal axis reflects global variability as an inverse function of sympathetic modulation (SD2) (23,24).

Figure 3.4. demonstrates how the poincaré plot pattern, time signal and power spectrum changes with five different manoeuvres: supine, controlled breathing, standing, exercise and a recovery period. The characteristic poincaré plot change pattern with each bodily manoeuvre is apparent. According to visual analysis it is firstly clear that the poincaré plot of a healthy subject is marked by an elliptic pattern (23). This pattern is larger for the supine bodily position, more scattered with controlled breathing, narrower in the standing position, and significantly smaller (reduced) during exercise. During the recovery phase, the pattern is similar to the standing pattern (24).

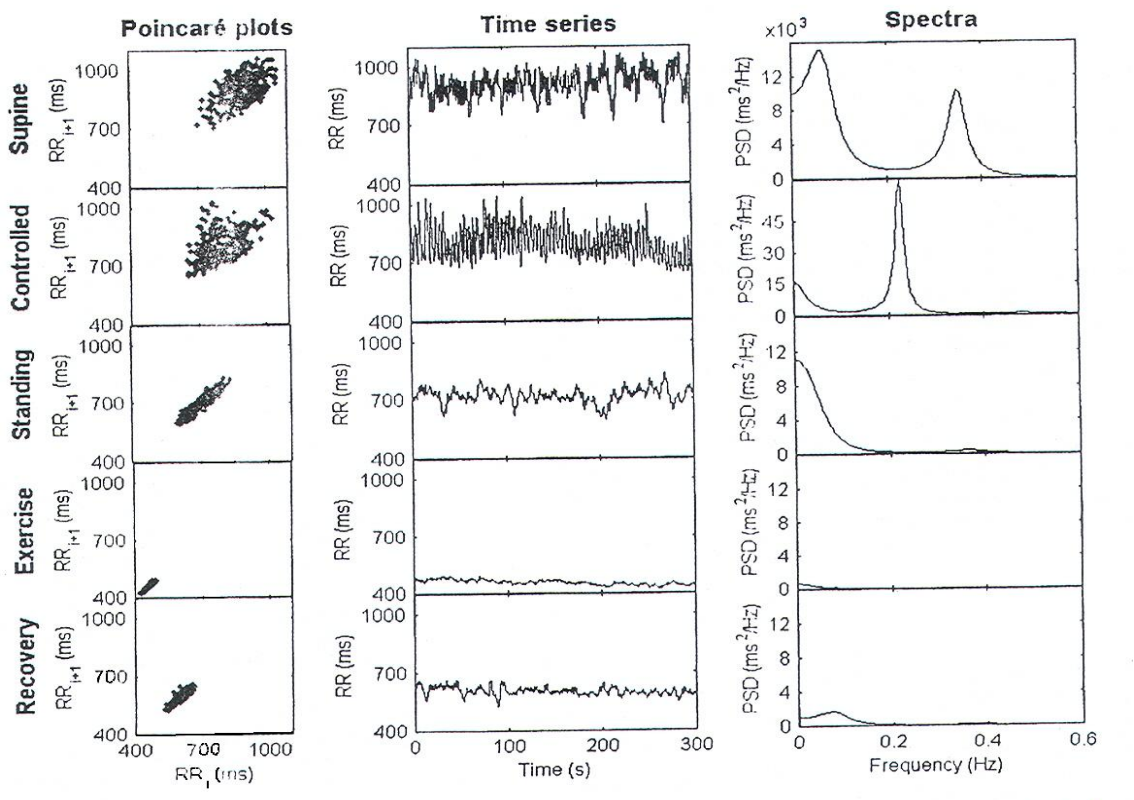


Figure 3.4. Poincaré plots, time series and spectra throughout five different manoeuvres for a representative subject. Note how the pattern is larger for the supine bodily position and recovery phase, more scattered with controlled breathing, narrower in the standing position, and significantly smaller (reduced) during exercise. Figure taken from *Woo, M.A./ Journal of the American College of Cardiology 1994;23:565-9 (24).*

Keeping in mind that the transversal axis represents the vagal, and the longitudinal axis the sympathetically induced R-R intervals, the physiological interpretation of these characteristic patterns is straightforward. When vagal and sympathetic activity are balanced (during supine position), the Poincaré plot's elliptic pattern is relatively scattered, whereas the pattern become even more dispersed when vagal modulation dominates (during controlled breathing). The elliptic pattern has a smaller dispersion with greater sympathetic influence (during exercise), with the minimum dispersion when vagal influence is suppressed in the midst of sympathetic activation (during exercise) (24).

In summary it can be said that there is a clear connection between the shape of the poincaré plot and the ANS activity. The narrower the pattern, the larger the sympathetic activity. A more scattered the plot, is indicative of increased vagal activity (23).

3.5. Filtering

Adequate removal of artifacts is critical for reasonably unbiased analysis. Most typical artifacts in HRV analysis are missed beats. The removal of missed beats does not result in any loss of information, but restores the original R-R series. The elimination of ectopic or abnormal sinus beats is more problematical though, as it involve the loss of information. To solve this problem, upper and lower bounds are placed regarding the changes in heart rate, so that R-R intervals are not allowed to vary more than 20% from their previous intervals. This can be done using an autonomic filter or RR statistics. It is thus possible to exclude outliners from analysis based on accumulated estimation of the RR probability distributions (4,19).

Tarvainen, Ranta-aho and Karjalainen (the same authors that developed the software for Advanced HRV Analysis) offered a detrending method to apply in the process of HRV analysis. This method is based on smoothness priors approach and operates like a time-varying FIR high pass filter. Using this approach, it is possible to adjust the frequency response to different situations by changing one single regularisation parameter (λ). The soothing parameter λ should be selected in such a way that the detrending does not affect the spectral components of interest significantly. For instance: if λ is adjusted properly, RSA can be successfully quantified through separation from the other frequency components of HRV (17).

Using this method, the distortion of data end points is also avoided, because the filtering effect is attenuated in the beginning and end of the data (17). The effect of detrending on time and frequency domain analysis of HRV will be demonstrated in the second part of this chapter, namely Section B.

3.6. Confounders and limitations in the interpretation of HRV and autonomic function

The significance and meaning of many of the HRV measures are rather complex. If researchers and clinicians do not recognise this, there is a potential for incorrect conclusions and unfounded extrapolations (1). Some of these pitfalls, identified through the technique evaluation for this study (section B), as well as by others workers in the field, are discussed next.

I. HRV determinations may not be meaningful in patients with a high degree of non-respiratory sinus arrhythmia (erratic sinus rhythm) (1). These cases are associated with abnormal-looking, blurred power spectral plots and exaggerated HRV.

II. HRV are affected by extrinsic factors like physical and mental activity, talking, emotions, disturbing thoughts and environmental temperatures (5). Great care needs to be taken to see to it that subjects do exactly as they are told when HRV recordings are performed so that these factors can be minimised.

III. The computation of HRV from data with more than 20% ectopic beats is ill-advised for it will not grant reliable results (1).

IV. It is important to keep in mind that a small RSA persists after combined pharmacologic cardiac sympathetic blockade and after cardiac transplantation (before autonomic reinnervation). These findings are indicative of a part of RSA not resulting from vagal activity, but possibly from an intracardiac origin (9). It is for instance known that baroreceptor reflexes contributes to RSA (12). Therefore researchers should be cautious in interpreting RSA results.

B. TECHNIQUE EVALUATION

1. Aim

The purpose of the technique evaluation was to establish whether the recording of R-R intervals with the Polar Vantage heart rate monitor and analysis of the intervals with the HRV Analysis Software 1.1 represent a reliable assessment tool for HRV to be used in this study. The technique was evaluated by determining the following:

- Technique Reproducibility (direct and indirect measures)
- Interpersonal Variation
- Intrapersonal Variation
- Sensitivity and response to stressors

Technique reproducibility was evaluated by comparing direct and indirect recordings, interpersonal and intrapersonal variation by determining the variation in HRV measures between subjects and within the same individual, and sensitivity and response to stressors by evaluating the effect of music on HRV.

2. Materials and Methods

2.1. Data collection

The R-R intervals were recorded using the Polar S810 heart rate monitor (indirect) and the Polar Advantage interface system (direct) simultaneously. HRV data recordings were made over short periods of time (20-30 min), with interventions, under carefully controlled laboratory conditions. Refer to Chapter 2 for a detailed explanation on how the Polar heart rate monitors are operated. At the end of each session, the Polar Precision Performance computer program was used to download the indirect R-R interval recordings the computer.

2.2. Experimental design

Nine healthy volunteers participated in the study. Baseline recordings, 20 minutes in duration, were obtained from each of the nine volunteers on six consecutive days. The final two recordings for each subject (day 5 and 6) consisted of a 20 minutes baseline recording followed by ten minutes of either raucous or soothing music. Participants were expected to remain in the supine position for the duration of every recording. Recordings were made on the same time of day to exclude the possible effect of circadian rhythms.

Schematic representation of technique evaluation study design
(every experimental volunteer took part for 6 days):

Day 1: → Baseline recording (20 min)
Day 2: → Baseline recording (20 min)
Day 3: → Baseline recording (20 min)
Day 4: → Baseline recording (20 min)
Day 5: → Baseline recording (20 min) + Soothing Music (10 min)
Day 6: → Baseline recording (20 min) + Raucous Music (10 min)

2.3. Analysis of the data

The process involved in the analysis of R-R intervals is set out in a flow diagram (Figure 2.3) and involves the following processes:

2.3.1. Polar Precision Performance

As soon as the R-R interval data has been downloaded, Polar Precision Performance displays the instantaneous heart rate (HR) in beats per second (bps) across time (in seconds). The first step is to change the curve properties to R-R intervals, transforming the data to a tachogram, displaying R-R intervals (in milliseconds) across time.

The importance of error correction in the analysis of HRV data has been explained in 3.5., section A (p. 3.19). Missed beats are filtered in Polar Precision with a low filter power and a minimum protection zone of 20 bpm. Data are then saved as a 'HRM'-file, which can be read by HRV Analysis Software.

2.3.2. HRV Analysis Software 1.1.

Time- and frequency domain parameters were calculated over the 20-minute baseline and 10-minute intervention-recording period using a FFT algorithm. Only the FFT based

spectrum is used in the analysis of the technique evaluation and fibromyalgia study as it gives more robust results for all data, whereas the AR spectrum, according to Tarvainen (2003), 'sometimes suffers from numerical problems and give unreasonable results' (25). HRV Analysis Software 1.1 applies the Welch's method in FFT analysis (17).

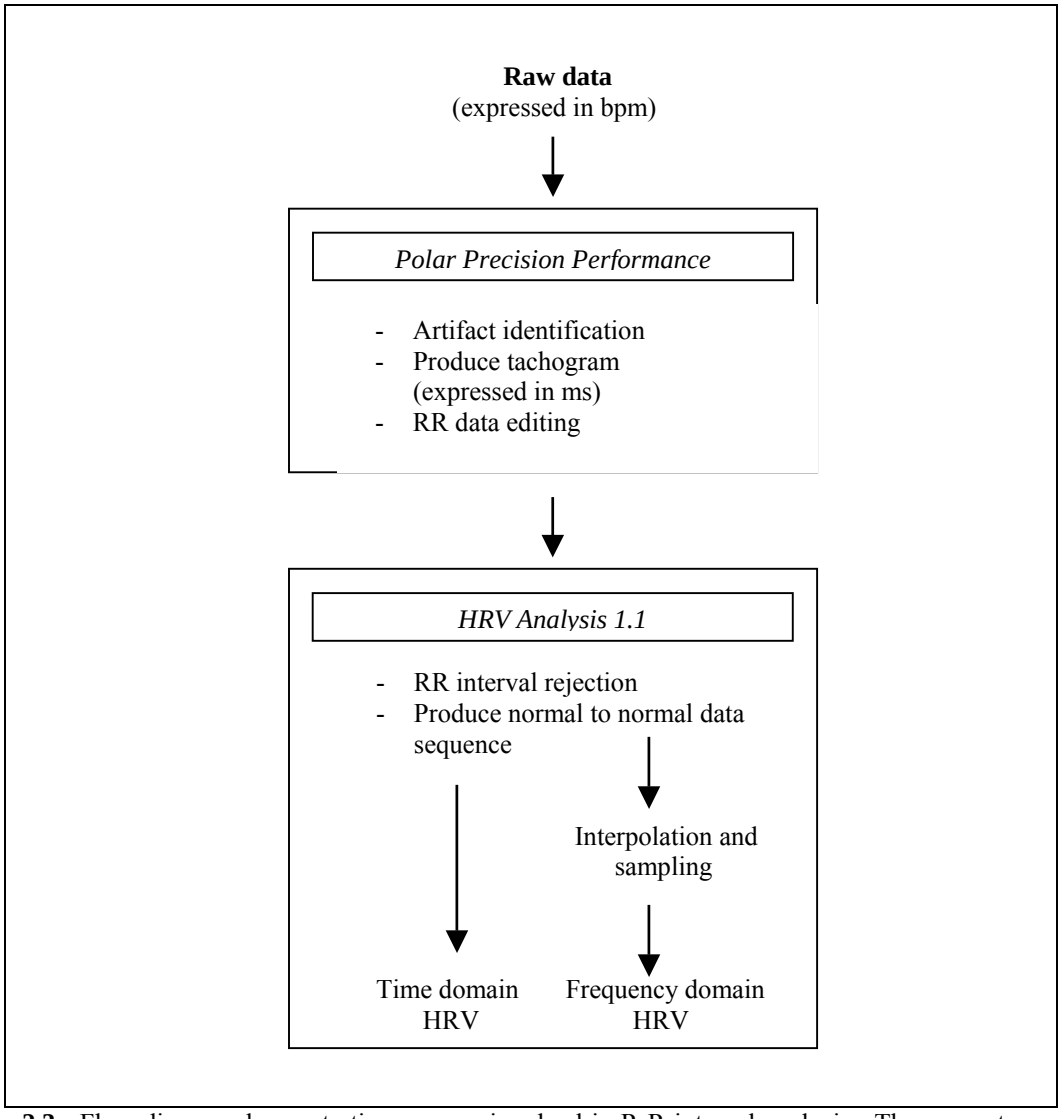
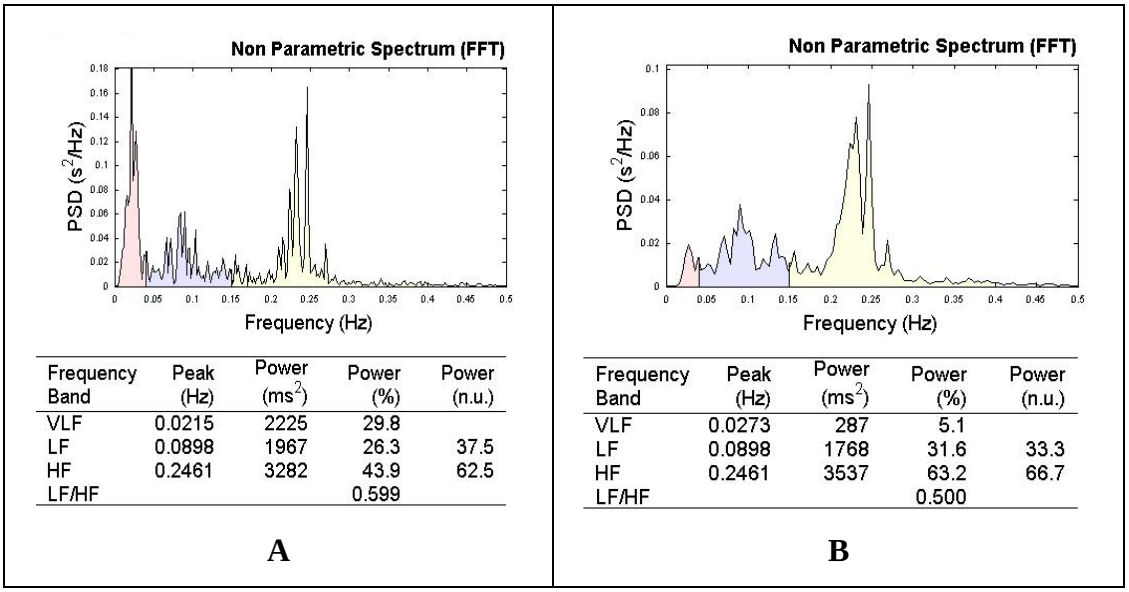


Figure 2.3. Flow diagram demonstrating process involved in R-R interval analysis. The computer program used in each step of analysis is indicated in *italics.*

It was necessary to change certain of the settings in the program before the HRV measures can be calculated. Firstly the ranges for the frequencies were set up at 0 – 0.04 Hz for the VLF band, 0.04 – 0.15 Hz for the LF band, and 0.15 – 0.4 Hz for the HF band. In HRV Analysis 1.1, the R-R series was detrended with the 'smoothness priors' trend and the 'eye' model. λ was used to adjust the soothing according to the researcher's needs. With an increase of λ ($500 < \lambda > 1000$), the lowest frequencies were removed. A decreased λ

(100< λ >400) resulted in the removal of the higher frequencies (17). According to advise from the developers of the software for this specific data set, the regularisation parameter (λ) was set to 500 (26).

R-R interval time series is an irregularly time-sampled series and should be interpolated before the spectrum can be estimated (17). A cubic interpolation rate of 4 Hz was used to minimise the VLF component of HRV, as only the LF and HF bands are important in assessing parasympathetic-sympathetic balance (27). This way the effect of hormonal rhythms (evident in frequencies below 0.3 Hz) was excluded from the analysis. Figure 2.3. demonstrates the effect of the default λ and interpolation rate (1000 and 2 Hz respectively) on the respective frequency bands in comparison to the preferred 500 and 4 Hz setting.



Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF	0.0215	2225	29.8	
LF	0.0898	1967	26.3	37.5
HF	0.2461	3282	43.9	62.5
LF/HF			0.599	

A

Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF	0.0273	287	5.1	
LF	0.0898	1768	31.6	33.3
HF	0.2461	3537	63.2	66.7
LF/HF			0.500	

B

Figure 2.3.2. The effect of different settings in HRV Analysis Software on the respective frequency bands for a representative participant. **A** λ=1000, interpolation rate = 2Hz, **B** λ=500, interpolation rate = 4Hz. Note that using the settings in **B**, the VLF component is significantly reduced for the Welch's method (FFT).

Since the data obtained from the respective participants are going to be compared to each other, the same settings were used to analyse all data sets.

2.3.3. Statistical analysis

Statistical analysis for the technique evaluation was performed using BMDP Statistical Software, Inc. and Statistix for Windows, Version 2.0. Both descriptive and inferential statistics were calculated for the four evaluations done in the technique evaluation. Direct and indirect measures were compared with the Wilcoxon statistical test (this test is not

dependant on the distribution of the data). Interpersonal variation (the variation in HRV between subjects) was calculated with the ANOVA statistical test, which tests differences in means. If the variances between the subjects were equal, a normal ANOVA test was applied, if it was unequal, the Welch test was used. The standard deviation of the means calculated for all the respective variables demonstrated the intrapersonal variation (the variation in HRV within the same subject). Finally, the sensitivity of the method to stressors was evaluated by means of the Wilcoxon nonparametric test.

3. Results

3.1 Technique reproducibility (direct vs indirect recordings)

3.1.1 Data summary

The first recording of subject 5 was used to demonstrate technique reproducibility with regard to direct and indirect recordings using Polar heart rate monitors. The analysed data obtained from the direct (interface) and indirect (Polar watch) recordings for a representative subject are set out Table 3.1.1. (The same data is available for all the subjects but is not included in the chapter because it granted identical results).

Table 3.1.1. *Data summary of the indirect and direct measures of a representative subject*

Variable	IND 1	DIR 1	IND 2	DIR 2	IND 3	DIR 3
Time domain						
Mean RR (s)	0.88	0.88	0.89	0.89	0.89	0.89
RR STD (s)	0.04	0.04	0.05	0.05	0.05	0.05
Mean HR (bpm)	68.43	68.46	67.95	67.85	68.00	67.85
HR STD (bpm)	3.62	3.62	4.21	4.24	4.61	4.24
RMSSD (ms)	40.97	41.19	53.17	53.76	54.66	53.76
pNN50 (%)	22.52	22.82	39.44	39.84	39.16	39.84
SDANN (ms)	9.31	8.78	46.15	45.53	10.50	45.53
RR triang. ind.	0.08	0.08	0.11	0.11	0.10	0.11
TINN (ms)	235.00	235.00	325.00	325.00	305.00	325.00
SD1 (ms)	29.10	29.25	37.74	38.16	38.81	38.16
SD2 (ms)	61.65	61.48	87.92	86.97	79.37	86.97
Frequency domain						
LF (ms^2)	198.25	201.33	288.36	299.42	241.54	299.42
HF (ms^2)	452.12	460.25	656.57	664.53	698.54	664.53
TP (ms^2)	684.10	695.69	987.11	1006.51	989.12	1006.51
LF n.u.	30.48	30.43	30.52	31.06	25.69	31.06
HF n.u.	69.52	69.57	69.48	68.94	74.31	68.94
LF/HF	0.44	0.44	0.44	0.45	0.35	0.45

Explanation: Note how the time and frequency domain data for the direct and indirect recordings is almost identical. **Abreviations**: IND, indirect recording; DIR, direct recording; RR triang. ind., RR triangular index.

Table 3.1.1. *Data summary of the indirect and direct measures of subject 5 – continued*

Variable	IND 4	DIR 4	IND 5	DIR 5	IND 6	DIR 6
Time domain						
Mean RR (s)	0.84	0.89	0.71	0.71	0.81	0.81
RR STD (s)	0.05	0.05	0.03	0.03	0.05	0.05
Mean HR (bpm)	71.64	67.76	84.36	84.36	74.39	74.25
HR STD (bpm)	4.48	4.32	4.22	4.22	4.74	4.75
RMSSD (ms)	50.74	53.30	30.01	30.01	48.54	48.47
pNN50 (%)	36.08	38.87	6.44	6.44	34.78	34.51
SDANN (ms)	33.29	13.66	34.42	34.42	30.64	28.87
RR triang. ind.	0.10	0.10	0.06	0.06	0.11	0.11
TINN (ms)	395.00	285.00	190.00	190.00	285.00	285.00
SD1 (ms)	36.01	37.84	21.33	21.33	34.45	34.40
SD2 (ms)	85.44	72.94	64.29	64.29	77.77	76.41
Frequency domain						
LF (ms^2)	275.96	226.46	136.05	136.05	299.37	310.34
HF (ms^2)	639.94	683.31	285.77	285.77	690.04	702.01
TP (ms^2)	951.46	957.25	450.68	450.68	1023.23	1046.12
LF n.u.	30.13	24.89	32.25	32.25	30.26	30.66
HF n.u.	69.87	75.11	67.75	67.75	69.74	69.34
LF/HF	0.43	0.33	0.48	0.48	0.43	0.4

Explanation: Note how the time and frequency domain data for the direct and indirect recordings is almost identical. **Abbreviations**: IND, indirect recording; DIR, direct recording; RR triang. ind., RR triangular index.

3.1.2. Descriptive and inferential statistics

Table 3.1.2. presents the calculated mean, with its standard deviation for each variable. P-values, calculated with the Wilcoxon statistical test, are provided for the difference between direct and indirect values for a specific variable.

Table 3.1.2.a *The mean, standard deviation and p-value for the time domain variables*

Variable	Indirect variable mean (SD)	Direct variable mean (SD)	I – D variable mean (SD)	P-value
Mean RR (s)	0.85 (0.07)	0.84 (0.07)	0.01 (0.02)	0.1250
RR STD (s)	0.04 (0.01)	0.04 (0.01)	- 0.01 (0.01)	0.6250
Mean HR (bpm)	71.76 (6.67)	72.46 (6.36)	- 0.71 (1.56)	0.1250
HR STD (bpm)	4.23 (0.36)	4.31 (0.40)	- 0.08 (0.16)	0.8125
RMSSD (ms)	46.57 (9.54)	46.35 (9.33)	0.40 (1.17)	0.6250
pNN50 (%)	30.38 (13.41)	29.73 (12.99)	0.65 (1.10)	0.1250
SDANN (ms)	29.46 (15.61)	27.38 (14.55)	2.08 (17.83)	0.6250
RR triang. ind.	0.10 (0.02)	0.09 (0.02)	0.01 (0.01)	0.3125
TINN (ms)	274.17 (52.95)	289.17 (71.44)	- 15.00 (47.22)	1.0000
SD1 (ms)	33.19 (6.76)	32.91 (6.61)	0.28 (0.84)	0.6250
SD2 (ms)	74.84 (10.86)	76.07 (10.85)	-1.23 (6.44)	0.4375

p-value calculated with Wilcoxen statistical test, note that there are no significant differences

Table 3.1.2.b *The mean, standard deviation and p-value for frequency domain variables*

Variable	Indirect variable mean (SD)	Direct variable mean (SD)	I – D variable mean (SD)	P-value
LF (ms²)	245.50 (69.73)	239.92 (62.78)	5.58 (34.25)	0.4375
HF (ms²)	576.73 (167.75)	570.49 (166.13)	6.24 (24.81)	0.4375
TP (ms²)	860.46 (237.31)	847.62 (230.39)	12.84 (8.73)	0.6250
LF n.u. (%)	30.06 (2.61)	29.88 (2.20)	0.17 (3.36)	0.6250
HF n.u. (%)	69.94 (2.61)	70.11 (2.20)	-0.17 (3.36)	0.6250
LF/HF	0.43 (0.05)	0.43 (0.04)	0.01 (0.06)	0.6250

p-value calculated with Wilcoxon statistical test, note that there are no significant differences

3.2 Interpersonal variation and intrapersonal variation

3.2.1. Data summary

The individual data for the 6 recordings (on the 6 consecutive days) for each of the nine participants can be found in Table 3.2.1. in the Appendix to this chapter.

DEMONSTRATION OF INTRAPERSONAL VARIATION

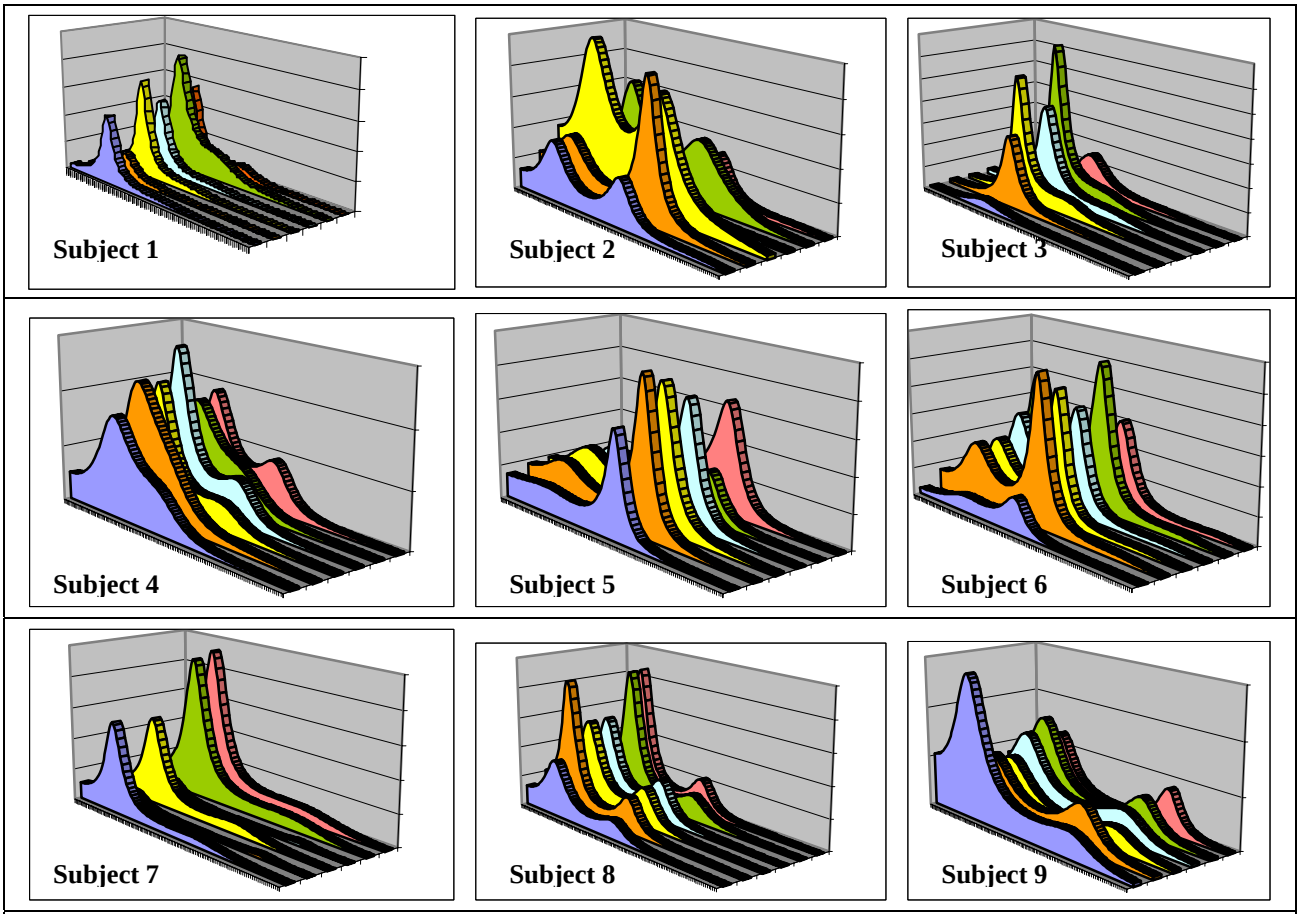


Figure 3.2.1.a Power spectral density graphs of the 6 recordings for each of the nine subjects. The 6 recordings on the 6 consecutive days for a specific subject is presented on the same axes to illustrate the similarity within an individual with regard to the power in the frequency domain. X-axis: Frequency in Hz; Y-axis: Power spectral density (PSD) in s²/Hz. The area under each curve shows the amount of power in the frequency domain.

Key: recording 1 recording 2 recording 3 recording 4 recording 5 recording 6

DEMONSTRATION OF INTERPERSONAL VARIATION

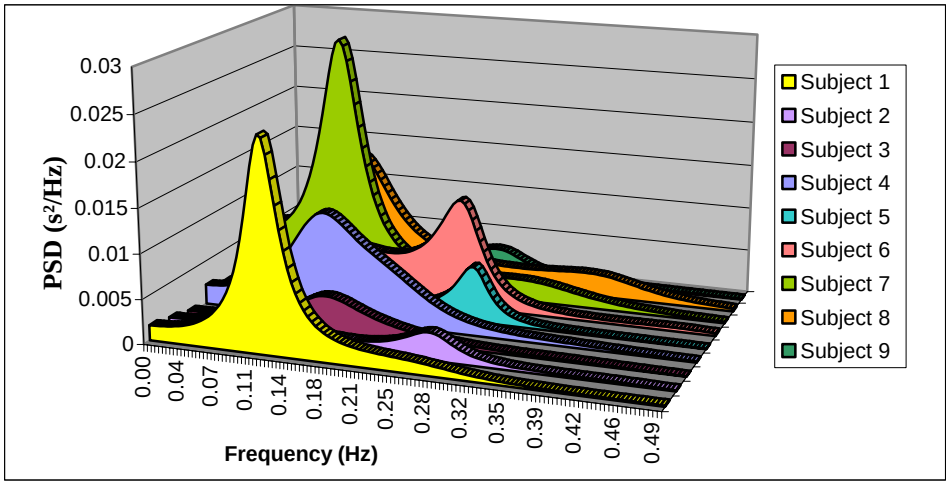


Figure 3.2.1.b Power spectral density (PSD) graph for the first recording of each of the nine subjects. The 9 first recordings are presented on the same axes to illustrate the diversity between individuals with regard to the power in the frequency domain (in comparison to Figure 3.2.1.a).

3.2.2 Descriptive and inferential statistics

For each subject, means and standard deviations were calculated for the 6 recordings (observations) made on the 6 consecutive days (Table 3.2.2.).

Table 3.2.2.a *Time domain means and standard deviations for each subject*

Variable	Subject 1 (6 observ)	Subject 2 (6 observ)	Subject 3 (6 observ)	Subject 4 (6 observ)	Subject 5 (6 observ)
Mean RR (s)	0.86 (0.07)	0.89 (0.07)	0.97 (0.06)	0.87 (0.03)	0.84 (0.07)
RR STD (s)	0.06 (0.02)	0.05 (0.01)	0.07 (0.02)	0.06 (0.00)	0.04 (0.01)
Mean HR (bpm)	70.43 (5.59)	67.74 (4.78)	62.48 (4.10)	70.04 (2.54)	72.46 (6.36)
HR STD (bpm)	5.47 (0.88)	3.97 (0.71)	4.75 (1.01)	5.43 (0.30)	4.31 (0.40)
RMSSD (ms)	54.41 (22.87)	52.81 (16.57)	80.73 (26.88)	52.28 (3.39)	46.35 (9.33)
pNN50 (%)	24.85 (14.46)	26.44 (12.10)	45.24 (17.56)	28.09 (3.04)	29.73 (12.99)
SDANN (ms)	10.62 (4.05)	16.85 (10.66)	21.03 (14.89)	20.67 (6.32)	27.38 (14.55)
RR triang. ind.	0.13 (0.04)	0.10 (0.03)	0.15 (0.04)	0.12 (0.01)	0.09 (0.02)
TINN (ms)	353.33 (81.83)	353.33 (163.02)	398.33 (99.18)	295.83 (12.81)	289.17 (71.44)
SD1 (ms)	38.70 (16.22)	37.54 (11.76)	57.27 (19.06)	37.18 (2.40)	32.91 (6.61)
SD2 (ms)	102.69 (26.53)	82.91 (27.28)	102.98 (28.72)	112.20 (6.83)	76.07 (10.85)
Variable	**Subject 6 (6 observ)**	**Subject 7 (6 observ)**	**Subject 8 (6 observ)**	**Subject 9 (6 observ)**	**p-value**
Mean RR (s)	0.91 (0.06)	0.86 (0.06)	0.84 (0.04)	0.86 (0.05)	0.8886
RR STD (s)	0.10 (0.02)	0.07 (0.03)	0.06 (0.01)	0.06 (0.01)	0.0243*
Mean HR (bpm)	67.70 (3.96)	71.06 (4.43)	72.60 (3.88)	70.48 (4.24)	0.8584
HR STD (bpm)	7.89 (1.18)	6.34 (1.56)	6.35 (0.63)	5.70 (0.70)	0.0184*
RMSSD (ms)	114.16 (27.15)	62.64 (29.51)	59.56 (6.80)	44.67 (8.40)	0.0552
pNN50 (%)	52.83 (11.23)	26.43 (16.02)	32.49 (6.91)	23.02 (7.77)	0.2941
SDANN (ms)	26.87 (12.83)	28.05 (11.47)	22.13 (7.87)	27.48 (12.03)	0.3242
RR triang. ind.	0.18 (0.04)	0.11 (0.04)	0.10 (0.01)	0.12 (0.02)	0.1287
TINN (ms)	510.0 (105.02)	399.17 (180.40)	345.83 (63.52)	309.17 (55.35)	0.0956
SD1 (ms)	81.10 (19.30)	44.65 (20.97)	42.37 (4.84)	31.93 (6.01)	0.0563
SD2 (ms)	161.41 (33.73)	129.90 (42.87)	106.15 (10.29)	109.13 (19.46)	0.0146*

* indicates significant difference ($p \leq 0.05$), standard deviation is indicated in brackets.
Standard deviations indicative of the intrapersonal variation. P-values (calculated with ANOVA) indicative of interpersonal variation. **Abbreviations**: Obsev., observation; RR triang. ind., RR triangular index.

Table 3.2.2.b *Frequency domain means and standard deviations for each subject*

Variable	Subject 1 (6 observ)	Subject 2 (6 observ)	Subject 3 (6 observ)	Subject 4 (6 observ)
LF (ms²)	1295.96 (542.39)	376.84 (202.01)	961.93 (735.74)	768.99 (140.59)
HF (ms²)	637.75 (578.50)	510.42 (295.28)	1559.54 (665.89)	706.84 (129.07)
TP (ms²)	1981.72 (1093.52)	962.99 (532.55)	2553.04 (1268.46)	1522.30 (253.51)
LF n.u.	70.04 (8.64)	42.97 (3.04)	36.25 (12.72)	52.04 (3.75)
HF n.u.	29.96 (8.64)	57.03 (3.04)	63.75 (12.72)	47.96 (3.75)
LF/HF	2.53 (0.80)	0.76 (0.09)	0.62 (0.33)	1.10 (0.18)
Variable	**Subject 5 (6 observ)**	**Subject 6 (6 observ)**	**Subject 7 (6 observ)**	**Subject 8 (6 observ)**
LF (ms²)	239.92 (62.78)	1817.04 (839.80)	1777.50 (1256.14)	661.80 (176.47)
HF (ms²)	570.49 (166.13)	2852.37 (1031.50)	701.38 (528.55)	611.45 (123.61)
TP (ms²)	847.62 (230.39)	4840.75 (1871.99)	2587.51 (1844.06)	1337.29 (264.65)
LF n.u.	29.89 (2.20)	37.84 (4.84)	72.74 (1.87)	51.77 (5.17)
HF n.u.	70.11 (2.20)	62.16 (4.84)	27.26 (1.87)	48.23 (5.17)
LF/HF	0.43 (0.04)	0.62 (0.13)	2.68 (0.25)	1.09 (0.23)
Variable	**Subject 9 (6 observ)**	**p-value**		
LF (ms²)	0.86 (0.05)	0.0009*		
HF (ms²)	0.06 (0.01)	0.0331*		
TP (ms²)	70.48 (4.24)	0.0102*		
LF n.u.	5.70 (0.70)	0.0001*		
HF n.u.	44.67 (8.10)	0.0001*		
LF/HF	23.02 (7.77)	0.0001*		

* indicates significant difference ($p \leq 0.05$), standard deviation is indicated in brackets.
Standard deviations indicative of the intrapersonal variation. P-values (calculated with ANOVA) indicative of interpersonal variation. **Abbreviations**: Obsev., observation; RR triang. ind., RR triangular index.

In Table 3.2.2.a) and b), the standard deviation calculated for the means gives an indication of the amount of variance in HRV parameters within an individual (intrapersonal variation). The p-values calculated for the differences between the respective experimental subjects, is indicative of the amount of variance in HRV parameters between subjects (interpersonal variation).

3.3. Sensitivity and response to stressors

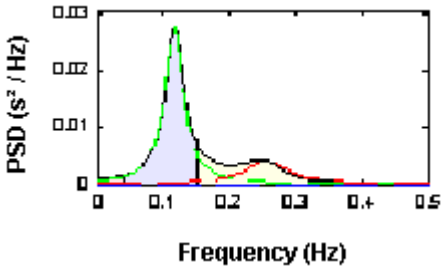
3.3.1. Data summary

During the last two recordings for each subject, the sensitivity of the technique was evaluated by exposing the experimental subjects to either raucous or soothing music. After the results were studied, it became apparent that two distinctive groups could be distinguished on the basis of autonomic balance. The first, the sympathetic dominant group, had a LF/HF ratio > 1 during resting conditions. The other, the parasympathetic dominant group, a LF/HF ratio < 1. The following PSD graphs demonstrate how these two groups differ in their autonomic response to music. The low frequencies (sympathetic activation) are indicated in blue and the high frequencies (vagal activation) in yellow.

SYMPATHETIC DOMINANT GROUP

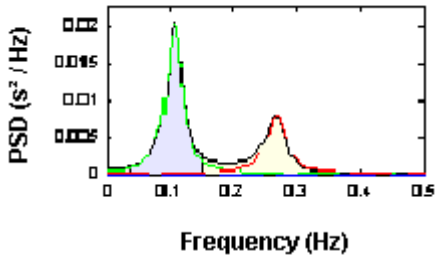
Effect of soothing music on ANS

Subject 1



LF (%)	67.34
HF (%)	32.66
LF/HF	2.06

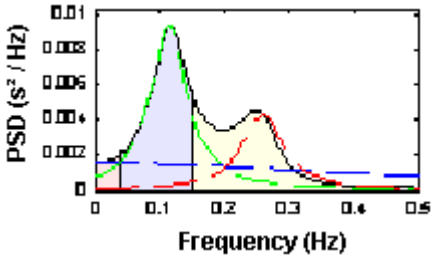
Baseline recording



LF (%)	57.20
HF (%)	42.80
LF/HF	1.34

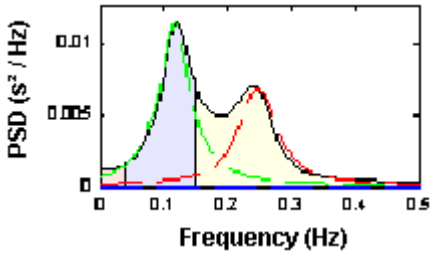
Effect of soothing music

Subject 4



LF (%)	50.08
HF (%)	49.92
LF/HF	1.00

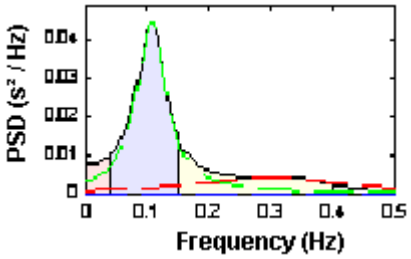
Baseline recording



LF (%)	32.27
HF (%)	67.73
LF/HF	0.48

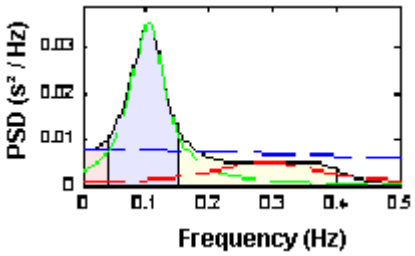
Effect of soothing music

Subject 7



LF (%)	71.50
HF (%)	28.50
LF/HF	2.51

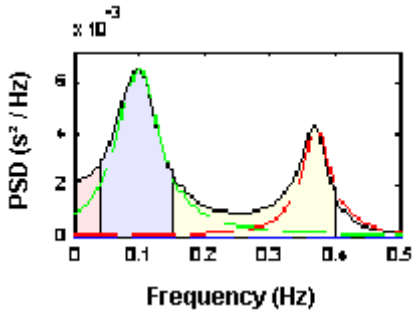
Baseline recording



LF (%)	56.27
HF (%)	43.73
LF/HF	1.29

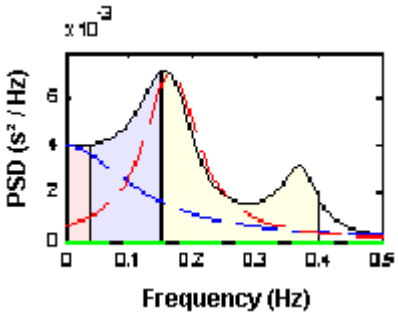
Effect of soothing music

Subject 8



LF (%)	55.33
HF (%)	44.67
LF/HF	1.24

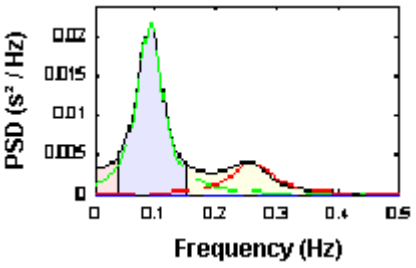
Baseline recording



LF (%)	46.68
HF (%)	53.32
LF/HF	0.88

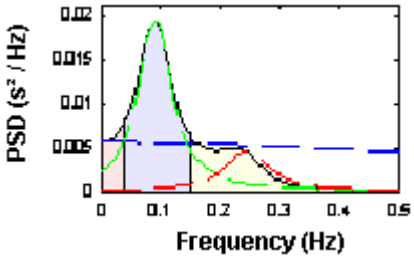
Effect of soothing music

Subject 9



LF (%)	71.49
HF (%)	28.51
LF/HF	2.51

Baseline recording

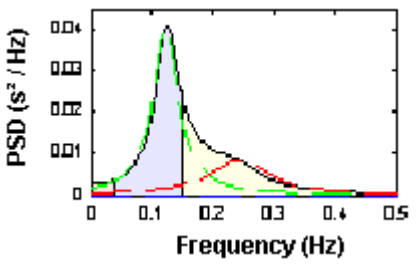


LF (%)	57.81
HF (%)	42.19
LF/HF	1.37

Effect of soothing music

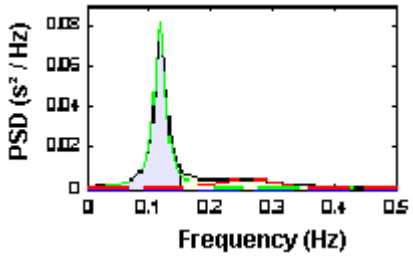
Effect of raucous music on ANS

Subject 1



LF (%)	53.78
HF (%)	46.22
LF/HF	1.16

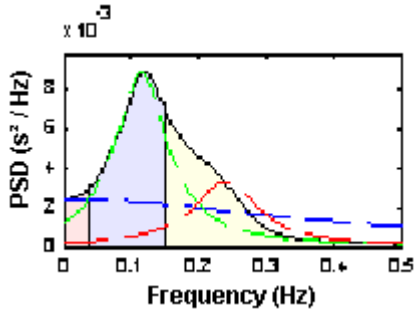
Baseline recording



LF (%)	76.09
HF (%)	23.91
LF/HF	3.18

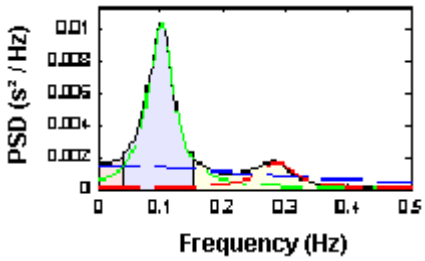
Effect of raucous music

Subject 4



LF (%)	53.54
HF (%)	46.46
LF/HF	1.15

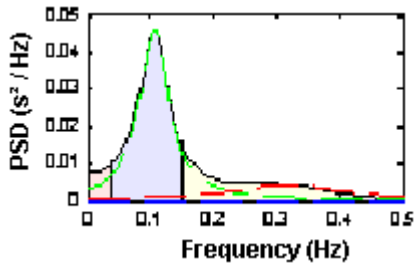
Baseline recording



LF (%)	72.88
HF (%)	27.12
LF/HF	2.69

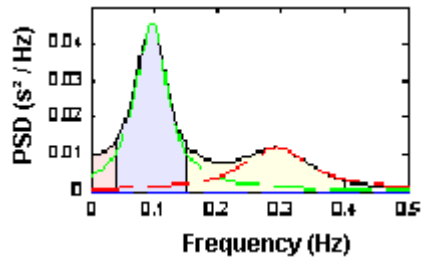
Effect of raucous music

Subject 7



LF (%)	69.98
HF (%)	30.02
LF/HF	2.33

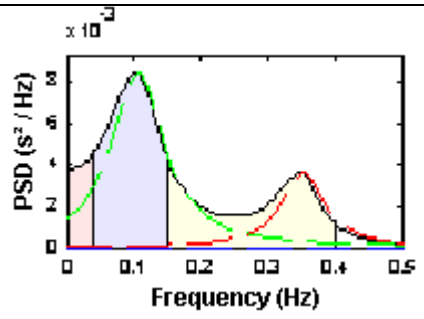
Baseline recording



LF (%)	71.28
HF (%)	28.72
LF/HF	2.48

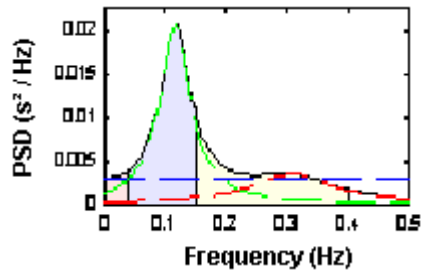
Effect of raucous music

Subject 8



LF (%)	48.79
HF (%)	51.21
LF/HF	0.95

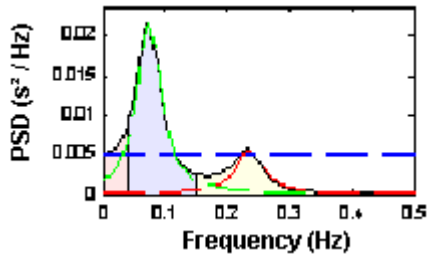
Baseline recording



LF (%)	57.51
HF (%)	42.49
LF/HF	1.35

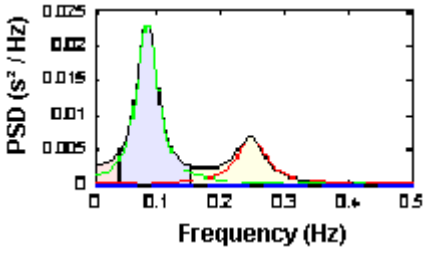
Effect of raucous music

Subject 9



LF (%)	70.85
HF (%)	29.15
LF/HF	2.43

Baseline recording



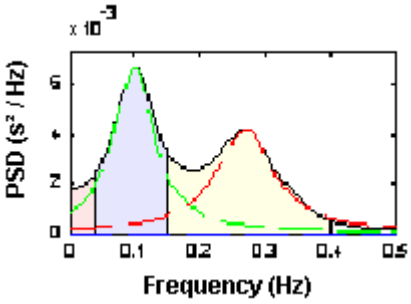
LF (%)	72.79
HF (%)	27.21
LF/HF	2.68

Effect of raucous music

PARASYMPATHETIC DOMINANT GROUP

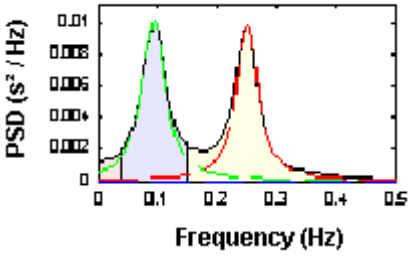
Effect of soothing music on ANS

Subject 2



LF (%)	39.05
HF (%)	60.95
LF/HF	0.64

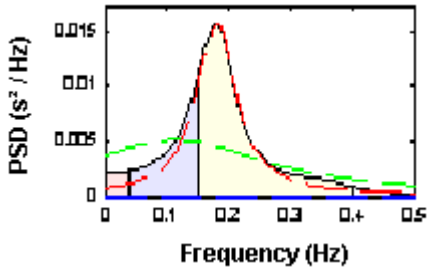
Baseline recording



LF (%)	57.20
HF (%)	42.80
LF/HF	1.34

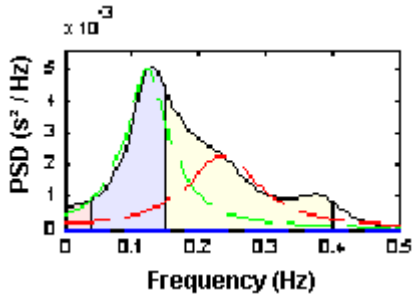
Effect of soothing music

Subject 3



LF (%)	22.95
HF (%)	77.05
LF/HF	0.30

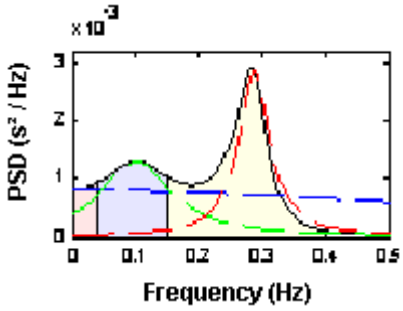
Baseline recording



LF (%)	28.48
HF (%)	71.52
LF/HF	0.40

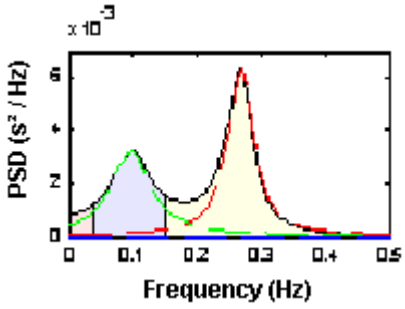
Effect of soothing music

Subject 5



LF (%)	32.25
HF (%)	67.75
LF/HF	0.48

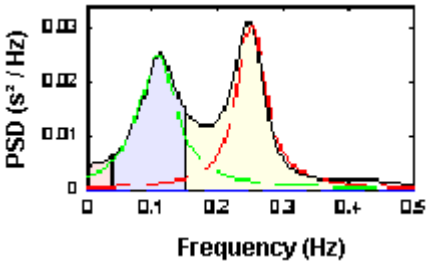
Baseline recording



LF (%)	41.31
HF (%)	58.69
LF/HF	0.70

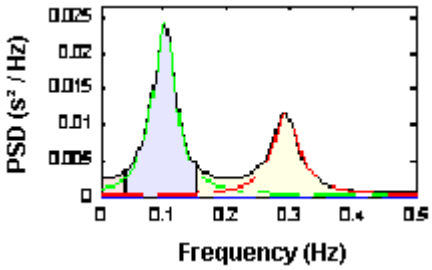
Effect of soothing music

Subject 6



LF (%)	39.38
HF (%)	60.62
LF/HF	0.65

Baseline recording

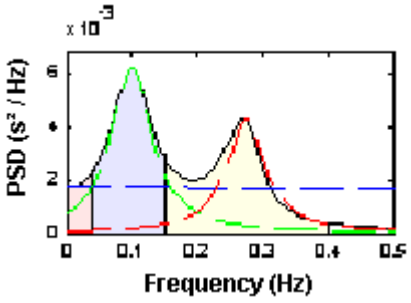


LF (%)	57.70
HF (%)	42.30
LF/HF	1.36

Effect of soothing music

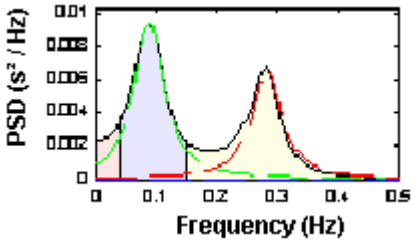
Effect of raucous music on ANS

Subject 2



LF (%)	46.04
HF (%)	53.96
LF/HF	0.85

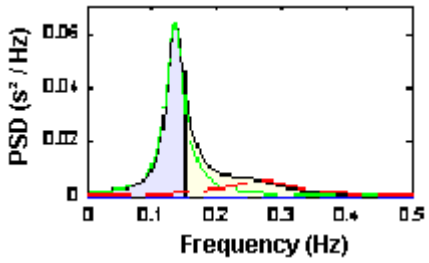
Baseline recording



LF (%)	35.65
HF (%)	64.35
LF/HF	0.55

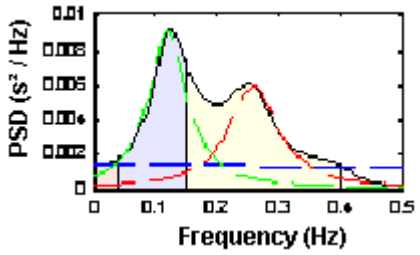
Effect of raucous music

Subject 3



LF (%)	46.81
HF (%)	53.19
LF/HF	0.88

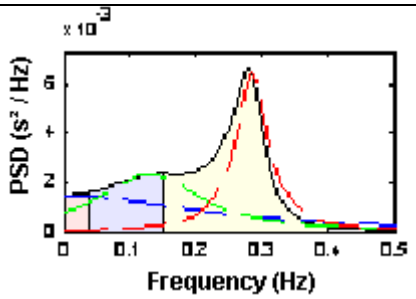
Baseline recording



LF (%)	38.85
HF (%)	61.15
LF/HF	0.64

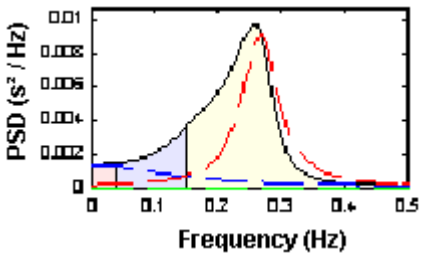
Effect of raucous music

Subject 5



LF (%)	30.26
HF (%)	69.74
LF/HF	0.43

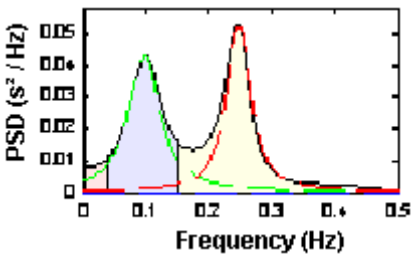
Baseline recording



LF (%)	12.61
HF (%)	87.39
LF/HF	0.14

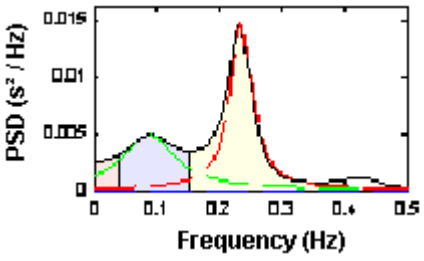
Effect of raucous music

Subject 6



LF (%)	43.71
HF (%)	56.29
LF/HF	0.78

Baseline recording



LF (%)	25.27
HF (%)	74.73
LF/HF	0.34

Effect of raucous music

3.3.2. Descriptive and inferential statistics

Table 3.3.2.a *The means and standard deviation of the effect of different types of music on the autonomic nervous system*

	Baseline		**Soothing music**		**Baseline**		**Raucous music**	
Sympathetic Group		**nu (%)**		**nu (%)**		**nu (%)**		**nu (%)**
Mean HR (bpm)	70.05 (1.98)		66.53 (2.68)		68.79 (5.23)		68.35 (5.71)	
TP (ms²)	2199.90 (1493.20)		1942.00 (606.71)		2603.50 (1490.30)		3247.90 (2231.70)	
LF (ms²)	1406.30 (1105.30)	63.15	927.03 (410.98)	50.04	1515.10 (1013.20)	59.39	1996.90 (1770.00)	70.11
HF (ms²)	704.20 (343.39)	36.85	899.80 (262.56)	50.00	962.27 (559.31)	40.61	877.21 (573.15)	29.89
LF/HF	1.86 (0.71)		1.07 (0.39)		1.61 (0.71)		2.48 (0.68)	
Parasympathetic Group		**nu (%)**		**nu (%)**		**nu (%)**		**nu (%)**
Mean HR (bpm)	70.29 (10.37)		68.76 (8.80)		65.21 (6.65)		65.36 (5.95)	
TP (ms²)	2029.20 (1873.60)		1459.0 (1005.90)		3185.40 (2855.40)		1344.90 (366.12)	
LF (ms²)	687.94 (746.70)	33.41	729.18 (625.72)	46.17	1349.10 (1275.00)	41.71	377.09 (242.37)	28.09
HF (ms²)	1274.90 (1099.90)	66.589	674.50 (326.75)	53.83	1737.60 (1560.00)	58.30	922.98 (238.98)	71.91
LF/HF	0.52 (0.17)		0.95 (0.48)		0.74 (0.21)		0.42 (0.22)	

Table 3.3.2.b *The means, standard deviation and p-values for the change in autonomic activity in response to different types of music*

	Δ (Basal – Soothing music) Means (SD)			**Δ (Basal – Raucous music) Means (SD)**		
Sympathetic Group		**p-value (within)**			**p-value (within)**	**p-value**
Mean HR (bpm)	3.52 (1.82)	p = 0.0591		0.44 (2.95)	p = 0.7874	
TP (ms²)	257.90 (1386.50)	p = 1.0000		- 644.43 (889.90)	p = 0.1775	
LF (ms²)	479.24 (944.11)	p = 0.4185		- 481.79 (837.04)	p = 0.4185	
LF (nu)	13.10 (3.73)	p = 0.0591		- 10.72 (9.73)	p = 0.0591	
HF (ms²)	- 195.59 (408.96)	p = 0.2807		85.06 (477.85)	p = 0.7874	
HF (nu)	- 13.10 (3.73)	p = 0.0591	**p-value**	10.72 (9.73)	p = 0.0591	**p-value**
LF/HF	0.80 (0.36)	p = 0.0591	**(between)**	- 0.87 (0.85)	p = 0.0591	**(between)**
Parasympathetic Group						
Mean HR (bpm)	1.54 (2.54)	p = 0.5839	p = 0.1270	- 0.15 (4.27)	p = 0.8551	p = 0.9025
TP (ms²)	570.22 (1141.20)	p = 0.5839	p = 0.7302	1840.4 (2869.80)	p = 0.5839	p = 0.1508
LF (ms²)	- 41.24 (334.65)	p = 0.8551	p = 0.4841	972.02 (1240.90)	p = 0.1003	p = 0.1508
LF (nu)	- 12.76 (6.48)	p = 0.1003	p = 0.0079*	13.61 (5.23)	p = 0.1003	p = 0.0397*
HF (ms²)	600.37 (849.42)	p = 0.5839	p = 0.2381	814.61 (1572.60)	p = 0.5839	p = 0.5556
HF (nu)	12.76 (6.48)	P = 0.1003	p = 0.0397*	- 13.61 (5.23)	p = 0.1003	p = 0.0079*
LF/HF	- 0.43 (0.32)	p = 0.1003	p = 0.0079*	0.32 (0.08)	p = 0.1003	p = 0.0397*

p-values (within) calculated with Wilxoxon signed rank test, p-values (between) calculated with Wilxoxon rank sum test. *indicates statistical significant difference

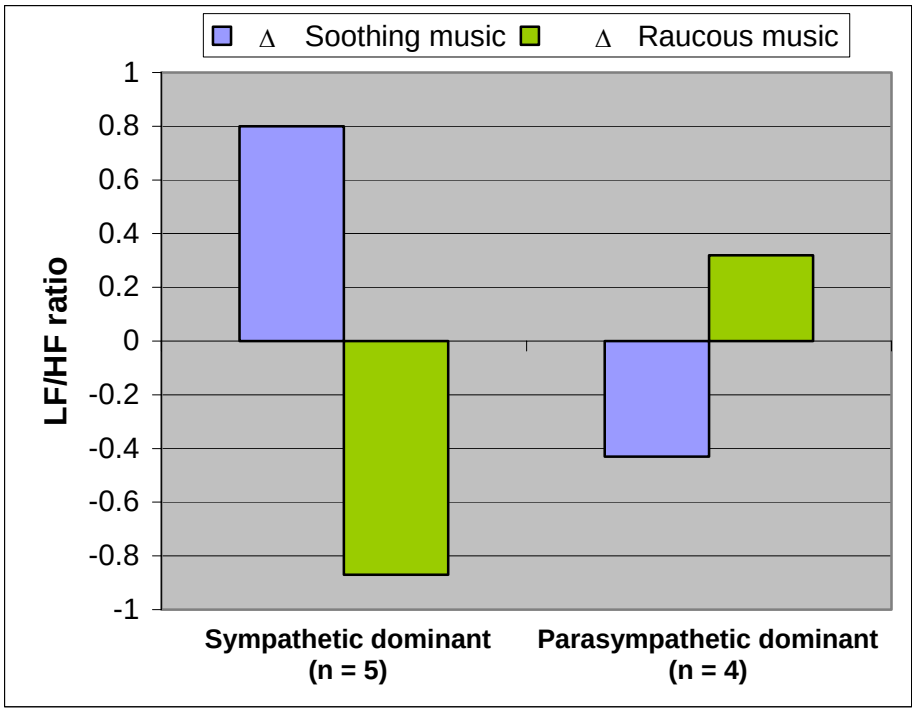


Figure 3.2.2. The mean effect of soothing and raucous music on subjects with different autonomic balances

4. Discussion

The analysis of HRV has attracted an extensive amount of interest in psychology and physiology and has therefore become an important measure in neuropsychology (1). The quantification and interpretation of HRV remains rather complex, though. The inaccurate quantification and interpretation of HRV patterns in psychophysiology (or in any other field) may obscure crucial issues or relationships and may hinder, rather than promote, psychophysiological applications (9).

Although our understanding of HRV is far from complete, it seems to be a marker of both dynamic and cumulative load. As a dynamic marker of load, HRV appears to be sensitive and responsive to acute stress. Under laboratory conditions, mental load – including making complex decisions, and public speech tasks – have been shown to lower HRV (20). As a marker of cumulative wear and tear, HRV has also been shown to decline with the aging process. Although resting heart rate does not change significantly with advancing age, there is a decline in HRV, which has been attributed to diminished efferent vagal tone and reduced beta-adrenergic responsiveness. By contrast, regular physical activity (which slows down the aging process) has been shown to raise HRV, presumable by increasing vagal tone (20).

The aim of this technique evaluation was to become acquainted with the analysis of R-R intervals as a measure of HRV, since this evaluation was to be used in the main fibromyalgia study. Apart from assessing the technique's reproducibility, a primary objective was to see how sensitive the technique would be in the assessment of the autonomic nervous system's response to stressors. Evaluating the effect of music on the sympathetic-parasympathetic balance was an ideal way to reach this goal, since music is a minor stressor. Thus, the method would have to be fairly sensitive to detect changes in autonomic nervous system activity in response to listening to music.

Firstly, technique reproducibility was evaluated. Table 3.1.2.a) and b) (Section 3) contain the means and standard deviations calculated for the mean RR, mean HR, RMSSD, pNN50, SDANN, RR triangular index, TINN, SD1, SD 2, LF, HF, total power and LF/HF ratio. According to the p-values calculated for these time and frequency domain variables, the difference between all the direct and indirect measures was statistically non-significantly ($p > 0.05$ for all of the variables). The similarity of the two measures was plainly seen in the raw data (Table 3.1.1, Section 3) as well. This is an indication that R-R recording using the Polar heart rate monitor (indirect) and interface (direct) has high reproducibility and therefore is a reliable tool in assessing HRV.

In order to determine the intra- and interpersonal variation of the subjects, it was necessary to compare the 6 recordings obtained from each of the nine subjects, firstly within each individual (intrapersonal), and then between the respective subjects (interpersonal). Table 3.2.2.a) (Section 3) summarises the time domain results for each subject. According to the standard deviations calculated for each of the variables, the amount of variability within each subject seemed to be rather similar to the variability in the rest. One participant, subject 4, seemed to have less variability than the rest of the participants, though. The same was observed when reviewing the standard deviations of the frequency domain results. Once again, subject 4 clearly had less variability than the rest of the study group. After completion of the experimental part of the study, this subject revealed that he used anti-depressive drugs (anti-depressants are known to lower HRV). Figure 3.2.1.a (Section 3) visibly illustrates intrapersonal variation in the power spectral components of HRV (frequency domain).

To demonstrate interpersonal variation, p-values were calculated for the differences in the time and frequency domain variables between the respective subjects (Table 3.2.2.a, b). As far as the time domain variables are concerned, statistically significant differences between the subjects were obtained for the standard deviation of the mean RR ($p = 0.0243$), the standard deviation of the mean HR ($p = 0.0184$), and SD2 ($p = 0.0146$). According to the standardisation criteria set out by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, the standard deviation of the mean RR is also referred to as SDANN (1). SDANN and SD2 give insight into the long-term components of HRV (18). Because the long-term variation of HRV is usually associated with the sympathetic modulation, it seems that, according to time domain measures, the subjects differ the most with regard to their sympathetic nervous system modulation of HRV. In the frequency domain, subjects differed significantly from each other for all the power spectral components of HRV (LF: $p = 0.0009$; LFnu: $p = 0.0001$; HF: $p = 0.0331$; HFnu: $p = 0.0001$; total power: $p = 0.0102$; and LF/HF: $p = 0.0001$). These results imply that the subjects had high interpersonal variance in the amount of activity exhibited by the sympathetic (LF and LFnu) and parasympathetic nervous system (HF and HFnu), the total amount of HRV (total power), and autonomic balance (LF/HF ratio). Thus, analysis in the time and frequency domain differed in the regard that frequency domain analysis was able to identify variances between the subjects not detected through time domain analysis. The clear differences in spectral power are illustrated in Figure 3.2.1.b).

During the evaluation of the autonomic nervous system activity in reaction to stressors, it was clear that the effect of music is strong enough to elicit an autonomic response in the subjects (the individual reactions to the different types of music is illustrated in Section 3.3.1.). The deviation from the baseline in response to the music was statistically non-significant for all the HRV parameters evaluated, though (see Table 3.3.2). What is of particular interest is the direction of change in response to the music. It seemed that the two groups of subjects distinguished on the basis of their autonomic balance (LF/HF ratio), the sympathetic ($LF/HF > 1$) and parasympathetic dominant group ($LF/HF < 1$), reacted in opposite ways from one another in response to the music played. This difference in reaction between the two groups is best described by the change in the LF/HF ratio. In response to the soothing music, the sympathetic dominant group's LF/HF ratio decreased ($\Delta = 0.80$, SD 0.36) while that of the parasympathetic dominant group increased ($\Delta = -0.43$, SD 0.32). In response to the raucous music, the sympathetic dominant group showed an increased LF/HF

ratio (Δ = - 0.87, SD 0.85), while the parasympathetic group's ratio decreased (Δ = 0.32, SD 0.08). What this basically implies is that the sympathetic dominant subjects react to the different types of music in the way expected: they seem to be excited by raucous music and calmed by soothing music. The parasympathetic subjects, however, react in a fairly unusual way: they are stimulated by soothing music and calmed by raucous music (see Figure 3.2.2., Section 3). The decreased LF/HF observed in the sympathetic dominant group in response to soothing music, is mainly due to decreased sympathetic activity (Δ LF = 479.24, SD 944.11), with some increased activity in the parasympathetic branch of the autonomic nervous system (Δ HF = - 195.59, SD 408.96). In the parasympathetic dominant group, major decreases in parasympathetic activity (Δ HF = 600.37, SD 849.42) was responsible for the sympathetic dominance (increased LF/HF ratio) during soothing music. As far as the raucous music was concerned, the predominance of the sympathetic branch (increased LF/HF ratio) in the sympathetic dominant group was caused by increases in sympathetic (Δ LF = - 481.79, SD 837.04) and decreases in parasympathetic activity (Δ HF = 85.06, SD 477.85). The parasympathetic group reacted to raucous music with decreases in both sympathetic (Δ LF = 972.02, SD 1240.90) and parasympathetic activity (Δ HF = 814.61, SD 1572.60). In addition to the opposite reaction of the sympathetic and parasympathetic branches observed in the two groups, the sympathetic dominant group also showed a greater reaction to the music played (see Figure 3.2.2.). The difference in the response to music between the two groups was statistically significant for the low and high frequency as well as the LF/HF ratio (soothing music: LFnu $p = 0.0397$, HFnu $p = 0.0079$, LF/HF ratio $p = 0.0397$; raucous music: LFnu $p = 0.0079$, HFnu $p = 0.0397$, LF/HF ratio $p = 0.0079$).

It would be interesting to extend this type of study to a larger sample to determine the reproducibility of these results and to assess the influence of personal preference in music styles on the autonomic response to different types of music. If these results were to be repeated in a larger study, it could hold interesting implications for practises such as music therapy. As soon as normative HRV values are available for the autonomic response to different music styles, music therapy practises could incorporate HRV recordings when examining the effectiveness of their therapies.

5. Conclusions

The technique evaluation of HRV showed that the recording of R-R intervals with the Polar heart monitors could be a reliable method for the evaluation of HRV on the condition that great care is taken not to use simplistic HRV myths in analysing and reporting results. Under carefully controlled laboratory conditions and with standardised protocols, this technique is able to provide reproducible results. The reproducibility of the technique was demonstrated by the similarity between direct and indirect measures as well as relatively low intrapersonal variation within the subjects evaluated.

Out of the results obtained by this study, it became apparent that there is high interpersonal variation between subjects. The high interpersonal variation holds implications for the assessment of the ability of the technique to detect changes in the sympathetic-parasympathetic balance of the autonomic nervous system. When calculating descriptive statistics for heart rate variability measures, high interpersonal variation will result in larger standard deviations for means, which in turn can result in non-significant p-values (even in the midst of clear differences between groups/ changes from baseline to intervention). To eliminate problems such as these, larger study groups are needed.

It is necessary to realise that analysis of HRV in the frequency domain, while providing clues to autonomic function, does not provide simple, unambiguous results. Inaccurate quantification and interpretation of HRV patterns should therefore be avoided by formulating an integrative and interdisciplinary perspective on the origins, quantification, and interpretation of patterns of HRV.

The technique evaluation for this study was presented at the Faculty Day of Health Sciences (UP) and the 31st Annual congress of the Physiology Society of Southern Africa.

C. APPENDIX TO CHAPTER – INDIVIDUAL SUBJECT DATA

Table 3.2.1. *The individual time and frequency domain measures for the 6 recordings (on the 6 consecutive days) for each of the nine subjects*

Subject	Observ	Mean RR (s)	RR STD (s)	Mean HR (bpm)	HR STD (bpm)	RMSSD (ms)	pNN50 (%)	SDANN (ms)	RR tri ind	TINN (ms)
1	1	0.84	0.06	71.63	5.41	47.34	20.77	10.14	0.13	365.00
	2	0.77	0.04	78.29	4.00	27.52	5.97	5.10	0.07	210.00
	3	0.85	0.06	71.43	6.15	49.75	22.28	11.16	0.14	350.00
	4	0.85	0.06	71.56	5.50	49.01	21.86	7.24	0.13	370.00
	5	1.00	0.09	61.06	6.57	96.70	50.29	14.54	0.19	465.00
	6	0.88	0.06	68.61	5.20	56.16	27.94	15.55	0.11	360.00
2	1	0.85	0.04	70.65	3.45	39.79	17.06	7.87	0.07	270.00
	2	0.87	0.05	69.21	3.94	57.70	23.97	11.53	0.09	665.00
	3	0.99	0.07	61.36	5.21	77.74	45.84	36.10	0.15	340.00
	4	0.80	0.03	74.80	3.17	30.07	8.72	9.30	0.07	190.00
	5	0.93	0.05	64.98	3.94	59.15	33.57	14.37	0.11	345.00
	6	0.92	0.05	65.40	4.14	52.43	29.48	21.93	0.11	310.00
3	1	0.86	0.03	69.65	2.93	32.22	9.94	10.28	0.08	225.00
	2	0.93	0.07	64.75	5.05	73.69	49.96	12.32	0.17	380.00
	3	0.98	0.09	61.85	5.51	99.86	50.57	24.03	0.17	415.00
	4	1.03	0.09	59.08	5.35	102.95	56.52	48.68	0.18	475.00
	5	1.03	0.09	59.06	5.45	99.02	55.43	9.07	0.18	510.00
	6	1.00	0.06	60.52	4.21	76.66	49.00	21.80	0.14	385.00
4	1	0.91	0.06	66.85	5.42	56.35	30.82	22.56	0.13	310.00
	2	0.90	0.06	67.13	5.43	56.04	30.20	15.45	0.13	310.00
	3	0.85	0.05	71.47	4.99	49.08	25.30	22.23	0.11	285.00
	4	0.86	0.06	70.58	5.24	52.62	29.02	15.40	0.13	300.00
	5	0.83	0.05	73.28	5.68	48.35	23.34	31.74	0.11	280.00
	6	0.86	0.05	70.92	5.81	51.26	29.89	16.66	0.11	290.00

Table 3.2.1. *The individual time and frequency domain measures for the 6 recordings (on the 6 consecutive days) for each of the nine subjects – continued*

Subject	Observ	Mean RR (s)	RR STD (s)	Mean HR (bpm)	HR STD (bpm)	RMSSD (ms)	pNN50 (%)	SDANN (ms)	RR tri ind	TINN (ms)
5	1	0.88	0.04	68.43	3.62	40.97	22.52	9.31	0.08	235.00
	2	0.89	0.05	67.95	4.21	53.17	39.44	46.15	0.11	325.00
	3	0.89	0.05	68.00	4.61	54.66	39.16	10.50	0.10	305.00
	4	0.84	0.05	71.64	4.48	50.74	36.08	33.29	0.10	395.00
	5	0.71	0.03	84.36	4.22	30.01	6.44	34.42	0.06	190.00
	6	0.81	0.05	74.39	4.74	48.54	34.78	30.64	0.11	285.00
6	1	0.83	0.06	72.72	5.54	64.32	33.13	16.12	0.10	370.00
	2	0.94	0.11	65.12	8.42	130.35	61.62	30.39	0.22	510.00
	3	0.92	0.10	66.92	8.40	116.79	54.77	30.51	0.18	490.00
	4	0.90	0.10	68.15	8.76	117.33	52.36	15.34	0.18	515.00
	5	0.99	0.12	61.99	8.19	144.45	65.18	19.73	0.23	695.00
	6	0.86	0.10	71.31	8.02	111.73	49.93	49.16	0.16	480.00
7	1	0.87	0.07	69.87	7.11	62.17	27.82	23.24	0.13	385.00
	2	0.78	0.03	77.07	4.40	28.14	6.72	26.79	0.07	205.00
	3	0.90	0.07	68.15	6.90	68.53	33.01	47.71	0.11	385.00
	4	0.79	0.03	76.23	4.35	28.77	7.19	13.80	0.07	205.00
	5	0.91	0.09	67.37	7.60	93.57	41.99	33.02	0.16	600.00
	6	0.90	0.10	67.67	7.71	94.66	41.84	23.75	0.14	615.00
8	1	0.89	0.07	67.83	6.82	68.69	35.75	20.22	0.11	465.00
	2	0.87	0.06	69.25	6.01	66.46	39.68	24.35	0.11	340.00
	3	0.78	0.05	78.22	6.25	51.36	20.56	33.75	0.09	330.00
	4	0.81	0.06	75.02	7.17	59.05	31.67	22.12	0.11	345.00
	5	0.82	0.06	74.02	6.50	57.72	29.73	23.09	0.11	320.00
	6	0.85	0.05	71.24	5.37	54.11	37.58	9.27	0.09	275.00
9	1	0.83	0.05	72.73	4.97	38.11	16.49	32.82	0.10	265.00
	2	0.78	0.05	77.09	5.08	30.89	10.45	10.46	0.10	225.00
	3	0.91	0.06	66.35	5.48	49.99	28.92	29.90	0.13	315.00
	4	0.91	0.06	66.65	5.58	49.28	29.77	28.52	0.13	325.00
	5	0.84	0.06	72.13	6.67	52.73	25.89	18.07	0.11	350.00
	6	0.89	0.06	67.93	6.41	47.04	26.57	45.09	0.13	375.00

Table 3.2.1. *The individual time and frequency domain measures for the 6 recordings (on the 6 consecutive days) for each of the nine subject s– continued*

Subject	Observ	SD1 (ms)	SD2 (ms)	LF (ms²)	HF (ms²)	TP (ms²)	LF n.u.	HF n.u.	LF/HF
1	1	33.70	99.20	1209.33	404.59	1613.92	74.93	25.07	2.99
	2	19.59	59.98	450.17	175.82	625.99	71.91	28.09	2.56
	3	35.44	108.84	1616.36	491.61	2107.97	76.68	23.32	3.29
	4	34.89	101.77	1283.37	414.94	1698.31	75.57	24.43	3.09
	5	68.67	143.22	2082.70	1789.65	3872.34	53.78	46.22	1.16
	6	39.91	103.15	1133.81	549.89	1683.70	67.34	32.66	2.06
2	1	28.30	63.89	262.14	295.22	557.37	47.03	52.97	0.89
	2	40.77	73.11	313.02	448.17	761.19	41.12	58.88	0.70
	3	55.28	126.21	745.60	1037.39	1782.98	41.82	58.18	0.72
	4	21.38	48.57	152.50	204.28	356.78	42.74	57.26	0.75
	5	42.03	95.35	396.31	618.54	1014.85	39.05	60.95	0.64
	6	37.46	90.33	391.50	458.90	850.40	46.04	53.96	0.85
3	1	22.88	54.83	205.46	274.10	479.56	42.84	57.16	0.75
	2	52.27	96.52	508.10	1769.84	2277.94	22.31	77.69	0.29
	3	70.83	114.37	2007.02	1849.01	3856.02	52.05	47.95	1.09
	4	73.05	138.61	918.62	2089.42	3008.04	30.54	69.46	0.44
	5	70.20	119.75	1703.57	1935.59	3639.17	46.81	53.19	0.88
	6	54.41	93.80	428.80	1439.30	1868.10	22.95	77.05	0.30
4	1	40.06	113.31	858.76	879.44	1738.20	49.41	50.60	0.98
	2	39.85	115.72	892.43	855.81	1748.24	51.05	48.95	1.04
	3	34.88	107.37	562.90	581.11	1144.01	49.20	50.80	0.97
	4	37.39	100.91	883.26	614.25	1497.51	58.98	41.02	1.44
	5	34.41	119.10	787.79	683.53	1471.32	53.54	46.46	1.15
	6	36.48	116.80	628.83	626.88	1255.70	50.08	49.92	1.00
5	1	29.10	61.65	198.25	452.12	650.36	30.48	69.52	0.44
	2	37.74	87.92	288.36	656.57	944.92	30.52	69.48	0.44
	3	38.81	79.37	241.54	698.54	940.08	25.69	74.31	0.35
	4	36.01	85.44	275.96	639.94	915.89	30.13	69.87	0.43
	5	21.33	64.29	136.05	285.77	421.82	32.25	67.75	0.48
	6	34.45	77.77	299.37	690.04	989.41	30.26	69.74	0.43

Table 3.2.1. *The individual time and frequency domain measures for the 6 recordings (on the 6 consecutive days) for each of the nine subjects – continued*

Subject	Observ	SD1 (ms)	SD2 (ms)	LF (ms²)	HF (ms²)	TP (ms²)	LF n.u.	HF n.u.	LF/HF
6	1	45.67	94.92	436.60	899.03	1335.62	32.69	67.31	0.49
	2	92.58	169.39	1671.28	3466.61	5137.88	32.53	67.47	0.48
	3	83.01	168.87	1748.86	3091.90	4840.76	36.13	63.87	0.57
	4	83.40	171.35	2252.83	3035.02	5287.85	42.60	57.40	0.74
	5	102.62	192.08	3002.02	3865.81	6867.83	43.71	56.29	0.78
	6	79.33	171.86	1790.62	2755.85	4546.48	39.38	60.62	0.65
7	1	44.42	153.77	1877.56	685.35	2562.91	73.26	26.74	2.74
	2	20.10	75.53	324.37	112.49	436.86	74.25	25.75	2.88
	3	48.87	157.57	1808.83	692.06	2500.89	72.33	27.67	2.61
	4	20.55	73.74	366.76	121.45	488.21	75.12	24.88	3.02
	5	66.57	159.02	3291.17	1311.59	4602.77	71.50	28.50	2.51
	6	67.38	159.79	2996.31	1285.34	4281.65	69.98	30.02	2.33
8	1	48.87	119.05	1014.64	702.85	1717.50	59.08	40.92	1.44
	2	47.24	102.89	652.65	797.00	1449.65	45.02	54.98	0.82
	3	36.55	104.23	565.96	487.40	1053.37	53.73	46.27	1.16
	4	42.03	114.08	592.35	624.20	1216.54	48.69	51.31	0.95
	5	41.06	107.33	548.02	575.19	1123.21	48.79	51.21	0.95
	6	38.47	89.30	597.15	482.05	1079.20	55.33	44.67	1.24
9	1	27.19	93.79	679.95	357.82	1037.77	65.52	34.48	1.90
	2	22.06	80.84	427.43	273.70	701.13	60.96	39.04	1.56
	3	35.71	112.76	951.01	588.99	1540.00	61.75	38.25	1.61
	4	35.25	113.81	912.94	602.49	1515.42	60.24	39.76	1.52
	5	37.62	116.77	1380.38	550.61	1930.99	71.49	28.51	2.51
	6	33.73	136.78	1160.80	477.65	1638.45	70.85	29.15	2.43

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CHAPTER 4
RESULTS

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A. SUBJECT DATA SUMMARY

A comprehensive description of all the results obtained for each one of the subjects is provided in the Appendix to this chapter (p. 4.35). This part of the work is separated from the rest as it is required as part of an MSc dissertation, but the reader does not necessarily have to read it to follow the study.

In the section to follow (Section A), short descriptions are given for each patient in Part I, and each control in Part II. In this section, the FIQ total score is out of 100 (severely afflicted patients usually obtain a score of 50-70). The symptom score was calculated from responses to the symptoms listed on the Review of Current Symptoms questionnaire. The total number of symptoms with which the subject presented was calculated out of a total of 100 symptoms. SAM-axis function is described in terms of the amount of variability (indicated by the total power in the frequency domain) and the subject's autonomic response to orthostatic stress (HRV should decrease in the standing position). HPA-axis function is reflected in basal cortisol levels (a normal cortisol level for the time the subjects were evaluated would be 4-8 ng/ml). The attachment style of the subjects is described as secure (low anxiety and avoidance), preoccupied (high anxiety, low avoidance), fearful-avoidant (high anxiety, high avoidance) and dismissing-avoidant (low anxiety, high avoidance).

Abbreviations: *FM: fibromyalgia; FIQ: Fibromyalgia Impact Questionnaire; SAM-axis: sympatho-adrenal-medullary stress-axis; HPA-axis: hypothalamic-pituitary-adrenal stress-axis; HRV: heart rate variability; BMI: Body Mass Index.*

I. Short description of each patient

Patient 1

Patient 1 is a 49-year-old female who has been suffering from FM for 31 years. Her symptoms first started to appear after a period of overexertion and major stress. She did not report any traumatic events during childhood (except for suffering from an eating disorder as a young adult). The patient's FIQ total score was 47.33 and symptom score 73. Assessment of the SAM-axis and HPA-axis function showed lowered HRV with a normal autonomic reaction to orthostatic stress (Supine - 232.99 ms^2; Standing – 10.40

ms²) and an elevated basal cortisol level of 11.5 ng/ml. Patient 1 is right-brain orientated and has a fearful-avoidant attachment style.

Patient 2

Patient 2 is a 45-year-old female who has been suffering from FM for 20 years. Her FM complaints started gradually. She reported traumatic school years (she wet her bed from 7 to 19 years of age), and an unfulfilling marriage for the past 26 years as possible triggers for her symptoms. The patient's FIQ total score was 73.34 and symptom score 36. Assessment of the SAM-axis and HPA-axis function indicated a normal autonomic reaction to orthostatic stress (Supine – 589.73 ms²; Standing – 149.60 ms²) and an elevated basal cortisol level of 10.0 ng/ml. Patient 2's preferred thinking style seems to be strongly influenced by the limbic brain function. She shows features characteristic of the dismissing attachment style.

Patient 3

Patient 3 is a 52-year-old female who has been suffering from FM for 25 years. Her symptoms started to appear gradually. As a child, Patient 3 had rheumatic fever. She reported the death of both her parents and husband (later in life) as possible contributing factors in the development of her complaints. The patient's FIQ total score was 74.00 and symptom score 77. Assessment of the SAM-axis and HPA-axis function showed marked lowered HRV (Supine – 53.11 ms²; Standing – discarded) and an elevated basal cortisol level of 10.5 ng/ml. Patient 3 gave a right-brain profile on testing and has a preoccupied attachment style.

Patient 4

Patient 4 is a 21-year-old female who has been suffering from FM for 3 years. Her symptoms started to appear gradually after a period of overexertion and psychological stress. She did not report any traumatic events during childhood (except for the diagnosis of diabetes three years earlier). The patient's FIQ total score was 35.62 and she presented with a total of 28 symptoms. Assessment of the SAM-axis and HPA-axis function showed extremely low HRV with an inability to mount an appropriate autonomic response to orthostatic stress (Supine – 3.38 ms²; Standing – 4.32 ms²) and a basal cortisol level within the normal range (6.5 ng/ml). Patient 4 is right-brain orientated and has a preoccupied attachment style.

Patient 5

Patient 5 is a 35-year-old male who has been suffering from FM for 8 years. His symptoms started to appear gradually. He reported a major traumatic incident at the age of seven. The patient's FIQ total score was 54.19 and he presented with a total of 44 symptoms. Apart from that, this patient does not show the typical profile exhibited by the other patients. Assessment of the SAM-axis and HPA-axis function showed a healthy HRV with a normal autonomic reaction to stress (Supine – 2776.54 ms^2; Standing – 1253.52 ms^2) and a basal cortisol level within the normal range (4.5 ng/ml). Patient 5 seems to be left-brain orientated and has a secure attachment style.

Patient 6

Patient 6 is a 55-year-old female who has been suffering from FM for 41 years. Her symptoms started to appear gradually from the age of 14. She reported being molested (age 4), a miscarriage, unfulfilling marriage and the death of her father as possible contributing factors in the development of her complaints. The patient's FIQ total score was 72.86 and symptom score 70. Assessment of the SAM-axis and HPA-axis function showed markedly low HRV with decreased autonomic reaction to orthostatic stress (Supine – 80.48 ms^2; Standing – 57.78 ms^2) and a basal cortisol level within the normal range (7.5) ng/ml. Patient 6 gave a right-brain profile on testing, together with a strong preference for thinking styles influenced by the left limbic brain function. She shows features characteristic of the dismissing attachment style.

Patient 7

Patient 7 is a 48-year-old female who has been suffering from FM for 28 years. Her symptoms first started to appear after a major psychological stressor. A possible etiological factor in the patient's past is the rheumatic fever she had as a child. The patient's FIQ total score was 74.41 and symptom score 95. Assessment of the SAM-axis and HPA-axis function showed marked lowered HRV with suboptimal autonomic reaction to stress (Supine – 49.39 ms^2; Standing – 18.28 ms^2) and a basal cortisol level within the normal range (6.5 ng/ml). Patient 7's preferred thinking is strongly influenced by the limbic brain function and she has a secure attachment style.

Patient 8

Patient 8 is a 33-year-old female who has been suffering from FM for 12 years. Her symptoms first started following an illness and two great psychological stressors (these occurred in short succession of one another). The patient's FIQ total score was 42.18 and symptom score 33. Assessment of the SAM-axis and HPA-axis function indicated a normal autonomic reaction in response to orthostatic stress (Supine – 602.99 ms^2; Standing – 102.33 ms^2) and an elevated basal cortisol level of 10.5 ng/ml. Patient 8 is right-brain orientated, and also exhibits a strong preference for thinking styles influenced by the left limbic brain function. She has a secure attachment style.

Patient 9

Patient 9 is a 40-year-old male who has been suffering from FM for 5 years. His symptoms first started to appear after a great psychological stressor. Early childhood trauma included an alcoholic father and the death of this parent. In adult life, he experienced his divorce to be especially distressing. The patient's FIQ total score was 87.85 and symptom score 47. Assessment of the SAM-axis and HPA-axis function showed markedly low HRV in the supine bodily position (Supine – 63.18 ms^2; Standing – 195.24 ms^2) and an elevated basal cortisol level of 9.5 ng/ml. Patient 9 gave a right-brain profile on testing, together with a strong preference for thinking styles influenced by the left limbic brain function. He has a preoccupied attachment style.

Patient 10

Patient 10 is a 63-year-old female who has been suffering from FM for 21 years. Her symptoms started to appear gradually. She did not report any traumatic events during childhood, but had a neck fusion at the age of 50. The patient's FIQ total score was 58.04 and symptom score 37. Assessment of the SAM-axis and HPA-axis function showed markly lower HRV in the standing bodily position (Supine – 2408.88 ms^2; Standing – 273.09 ms^2) and an exceptionally high basal cortisol level (16.5 ng/ml). Patient 10 is right-brain orientated, together with a strong preference for thinking styles marked by left cortical processing. She has a secure attachment style.

Patient 11

Patient 11 is a 33-year-old female who has been suffering from FM for 4 years. Her symptoms started to appear gradually. As a child, Patient 11 had polio. Her FIQ total

score was 60.59 and symptom score 35. Assessment of the SAM-axis and HPA-axis function showed markedly lower HRV with suboptimal autonomic reaction to orthostatic stress (Supine – 69.18 ms²; Standing – 33.49 ms²) and an elevated basal cortisol level of 9.0 ng/ml. Patient 11 gave a right-brain profile on testing, together with a strong preference for thinking styles influenced by the left limbic brain function. She shows features characteristic of the dismissing attachment style.

Patient 12

Patient 12 is a 41-year-old female who has been suffering from FM for 15 years. Her symptoms first started to appear after an operation. She reported to have had glandular fever and hepatitis in adult life. She also had an emotionally draining marriage which ended in divorce. The patient's FIQ total score was 58.58 and symptom score 95. Assessment of the SAM-axis and HPA-axis function showed markedly lower HRV with an inability to mount an appropriate autonomic response to orthostatic stress (Supine – 134.62 ms²; Standing – 139.92 ms²) and a basal cortisol level at the higher end of the normal range (8.0 ng/ml). Patient 12 is right-brain orientated, with a strong preference for thinking styles influenced by the left limbic brain function. She has a fearful-avoidant attachment style.

Patient 13

Patient 13 is a 46-year-old female who has been suffering from FM for 10 years. Her symptoms first started to appear following an accident. Patient 13 reported to have had a very stressful, unhappy childhood. The patient's FIQ total score was 53.33 and symptom score 21. Assessment of the SAM-axis and HPA-axis function showed low HRV with an inability to mount an appropriate response to orthostatic stress (Supine – 194.52 ms²; Standing – 191.0 ms²) and an elevated basal cortisol level of 10.0 ng/ml. Patient 13 gave a right-brain profile on testing, together with a strong preference for thinking styles influenced by the left limbic brain function. She shows features characteristic of the fearful-avoidant attachment style.

Patient 14

Patient 14 is a 38-year-old female who has been suffering from FM for 4 years. Her symptoms started to appear gradually. Traumatic incidents in adult life included a miscarriage, a difficult pregnancy, marital problems and a separation from her husband.

The patient's FIQ total score was 40.25 and symptom score 45. Assessment of the SAM-axis and HPA-axis function showed low HRV with suboptimal autonomic response to orthostatic stress (Supine – 231.80 ms²; Standing – 37.46 ms²) and an elevated basal cortisol level of 12.0 ng/ml. Patient 14 is left-brain orientated, with a strong preference for thinking styles influenced by the right limbic brain function. She has a secure attachment style.

Patient 15

Patient 15 is a 53-year-old female who has been suffering from FM for 20 years. Her symptoms started gradually with chronic colds and flues following her father's death. The patient's FIQ total score was 40.76 and symptom score 40. Assessment of the SAM-axis and HPA-axis function showed extremely low HRV with an inability to mount an appropriate autonomic reaction to orthostatic stress (Supine – 22.42 ms²; Standing – 22.15 ms²) and an elevated basal cortisol level of 10.0 ng/ml. Patient 15 seems to be right-brain orientated, together with a very strong preference for thinking styles influenced by the left limbic brain structures. She has a secure attachment style.

Patient 16

Patient 16 is a 52-year-old female who has been suffering from FM for 18 years. Her symptoms first started to appear after an operation and a period of overexertion and major stress. Traumatic early life experiences include her parents' divorce (age 2), being molested (age 4) and the rejection of her biological father. In adult life she lost her eldest son. The patient's FIQ total score was 49.67 and symptom score 58. Assessment of the SAM-axis and HPA-axis function showed markedly low HRV (Supine – 64.70 ms²; Standing – 109.58 ms²) and an elevated basal cortisol level of 12.0 ng/ml. Patient 16 gave a right-brain profile on testing and has a secure attachment style.

II. Short description of each control

Control 1

Control 1 is a 51-year-old, healthy female who has a BMI similar to that of Patient 1. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score and symptom score were 0.0. The control had a relative healthy amount of variability in heart rate with a normal autonomic response to orthostatic stress (Supine

– 500.97 ms²; Standing – 87.68 ms²) and a basal cortisol level within the normal range (6.0 ng/ml). Control 1 has a secure attachment style.

Control 2

Control 2 is a 44-year-old, healthy female who has a BMI similar to that of Patient 2. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score and symptom score were 0.0. The control had low HRV with an unusual autonomic response to stress (Supine – 123.43 ms²; Standing – 162.19 ms²) and a basal cortisol level slightly lower than the normal range (2.5 ng/ml). Control 2 has a secure attachment style.

Control 3

Control 3 is a 55-year-old, healthy female who has a BMI similar to that of Patient 3. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score was 6.05 and she had 2 symptoms. The control had a basal cortisol level within the normal range (4.0 ng/ml). Control 3 has a secure attachment style. This subject's HRV recording was discarded.

Control 4

Control 4 is a 21-year-old, healthy female who has a BMI similar to that of Patient 4. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score was 0.0 and she presented with 7 symptoms. The control had a relatively healthy amount of variability in heart rate with a normal autonomic response to orthostatic stress (Supine – 616.64 ms²; Standing – 87.87 ms²) and a basal cortisol level within the normal range (7.0 ng/ml). Control 4 has a secure attachment style.

Control 5

Control 5 is a 27-year-old, healthy male who has a BMI similar to that of Patient 5. He did not report any traumatic experiences or serious illnesses in his lifetime. The control's FIQ total score was 4.0 and he presented with 3 symptoms. The control had a healthy amount of variability in heart rate with a normal response to orthostatic stress (Supine – 2466.57 ms²; Standing – 1013.74 ms²) and a basal cortisol level within the normal range (5.5 ng/ml). Control 5 has a secure attachment style.

Control 6

Control 6 is a 55-year-old, healthy female who has a BMI similar to that of Patient 6. She reported having had hepatitis as a child and pneumonia as an adult. She also reported to have had a miscarriage. The control's FIQ total score was 0.0 and symptom score 5. The control had a relatively healthy amount of variability in heart rate with a normal autonomic response to orthostatic stress (Supine – 529.03 ms^2; Standing – 202.49 ms^2) and a basal cortisol level slightly lower than the normal range (3.0 ng/ml). Control 6 has a secure attachment style.

Control 7

Control 1 is a 55-year-old, healthy female who has a BMI similar to that of Patient 7. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score was 10.03 and she had one symptom. The control had a basal cortisol level within the normal range (7.5 ng/ml). Control 7 has a secure attachment style. This subject's HRV recording was discarded.

Control 8

Control 8 is a 36-year-old, healthy female who has a BMI similar to that of Patient 8. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score was 3.63 and she did not present with any symptoms. The control had lowered HRV with an unusual autonomic response to orthostatic stress (Supine – 52.51 ms^2; Standing – 65.03 ms^2) and a basal cortisol level within the normal range (7.5 ng/ml). Control 8 has a secure attachment style.

Control 9

Control 9 is a 31-year-old, healthy male who has a BMI similar to that of Patient 9. He did not report any traumatic experiences or illnesses in his lifetime. The control's FIQ total score was 0.0 and he had three symptoms. The control had a healthy amount of variability in heart rate with an unusual response to orthostatic stress (Supine – 1377.72 ms^2; Standing – 1625.26 ms^2) and a basal cortisol level within the normal range (5.0 ng/ml). Control 9 has a secure attachment style.

Control 10

Control 10 is a 60-year-old, healthy female who has a BMI similar to that of Patient 10. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score and symptom score was 0.0. The control had a relatively healthy amount of variability in heart rate with an unusual response to orthostatic stress (Supine – 339.86 ms^2; Standing – 850.59 ms^2) and a basal cortisol level within the normal range (8.5 ng/ml). Control 10 has a secure attachment style.

Control 11

Control 11 is a 39-year-old, healthy female who has a BMI similar to that of Patient 11. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score was 0.0 and she had one symptom. The control had a healthy amount of variability in heart rate with a normal autonomic response to orthostatic stress (Supine – 1487.19 ms^2; Standing – 1214.5 ms^2) and a basal cortisol level slightly higher than the normal range (9.0 ng/ml). Control 11 has a secure attachment style.

Control 12

Control 12 is a 40-year-old, healthy female who has a BMI similar to that of Patient 12. She reported an accident at 36 years of age. The control's FIQ total score was 28.48 and she presented with 7 symptoms. The control had a basal cortisol level within the normal range (5.5 ng/ml). Control 12 has a secure attachment style. This subject's HRV recording was discarded.

Control 13

Control 13 is a 49-year-old, healthy female who has a BMI similar to that of Patient 13. She did not report any traumatic experiences or serious illnesses in her lifetime. The control's FIQ total score was 11.58 and she presented with a total of 13 symptoms. The control had low HRV with a normal response to orthostatic stress (Supine – 125.62 ms^2; Standing – 92.23 ms^2) and a basal cortisol level slightly lower than the normal range (12.0 ng/ml). Control 13's attachment style was not evaluated.

Control 14

Control 14 is a 39-year-old female who has a BMI similar to that of Patient 14. At the age of 43 this control had a melanoma removed. The control's FIQ total score was 7.0

and she presented with a total of 13 symptoms. The control had a relatively healthy amount of variability in heart rate with a normal autonomic response to orthostatic stress (Supine – 359.30 ms²; Standing – 119.34 ms²) and a basal cortisol level within the normal range (8.0 ng/ml). Control 14 has a secure attachment style.

Control 15

Control 15 is a 52-year-old, healthy female who has a BMI similar to that of Patient 15. She did not report any traumatic experiences in her lifetime. The control's FIQ total score was 3.33 and she presented with one symptom. The control had a relative healthy amount of variability in heart rate with a normal autonomic response to orthostatic stress (Supine – 514.49 ms²; Standing – 162.19 ms²) and a basal cortisol level slightly lower than the normal range (3.0 ng/ml). Control 15 has a secure attachment style.

B. DESCRIPTIVE STATISTICS

1. Patient health questionnaire

1.1. Age

Mean age
Patient group: 43.94 yrs (SD 10.46) Youngest patient - 21 yrs, oldest patient – 63 yrs
Control group: 43.20 yrs (SD 11.19) Youngest control - 21 yrs, oldest control – 60 yrs
Statistical difference (Mann-Whitney test): p-value = 0.8898

Age interval classes for subjects

Figure 1.1. Bar graph demonstrating age interval classes for patients. Because controls were age-matched to patients, the same age intervals apply to the controls (thus the age intervals are the same for controls).

1.2. Gender

Patient group (n=16)
Female: 14 (87.5%)
Male: 2 (12.5%)

Control group (n=15)
Female: 13 (86.7%)
Male: 2 (13.3%)

The gender distribution for the two groups did not differ significantly

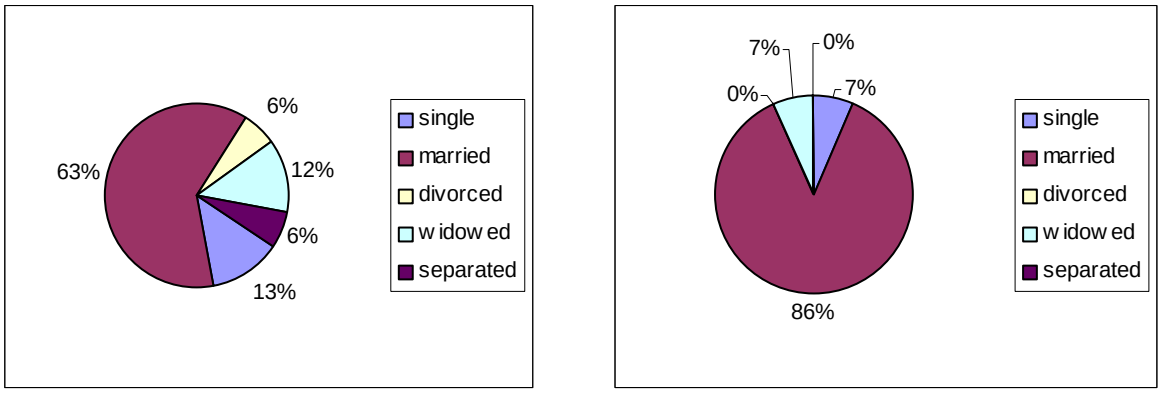
1.3. Body Mass Index (BMI)

Patient group (n=16)
Mean: 25.84 (SD 4.53)

Control group (n=15)
Mean: 24.64 (SD 3.18)

Statistical difference (Mann-Whitney test): p = 0.5015 (non-significant)

1.4. Marital status



A **B**

Figure 1.4. Pie graph demonstrating the marital status of subjects. **A**: Marital status of patients **B**: Marital status of controls (in these graphs 'single' refers to never married)

1.5. Highest qualification obtained

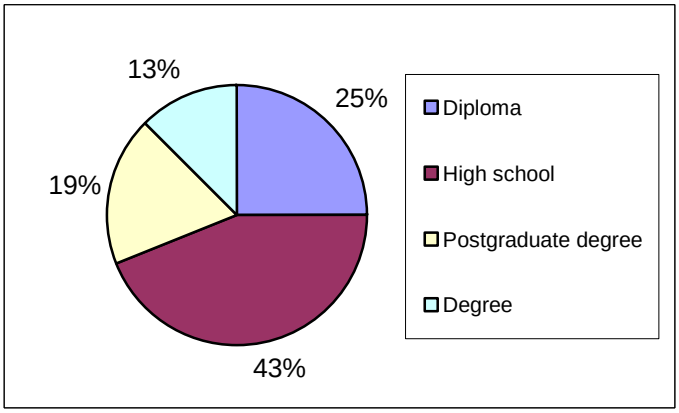


Figure 1.5.1. Pie graph demonstrating education level of patients (32 % of patients were graduates)

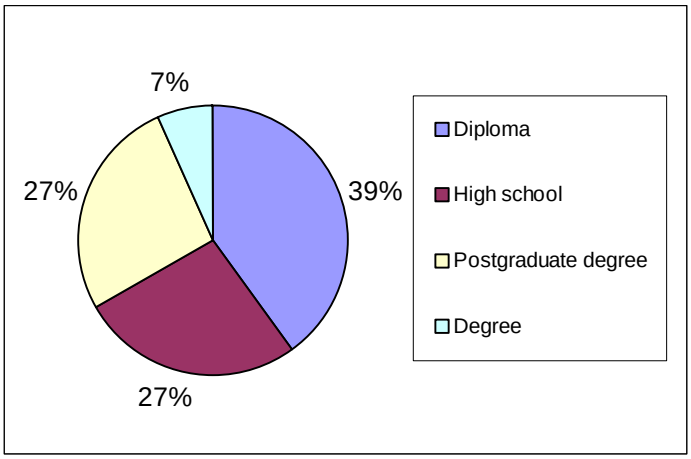


Figure 1.5.2 Pie graph demonstrating education level of controls (34 % of controls were graduates)

1.6. Employment status

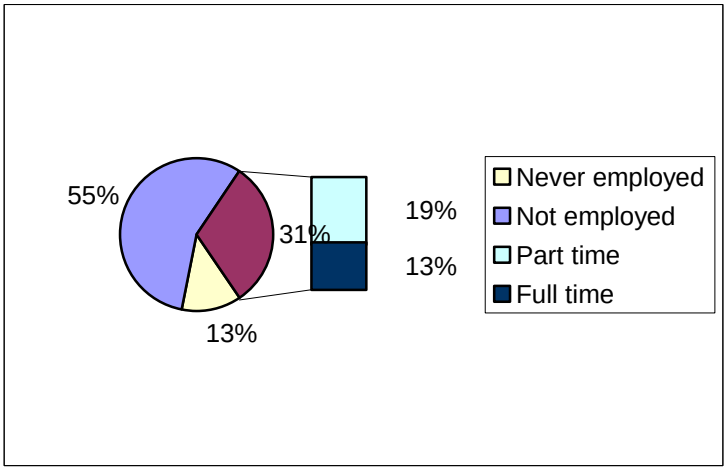


Figure 1.6.1 Pie graph demonstrating the employment status of patients (31 % of patients are currently employed)

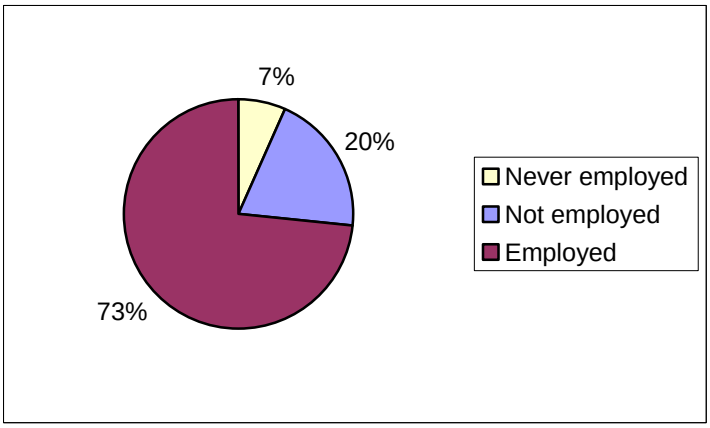


Figure 1.6.2 Pie graph demonstrating the employment status of controls (73 % of controls are currently employed)

1.7. Disability compensation

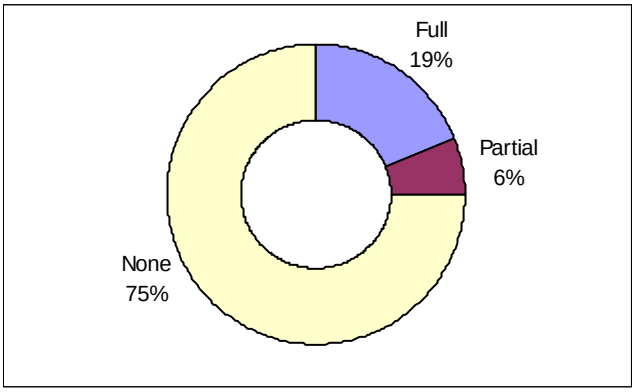


Figure 1.7. Graph demonstrating the disability compensation received by patients. (25 % of patients received disability compensation)

1.8. Fukuda CFS diagnostic criteria

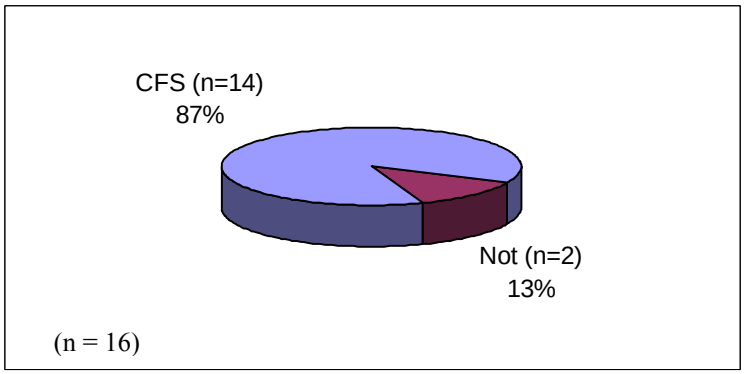


Figure 1.8. Pie graph showing percentage of patients fulfilling Fukuda chronic fatigue syndrome (CFS) diagnostic criteria (none of the controls subjects fulfilled the criteria).

1.9. Physical and psychological stressors in lifetime

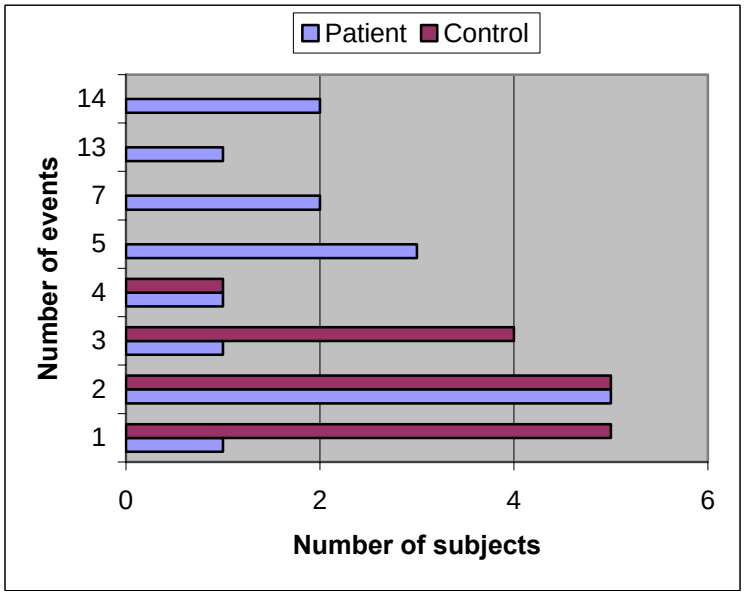


Figure 1.9.1. Bar graph showing the number of lifetime traumatic events for the patients and controls. The y-axis shows the number of events that occurred during the lifetime of the relevant subject on the x-axis.

Patient group (n=16)
Mean (SD): 5.50 (4.44)

Control group (n=14)
Mean (SD): 2.07 (0.96)

Statistical difference
P = 0.0071*

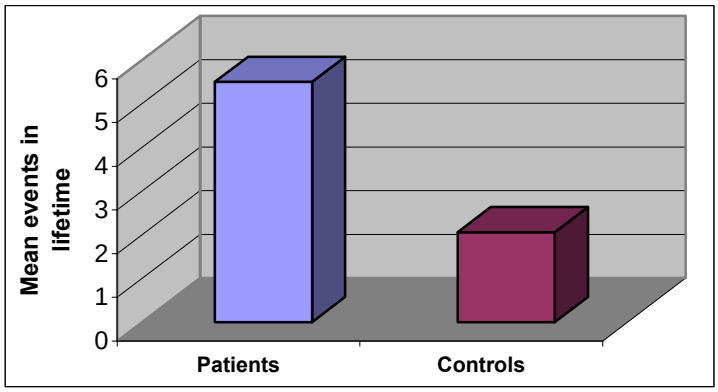


Figure 1.9.2. The mean traumatic events that occurred during the lifetime of patients and controls respectively. P-value obtained with Mann-Whitney test.
* indicates significant difference ($p \leq 0.05$)

1.10. Perceived events that preceded of FM onset

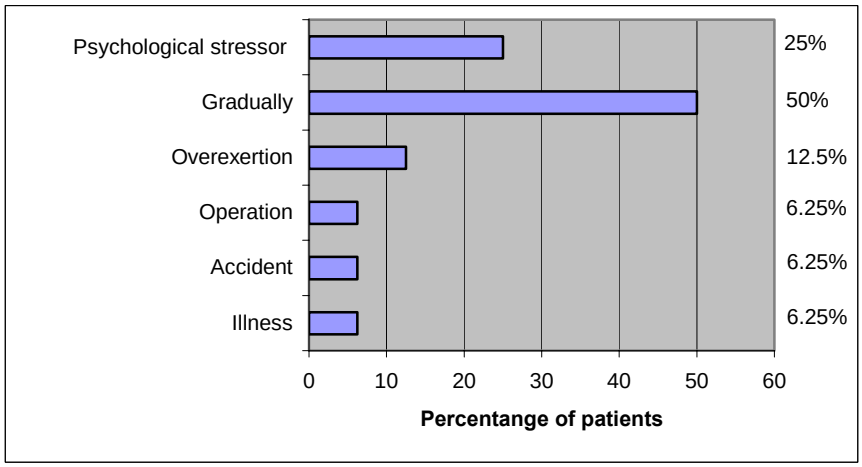


Figure 1.10. Bar graph showing the percentages of the different types of events patients reported to have preceded the onset of their FM complaints.

1.11. Age of onset

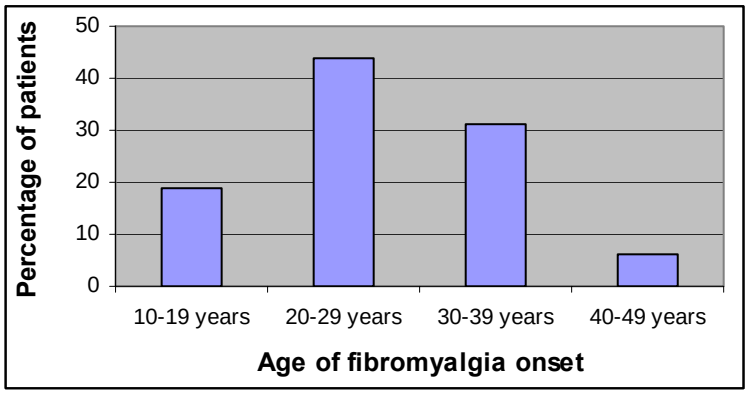


Figure 1.11. Bar graph indicating the most common age interval classes for the onset of fibromyalgia complaints. For each age interval class, the percentage of patients whose symptoms started to appear during that age is indicated on the vertical axis. The ages for onset ranged from 14 to 42 years of age.

1.12. Duration of FM complaints

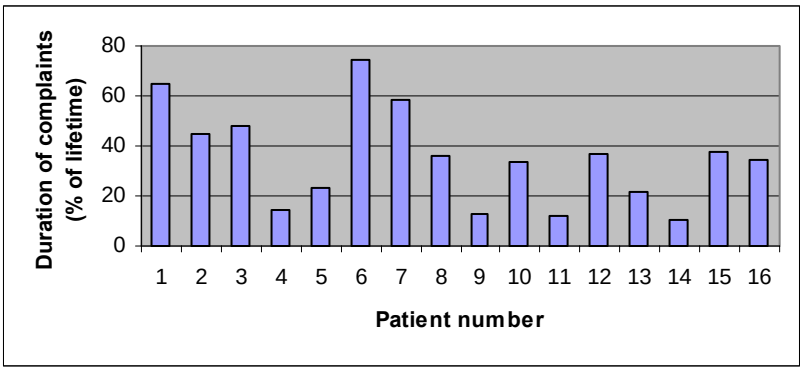


Figure 1.12. Bar graph showing the duration of FM complaints for each patient in terms of the percentage of the patients' lifetime he/she is suffering from FM.

Mean duration of complaints (only applicable to patients)
Mean (n=16): 16.56 (SD 11.03)
Minimum value: 3.00
Maximum value: 41.00

1.13. Natural history of FM complaints (disease progression)

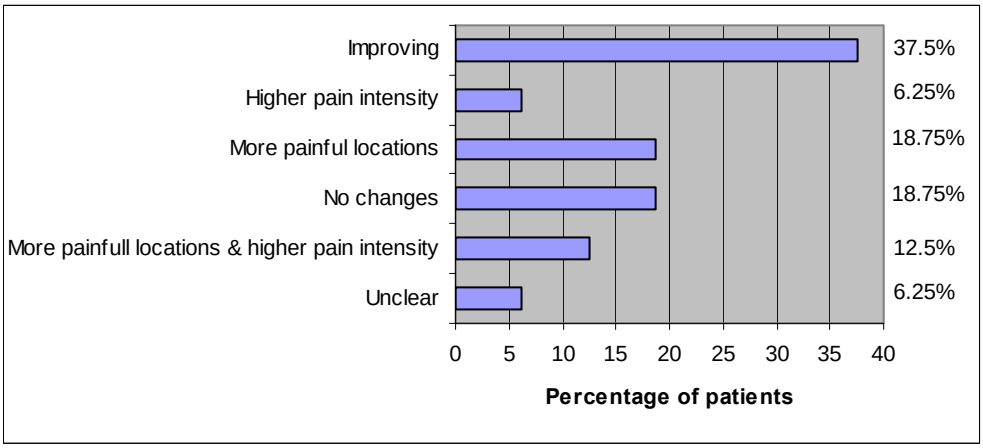


Figure 1.13. Natural history of complaints over previous 12 months as perceived by patients

1.14. Factors influencing FM complaints

Table 1.14. *Factors influencing FM complaints as perceived by patients*

Factors worsening fibromyalgia complaints	
Worse through stress	100 %
Worse through alcohol	50.0 %
Worse through exercise	37.5 %
Worse certain time of day	56.3 %
Worse through humidity changes	62.5 %
Worse through sleep	18.8 %
Worse through caffeine	43.8 %
Worse certain seasons	37.5 %
Worse through heat	56.3 %
Worse through barometric pressure changes	12.5 %
Worse through certain foods	31.3 %
Worse through sunlight	12.5 %
Worse through cold	68.8 %

Factors improving fibromyalgia complaints	
Better through mild exercise	43.8 %
Better through humidity changes	6.3 %
Better through sleep	75 %
Better through heat	18.8 %
Better through barometric pressure changes	6.3 %
Better through certain foods	6.3 %
Better through sunlight	25 %
Better through cold	6.3 %

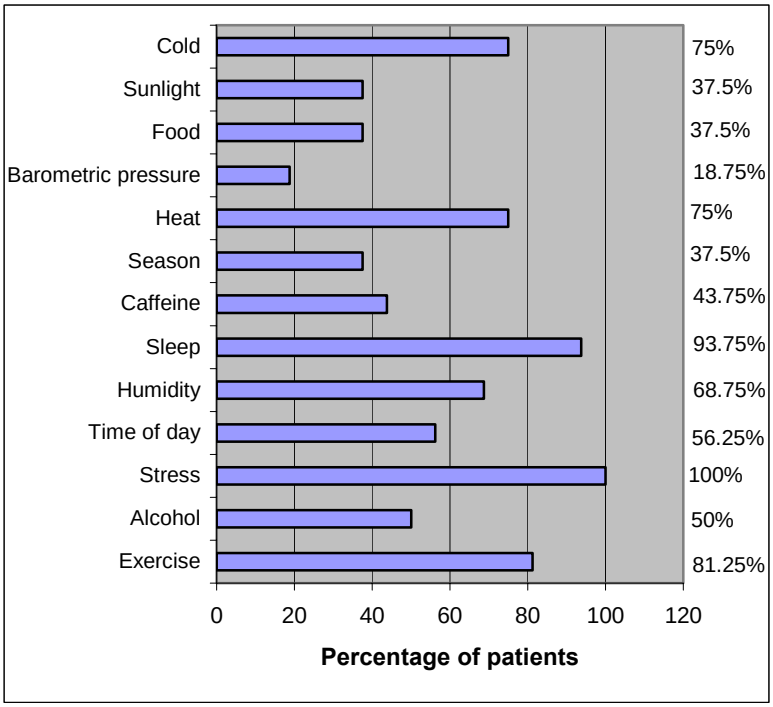


Figure 1.14. Bar graph showing the factors influencing FM symptom status as well as the percentage of patients who are affected by these factors. The effect of these factors on FM symptom status (whether it improves or worsens symptoms) differs from patient to patient.

1.15 Presence of allergies

The number of subjects suffering from allergies

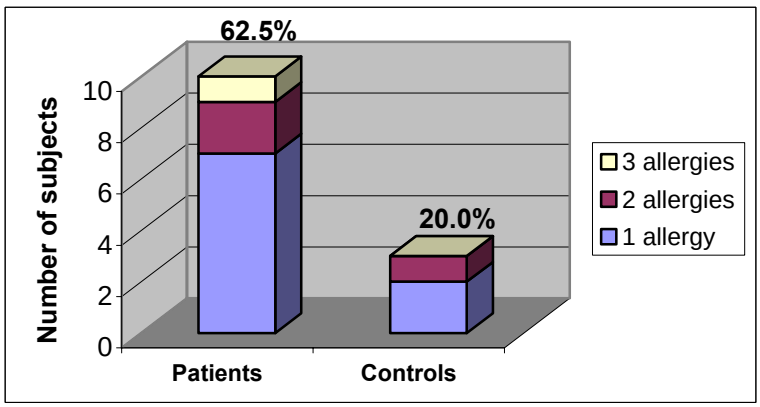


Figure 1.15. Fragmented bar graph showing the number of subjects suffering form allergies. The percentage of patients/controls suffering from allergies is displayed on top of the patient/control bar. Each bar also shows the proportion of the number of allergies each experimental group suffers from.

Means, standard deviation and statistical difference for the number of allergies patients and controls suffer from:
Patient group (n=16): 0.88 (SD 0.89)
Control group (n=15): 0.27 (SD 0.59)
Statistical difference (Mann-Whitney test): p-value = 0.0224*

1.16. Treatment program of patients

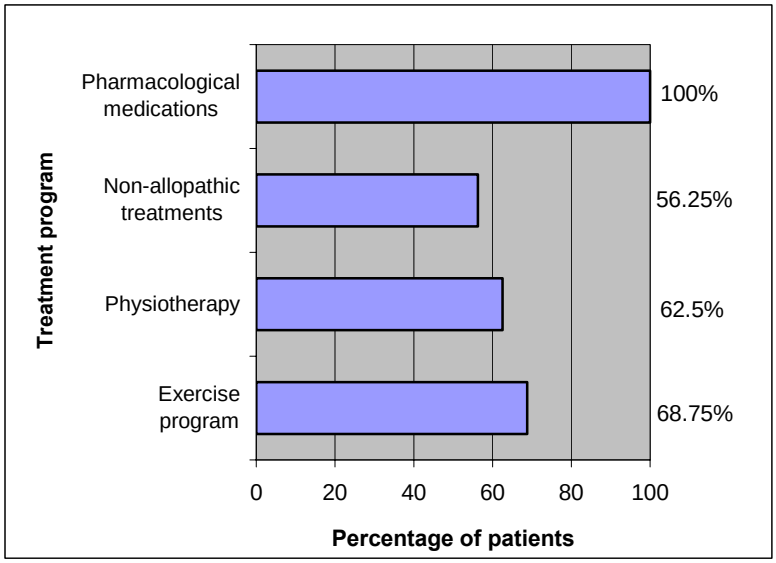


Figure 1.16.a Graph showing the percentages of patients using various treatments.

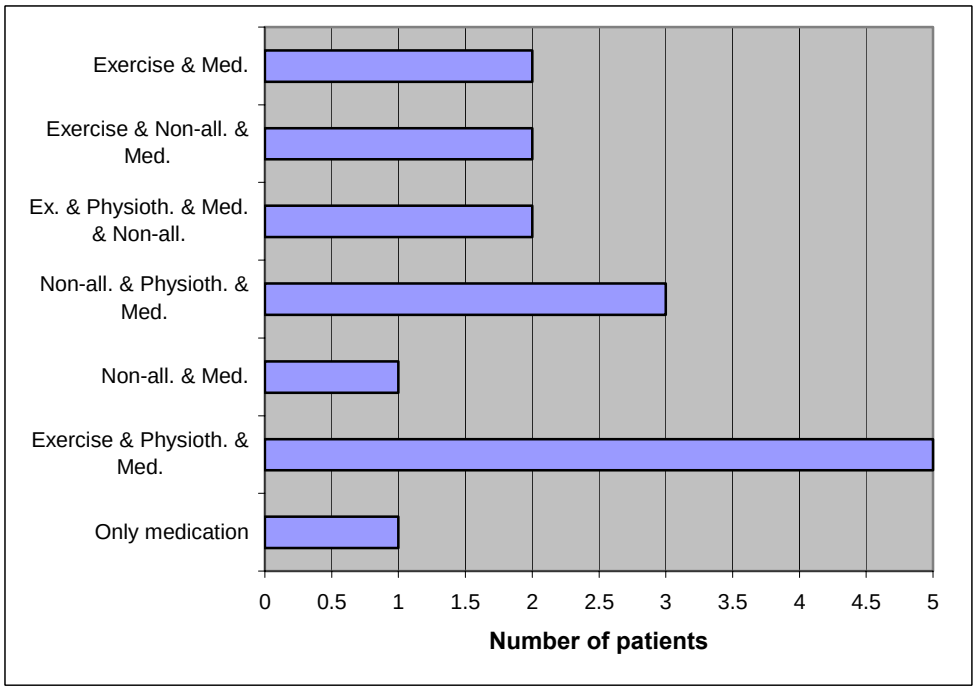


Figure 1.16.b The prevalence of combination therapy in the treatment of FM symptoms.

Table 1.16. *The influence of the treatment program followed on FM disease progression*

	Exercise	Physiotherapy	Medication	Non-allopathic
No change/ worse	6.25 %	6.25 %	43.75 %	6.25 %
Improving	0.00 %	6.25 %	25.00 %	6.25 %
		Statistical difference:	**P-value**	0.6468

The table displays the percentage of patients that showed no change or deterioration, or positive progress in response to various treatment programs. P-value calculated with ANOVA with age as a co-factor.

2. Review of current symptoms (RCS)

Table 2.1. *The mean, standard deviation and statistical difference for the total symptoms patients and controls presented with as indicated by the Review of current symptoms – questionnaire.*

	Mean (SD)	Minimum value	Maximum value	P-value
Patient group	51.69 (23.29)	21.00	95.00	
Control group	4.33 (5.33)	0.00	15.00	<0.0001*

This symptom score was calculated from responses to the symptoms listed on the Review of Current Symptoms questionnaire, and indicate the total number of symptoms the subjects presented with out of the total of 100 symptoms. P-value calculated with ANOVA with age as co-factor.
* indicates a significant difference ($p \leq 0.05$)

Table 2.2. *The means, standard deviation and statistical difference for the 15 symptom categories of the Review of current symptoms – questionnaire (see Figure 2.2.)*

Category number	Category	Patient Mean (SD)	Control Mean (SD)	P-value
1	Constitutional	1.77 (0.56)	0.13 (0.30)	< 0.0001*
2	Skin	0.89 (0.52)	0.02 (0.05)	< 0.0001*
3	Eyes	0.99 (0.63)	0.08 (0.21)	< 0.0001*
4	Ears	1.06 (0.70)	0.18 (0.60)	< 0.0001*
5	Nose/Throat	0.80 (0.56)	0.02 (0.06)	< 0.0001*
6	Mouth	0.64 (0.79)	0.02 (0.06)	0.0134*
7	Lymph nodes	0.97 (0.92)	0.03 (0.13)	< 0.0001*
8	Breast	0.48 (0.66)	0.00 (0.00)	0.3492
9	Lungs	0.92 (0.57)	0.03 (0.06)	< 0.0001*
10	Gastrointestinal	0.94 (0.56)	0.01 (0.06)	< 0.0001*
11	Muscles	2.53 (0.38)	0.22 (0.32)	< 0.0001*
12	Joints	1.52 (0.77)	0.00 (0.00)	< 0.0001*
13	G.U. and Hormonal	0.41 (0.46)	0.01 (0.04)	0.1169
14	Thyroid	0.71 (0.75)	0.00 (0.00)	0.0075*
15	Neuropsychiatric	0.99 (0.52)	0.04 (0.07)	< 0.0001*

Abbreviations: G.U. – genital-urinary tract. P-value calculated with ANOVA with age as co-factor.
* indicates a significant difference ($p \leq 0.05$); reason for non-significant p-value for category 8 and 13 is the great standard deviation in relation to the mean value in the patient group.

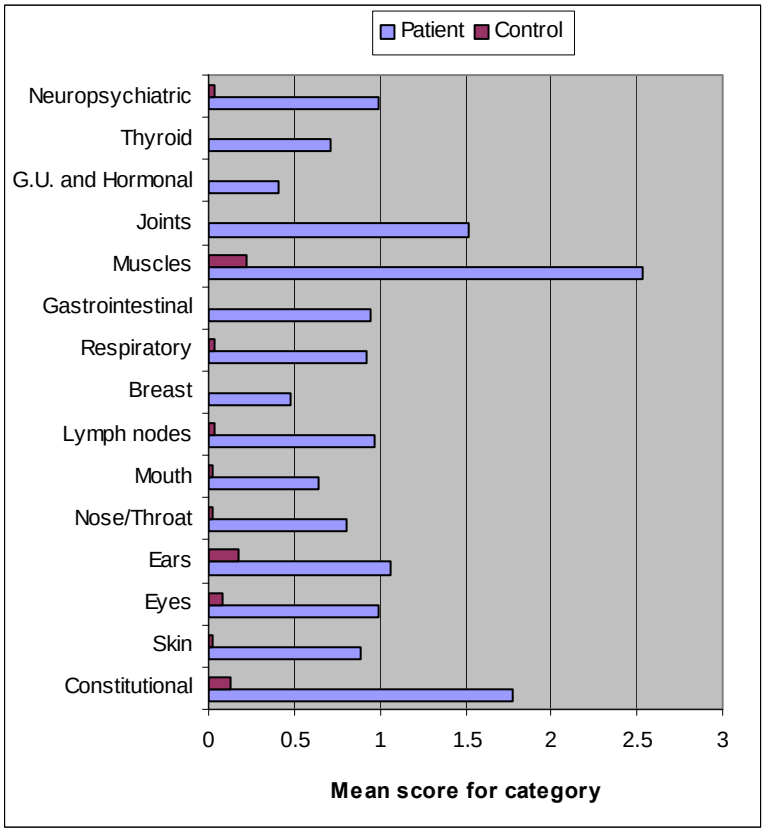


Figure 2.2. Bar graph showing the mean patient and control responses (ranging from 0 – absent; to 3 – severe) for each of the 15 symptom categories of the Review of current symptoms – questionnaire.

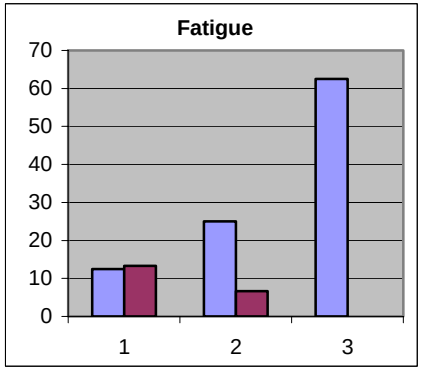
Table 2.3. *The prevalence (in percentage) of the most severe symptoms in patient group in comparison to controls (see Figure 2.3. on next page)*

Symptom	Patients	Controls
General fatigue	100.00%	20.00%
Sleep disturbances	93.75%	13.33%
Tight/ stiff muscles	100.00%	20.00%
Neck pain	100.00%	26.66%
Shoulder pain	93.75%	13.33%
Upper back pain	81.25%	0.07%
Lower back pain	100.00%	40.00%
Severe headaches	75.00%	0.00%

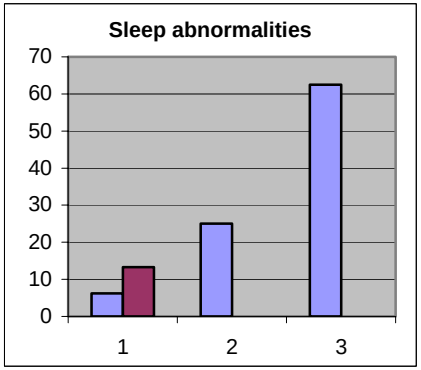
Table 2.4. *The prevalence of associated conditions in the patient and control group*

Associated condition	Patients	Controls
Chronic Fatigue Syndrome	87.50%	0.00%
Irritable Bowel Syndrome	50.94%	1.75%
Headaches	71.88%	13.14%
Premenstrual Syndrome	18.75%	6.67%
Thyroid problems	35.42%	0.00%
Self-assessed global anxiety	68.75%	0.00%
Self-assessed global depression	87.50%	0.07%

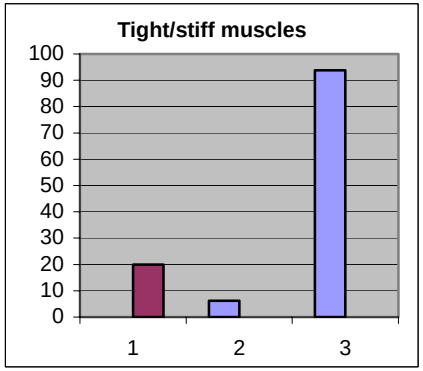
Chronic Fatigue Syndrome judged based on Fukuda diagnostic criteria. Irritable Bowel Syndrome based on the presence of bloating or passing gas, diarrhea, constipation, abdominal cramps and aches. Headaches based on the presence of mild/ moderate and severe headaches. Premenstrual Syndrome based on the presence of premenstrual and menstrual cramps. Thyroid problems based on presence of lump/mass in neck, cold or heat tolerance, history of x-ray to neck. Anxiety and depression is self-assessed by patient.



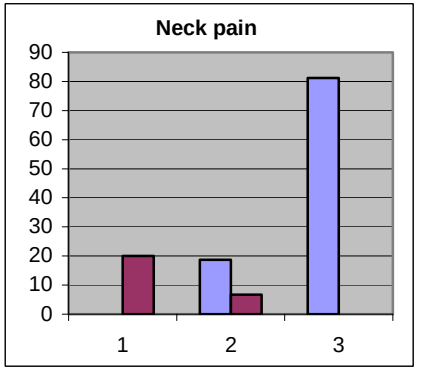
Patients (n=16)	*Controls (n=15)*
Mean: 2.5 (SD 0.73)	Mean: 0.3 (SD 0.59)



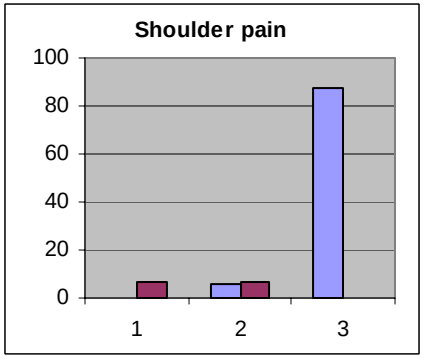
Patients (n=16)	*Controls (n=15)*
Mean: 2.4 (SD 0.89)	Mean: 0.1 (SD 0.35)



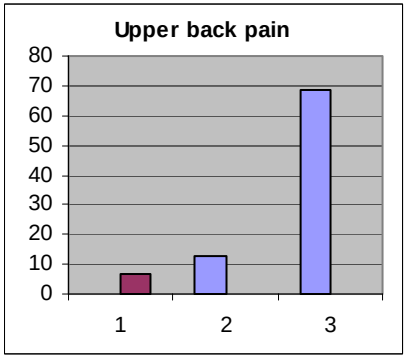
Patients (n=16)	*Controls (n=15)*
Mean: 2.9 (SD 0.25)	Mean: 0.2 (SD 0.41)



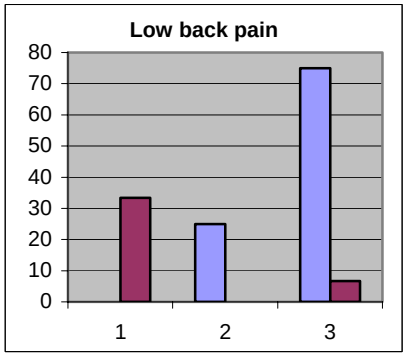
Patients (n=16)	*Controls (n=15)*
Mean: 2.8 (SD 0.40)	Mean: 0.3 (SD 0.62)



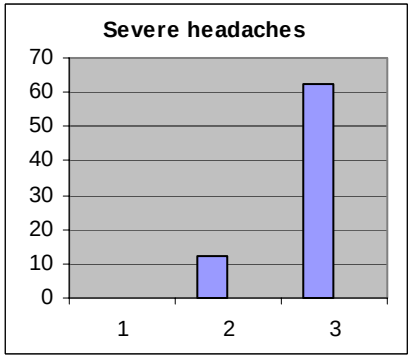
Patients (n=16)	*Controls (n=15)*
Mean: 2.8 (SD 0.77)	Mean: 0.2 (SD 0.56)



Patients (n=16)	*Controls (n=15)*
Mean: 2.3 (SD 1.20)	Mean: 0.1 (SD 0.26)



Patients (n=16)	*Controls (n=15)*
Mean: 2.8 (SD 0.45)	Mean: 0.5 (SD 0.83)



Patients (n=16)	*Controls (n=15)*
Mean: 2.1 (SD 1.31)	Mean: 0.0 (SD 0.00)

Figure 2.3. The mean response (ranging from 0 – absent; to 3 – severe) and standard deviation for the most severe symptoms associated with fibromyalgia. The statistical difference between patients and controls for each symptom is calcualted with ANOVA and found to be highly significant ($p = 0.0001$).

3. Fibromyalgia Impact Questionnaire (FIQ)

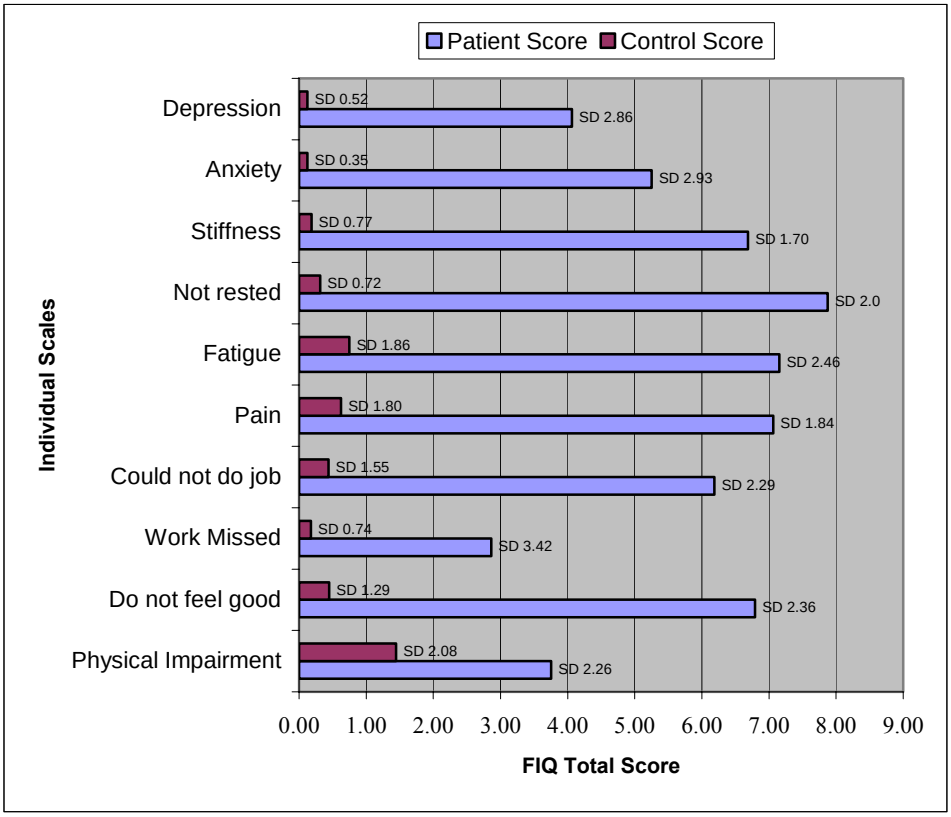


Figure 3.1. The mean total score for each of the individual scales on the Fibromyalgia Impact Questionnaire for patients and controls. Statistical difference between groups: $p < 0.0001$ (calculated with ANOVA with age as co-factor).

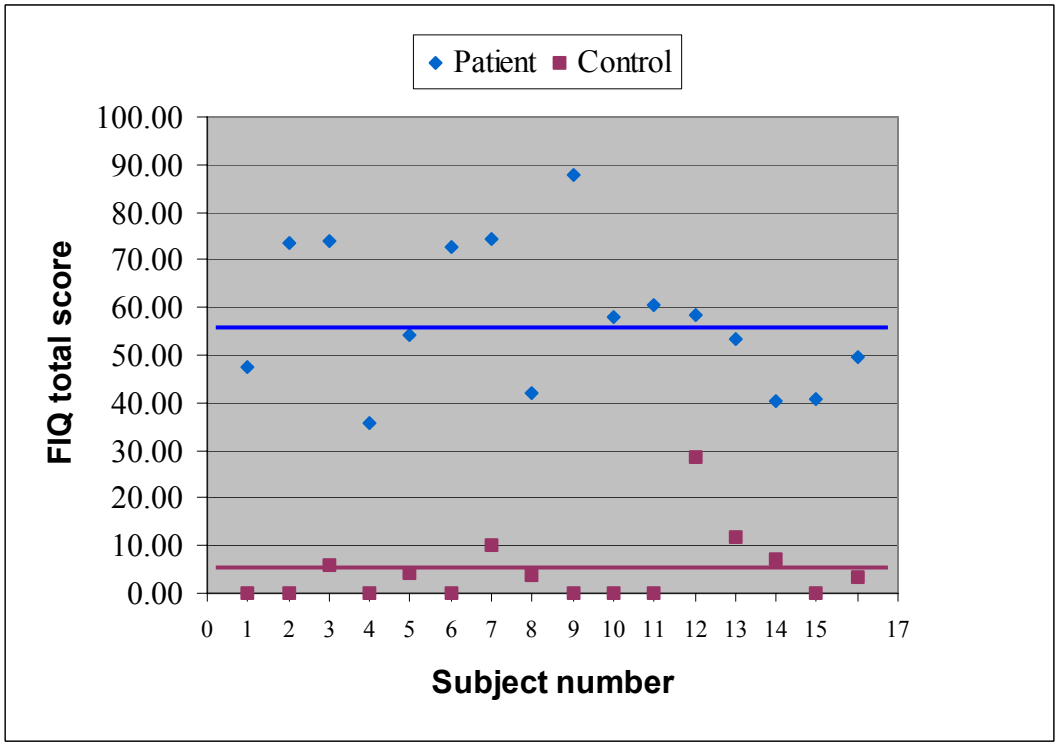


Figure 3.2. The Fibromyalgia Impact Questionnaire (FIQ) total scores for each subject pair. The strait line indicates the group mean: Patients – 57.69 (SD 15.19); Controls – 4.94 (SD 7.59). Statistical difference between groups: $p < 0.0001$ (calculated with ANOVA with age as co-factor).

4. Salivary cortisol levels

Patient group (n=16)
Mean cortisol level:
9.59 ng/ml (SD 2.79)

Control group (n=15)
Mean cortisol level:
5.60 ng/ml (SD 2.30)

Statistical difference
P-value: 0.0003*

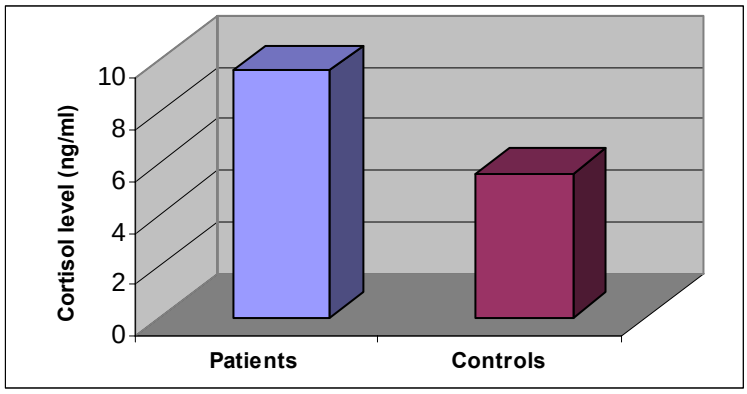


Figure 4. Mean cortisol levels for patients and controls. P-value obtained with Mann-Whitney test.
* indicates significant difference ($p \leq 0.05$)

5. R-R interval recordings (heart rate variability)

5.1 Physical stressor (orthostatic test)

Table 5.1.1. *The means, standard deviations and statistical difference for HRV measures after physiological compensation had occurred*

Variable	Patients *(n = 16)*	Controls *(n = 12)*	p-value
Supine – Mean (SD)			
Mean HR	75.48 (11.19)	65.12 (12.59)	0.0299*
LF (ms²)	167.55 (312.20)	297.73 (338.07)	0.3015
HF (ms²)	288.07 (546.59)	354.75 (406.41)	0.7256
LF (n.u.)	47.86 (23.12)	47.49 (19.29)	0.9647
HF (n.u.)	52.14 (23.12)	52.51 (19.29)	0.9647
LF/HF ratio	1.41 (1.36)	1.23 (1.02)	0.7050
Sitting – Mean (SD)			
Mean HR	77.76 (10.84)	69.01 (12.38)	0.0594
LF (ms²)	155.17 (222.51)	300.16 (261.46)	0.1254
HF (ms²)	133.62 (168.61)	325.09 (399.55)	0.0954
LF (n.u.)	51.33 (22.36)	53.90 (17.04)	0.7425
HF (n.u.)	48.67 (22.36)	46.10 (17.04)	0.7425
LF/HF ratio	1.64 (1.60)	1.47 (0.96)	0.7467
Standing – Mean (SD)			
Mean HR	93.29 (14.65)	82.53 (13.79)	0.0630
LF (ms²)	127.43 (264.04)	406.58 (494.82)	0.0969†
HF (ms²)	25.86 (33.60)	33.85 (34.49)	0.5495
LF (n.u.)	72.61 (17.96)	86.12 (8.97)	0.0188*†
HF (n.u.)	27.39 (17.96)	13.88 (8.97)	0.0188*†
LF/HF ratio	5.42 (5.36)	10.98 (10.11)	0.1046†

P-values calculated with the Pooled T-test
† indicates Separate T-test
* indicates significant difference ($p \leq 0.05$)

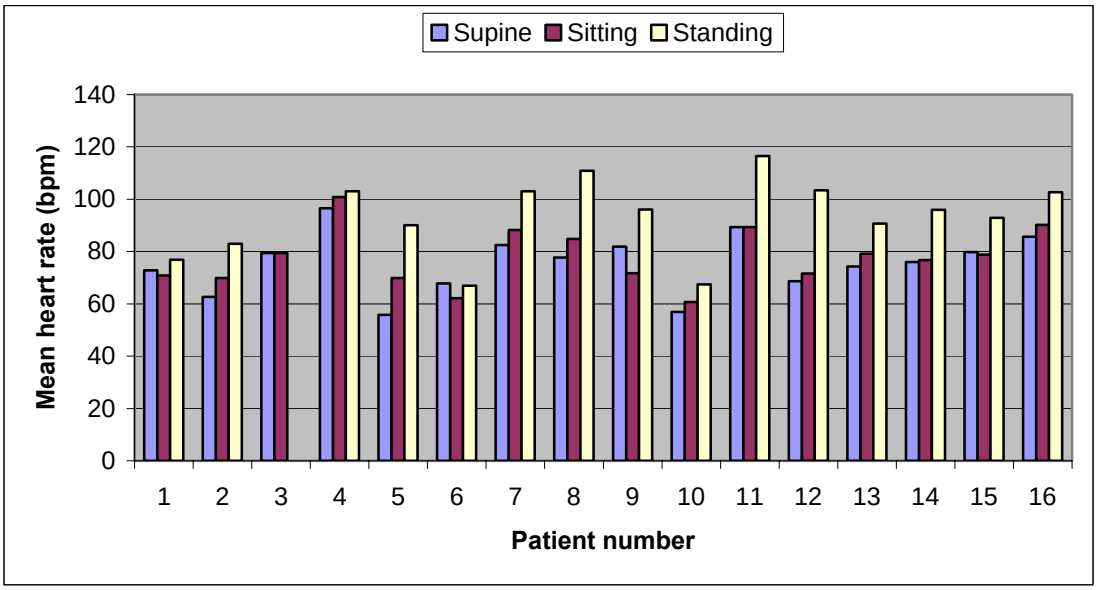


Figure 5.1.1.a Mean heart rates in the three bodily positions for the 16 patients.

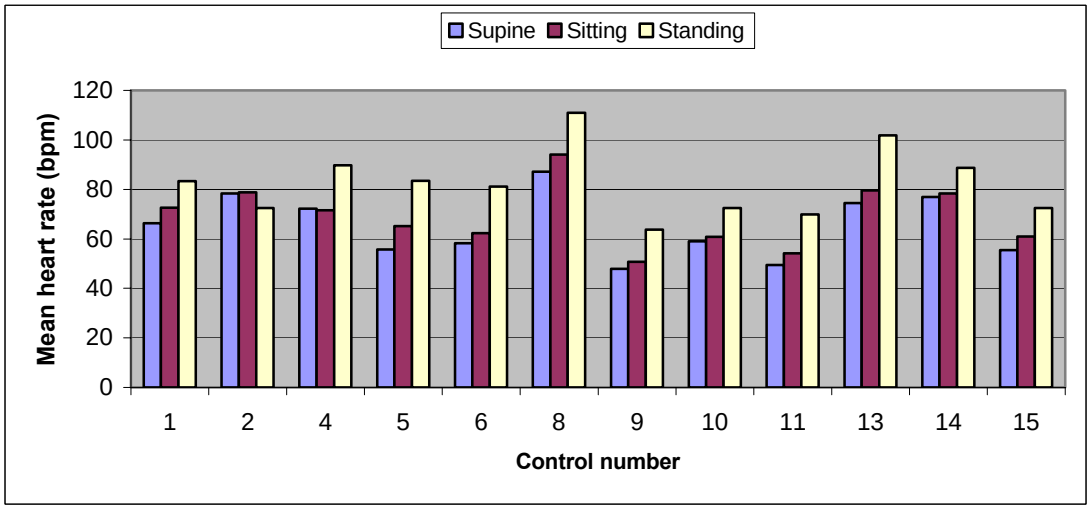
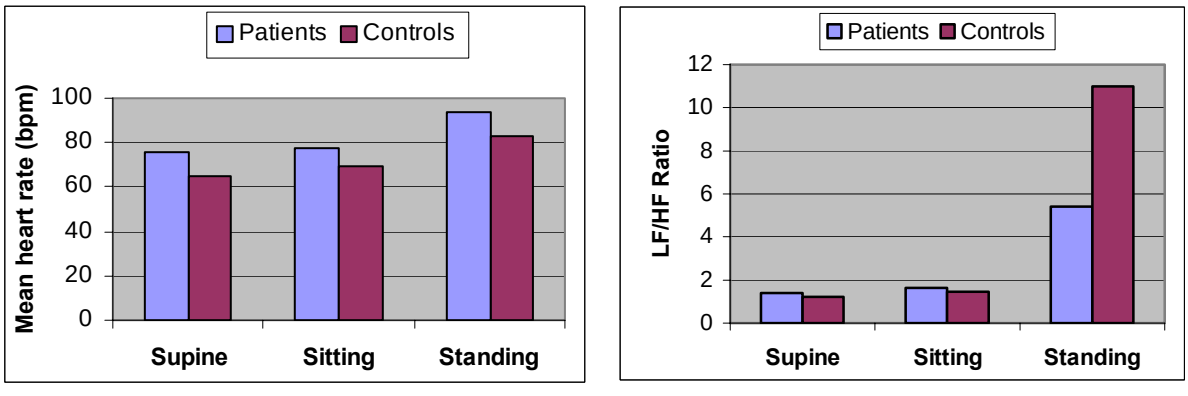
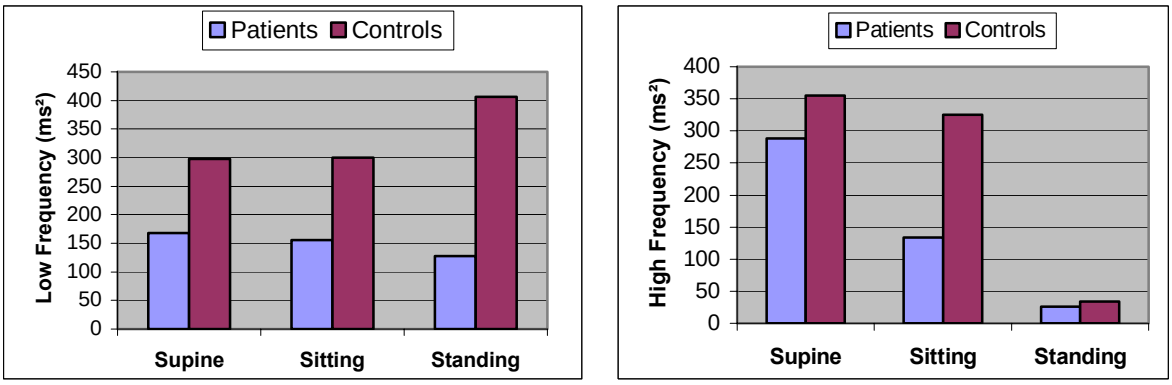


Figure 5.1.1.b Mean heart rates in the three bodily positions for the 15 controls.



A **B**

Figure 5.1.1.c Graphs illustrating different HRV measures for the supine, sitting and standing bodily position of the patients in relation to controls. These graphs illustrate HRV after physiological compensation to the bodily position had occurred (after 5 minutes in the specific position). **A** – Mean heart rate; **B** – LF/HF ratio.



C **D**

Figure 5.1.1.c Graphs illustrating different HRV measures for the supine, sitting and standing bodily position of the patients in comparison to controls. These graphs illustrate HRV after physiological compensation to the bodily position had occurred (after 5 minutes in the specific position).
C – low frequency (LF); **D** – high frequency (HF).

Table 5.1.2. *The means, standard deviation and statistical difference calculated for total power in frequency domain (s²/Hz)*

	Total power	**Patients *(n=16)* Mean (SD)**	**Controls *(n=14)* Mean (SD)**	**p**
1	0 – 5 min	523.74 (834.33)	829.67 (776.83)	0.1201
2	5 – 10 min	473.62 (849.45)	707.78 (715.83)	0.1066
3	10 – 15 min	284.41 (310.64)	981.46 (835.11)	0.0043*
4	15 – 20 min	309.78 (333.58)	666.48 (575.38)	0.0355*
5	20 – 25 min	431.80 (756.93)	522.89 (681.97)	0.1408
6	25 – 30 min	173.21 (309.57)	473.59 (548.73)	0.0437*

Explanation: Physical stressor **- 1**and **2**: supine, **3** and **4**: sitting, **5** and **6**: standing.
P-value calculated with ANOVA with age as co-factor
* indicates statistical significant difference between groups ($p \leq 0.05$)

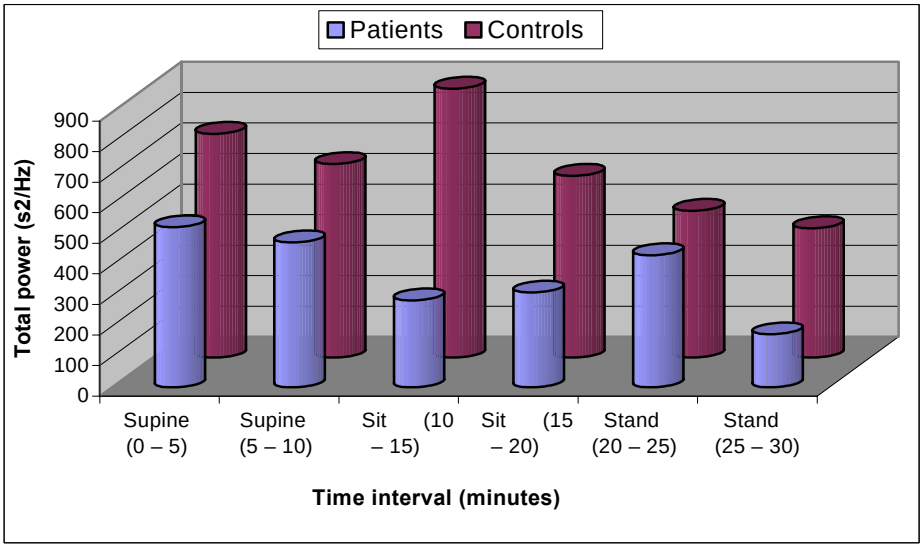


Figure 5.1.2. Physical stressor: The total power (in s²/Hz) calculated in 5-min intervals for the 3 bodily positions. The difference between the groups were statistical significant for sitting (10-15 min), sitting (15-20 min) and standing (25-30 min).

Table 5.1.3. *The means, standard deviation and statistical difference for HRV measures for the change from one bodily position to another (physiological compensation)*

	Δ Change 1 (Sitting – Supine)				
Variable	**Patients *(n = 16)* Mean (SD)**	**p†**	**Controls *(n = 12)* Mean (SD)**	**p†**	**p‡**
Mean HR	3.15 (4.43)	0.0113*	1.86 (7.03)	0.0597	0.5583
Mean HR (STD)	0.33 (0.98)	0.1961	0.81 (1.22)	0.0342*	0.2665
LF (ms²)	5.81 (312.64)	0.2343	246.01 (369.31)	0.0121*	0.0739
HF (ms²)	- 196.15 (540.54)	0.8361	- 6.92 (63.19)	0.8139	0.1848
LF/HF ratio	1.65 (2.41)	0.0084*	1.16 (1.75)	0.0186*	0.5595
Total power	- 189.21 (763.92)	0.3520	273.68 (389.66)	0.0121*	0.0666
	Δ Change 2 (Standing – Sitting)				
Mean HR	12.58 (9.42)	0.0002*	10.54 (7.16)	0.0060*	0.5426
Mean HR (STD)	0.40 (1.28)	0.3942	0.24 (1.35)	0.5303	0.7581
LF (ms²)	103.65 (353.97)	0.3343	125.61 (439.21)	0.4802	0.8867
HF (ms²)	- 5.19 (259.89)	0.0231*	- 264.12 (352.60)	0.0005*	0.0374*
LF/HF ratio	5.69 (8.62)	0.0015*	5.47 (4.13)	0.0005*	0.9348
Total power	106.05 (506.44)	0.9096	- 143.59 (541.33)	0.2721	0.2285

p†: statistical difference for the change from one bodily position to another within the patient and control group respectively, p-values calculated with Wilcoxon statistical test.
p‡: statistical difference for the difference between the two study groups with regard to the change from one bodily position to another, p-values calculated with Pooled T-test.

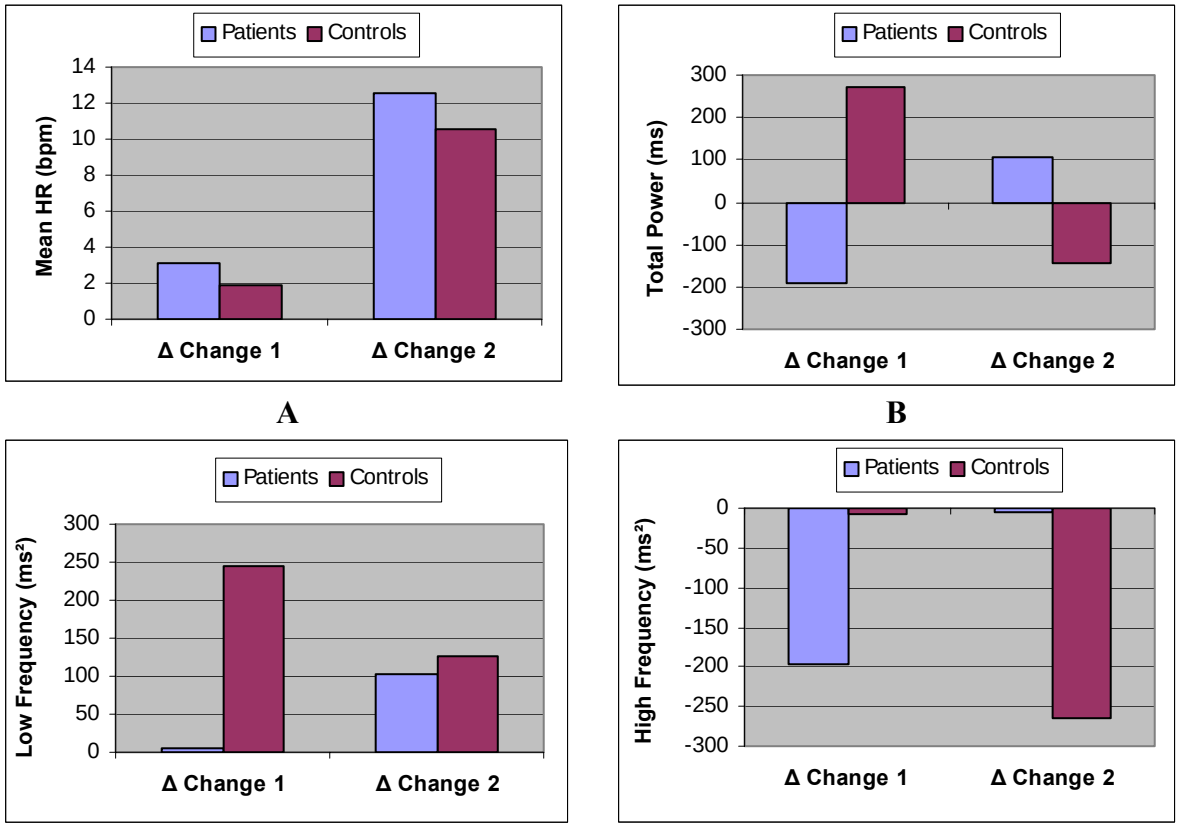


Figure 5.1.3. Graphs illustrating different HRV measures for the change from supine to sitting (change 1) and sitting to standing (change 2) of the patients in comparison to the controls. These graphs illustrate HRV during physiological compensation to the new bodily position (first 5 minutes in the specific position). **A** – mean heart rate; **B** – total power; **C** – low frequency (LF); **D** – high frequency (HF).

5.2. Psychological stressor

Table 5.2. *The means, standard deviation and statistical difference for HRV measures for the autonomic reaction to filling out the ECR-R questionnaire*

	Δ (Basal – ECR-R)				
Variable	**Patients *(n = 16)* Mean (SD)**	**p†**	**Controls *(n = 12)* Mean (SD)**	**p†**	**p‡**
Mean HR	- 2.52 (2.16)	0.0005*	- 0.78 (3.24)	0.5829	0.1250
Mean HR (STD)	- 0.20 (0.82)	0.6002	0.52 (1.13)	0.1167	0.0779
LF (ms²)	- 11.29 (97.16)	0.3824	176.53 (397.77)	0.5303	0.1368†
HF (ms²)	31.39 (40.54)	0.0107*	31.02 (79.65)	0.2393	0.9887†
LF (n.u.)	- 10.35 (14.84)	0.0192*	2.12 (18.92)	0.5829	0.0785
HF (n.u.)	10.35 (14.84)	0.0192*	- 2.12 (18.92)	0.5829	0.0785
LF/HF ratio	- 1.03 (2.47)	0.0546	1.03 (2.47)	0.2393	0.0489*

p†: statistical difference for the change from baseline to emotional stress within the patient and control group respectively, p-values calculated with Wilcoxon statistical test.
p‡: statistical difference for the difference between the two study groups with regard to the change from baseline to emotional stress, p-values calculated with Pooled T-test († separate T-test).

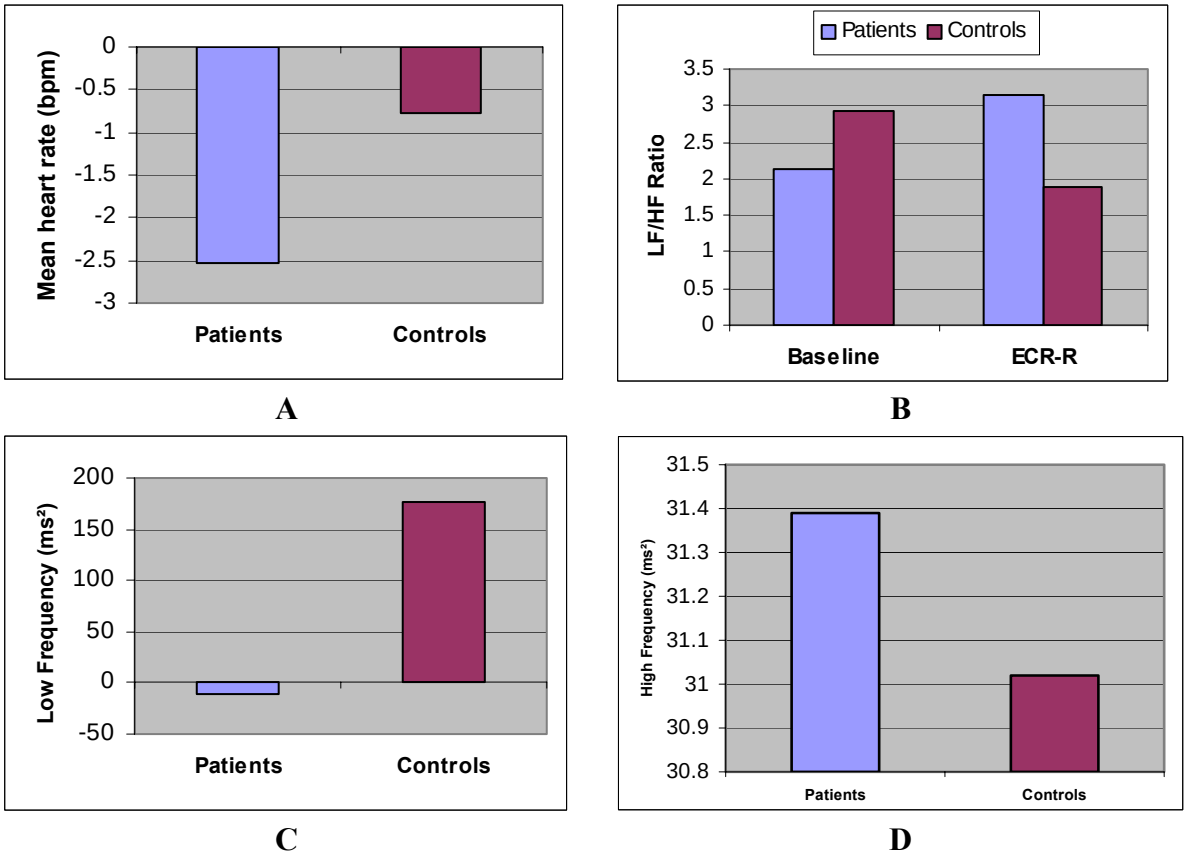


Figure 5.2.1 Graphs illustrating different HRV measures for the patients in comparison to the controls for the autonomic reaction to filling out the ECR-R questionnaire. These graphs illustrate HRV during physiological compensation to a psychological stressor. **A** – mean heart rate; **B** – LF/HF ratio; **C** – low frequency (LF); **D** – high frequency (HF).

Patient group (n = 13)
Baseline mean (SD):
200.00 (159.06)
ECR-R mean (SD):
189.13 (155.94)

Control group (n = 12)
Baseline mean (SD):
808.49 (735.51)
ECT-R mean (SD):
549.38 (466.57)

Statistical difference
p = 0.0100* (baseline)
p = 0.0201* (ECR-R)

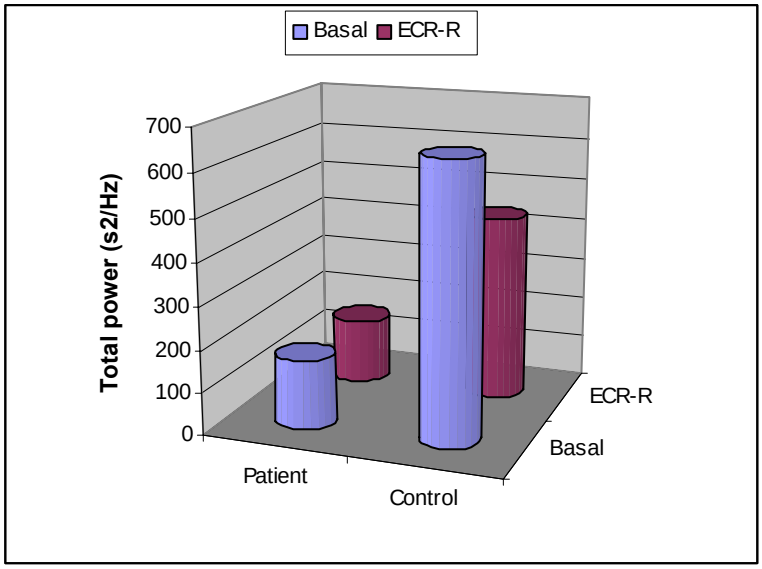


Figure 5.2.2. Psychological stressor: The total power (in s²/Hz) calculated from 5 minutes in the sitting bodily position as a baseline recording and 5 minutes of filling out the ECR-R questionnaire (still sitting), serving as the psychological stressor.
P-value calculated with ANOVA with age as co-factor
* indicates statistical significant difference between groups ($p \leq 0.05$)

6. Herrmann Brain Dominance Instrument (HBDI)

6.1. Profile scores

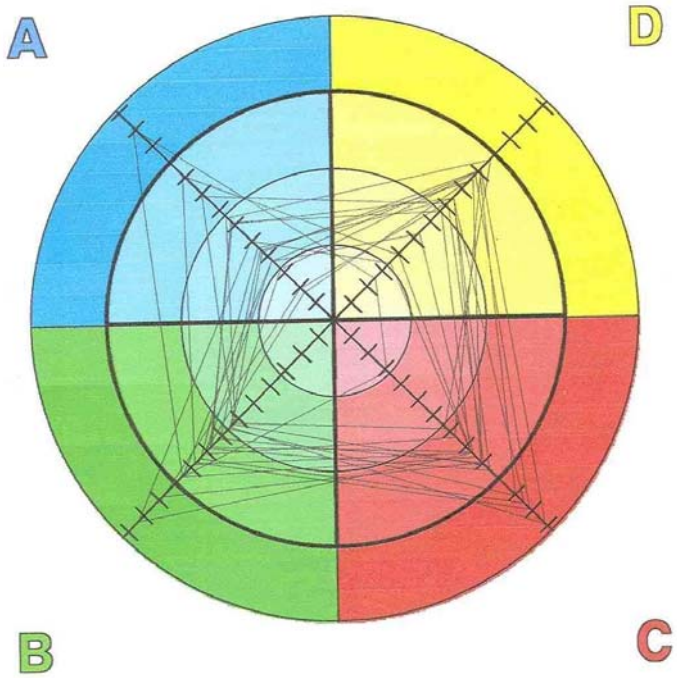


Figure 6.1.1. The group composite of all the patient profiles (the profiles of all the patients are plotted onto one graph). **Figure lables**: Quadrant A – cerebral left; quadrant B – limbic left; quadrant C – limbic right; quadrant D – cerebral right.

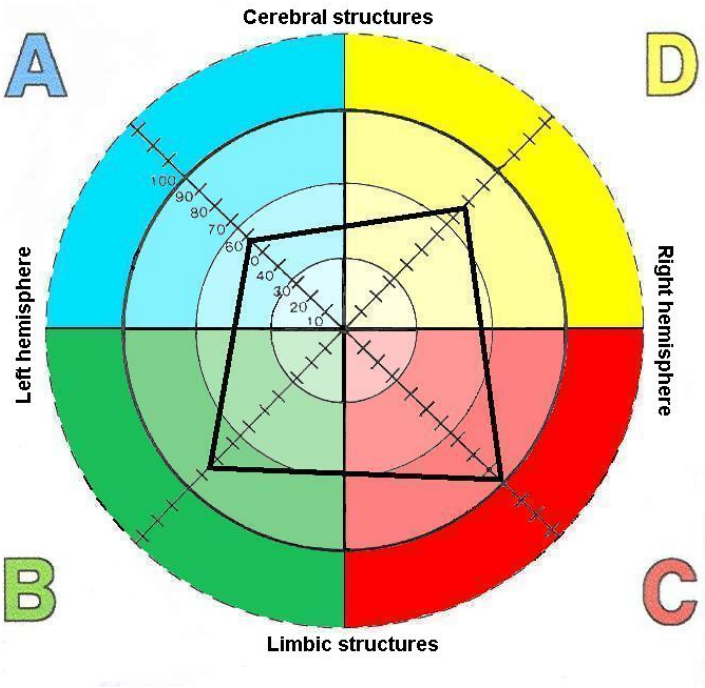
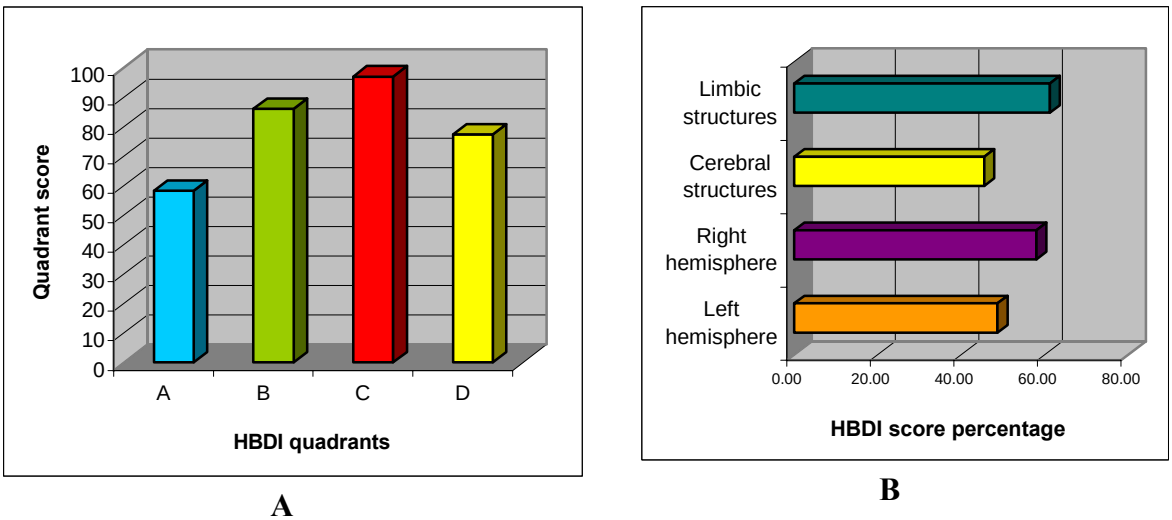


Figure 6.1.2. The mean profile for patients. **Figure lables**: Quadrant A – cerebral left; quadrant B – limbic left; quadrant C – limbic right; quadrant D – cerebral right.

Table 6.1. *The mean HBDI scores and standard deviations obtained by patients*

Variable	Means (SD) *(n=16)*	Variable	Means (SD) *(n=16)*
Quadrant A	54.56 (26.87)	Limbic structures	57.4 (7.46)
Quadrant B	80.69 (18.50)	Cerebral structures	42.63 (7.46)
Quadrant C	90.94 (22.92)	Right hemisphere	54.38 (11.99)
Quadrant D	72.56 (22.29)	Left hemisphere	45.63 (11.99)



A **B**

Figure 6.1.3. Bar graphs demonstrating the mean scores obtained by patients on the HBDI. **A** Scores obtained for each one of the four HBDI quadrants respectively. **B** Scores obtained for the four brain halves. The limbic structure percentage were composed by adding the scores obtained for quadrant B and C from figure **A** together; the cerebral structure percentage is the sum of quadrant A- and D-scores; the right hemisphere percentge is produced by adding quadrant C and D together; and the left hemisphere percentage is the sum of quadrant A- and B-scores.

6.2. Adjective pairs

Quadrant A:
Mean (SD): 4.63 (2.50)

Quadrant B:
Mean (SD): 6.19 (2.26)

Quadrant C:
Mean (SD): 8.63 (2.25)

Quadrant D:
Mean (SD): 4.56 (2.03)

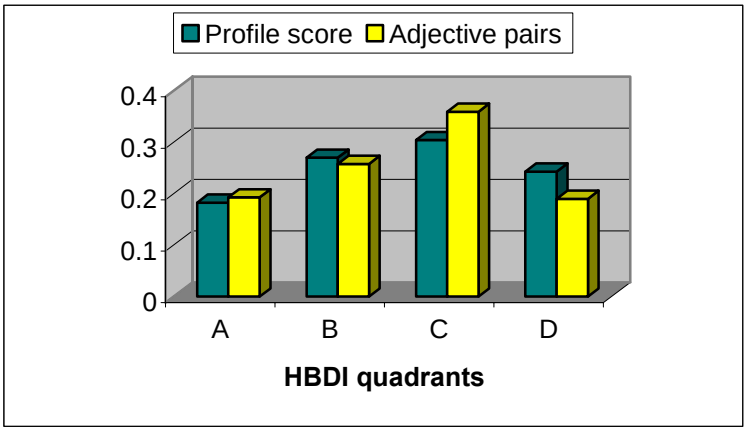


Figure 6.2. Patient adjective pair scores in relation to profile scores (adjective pair scores are indicative of quadrant preferences during stress)

6.3. Generic code/ Profile code

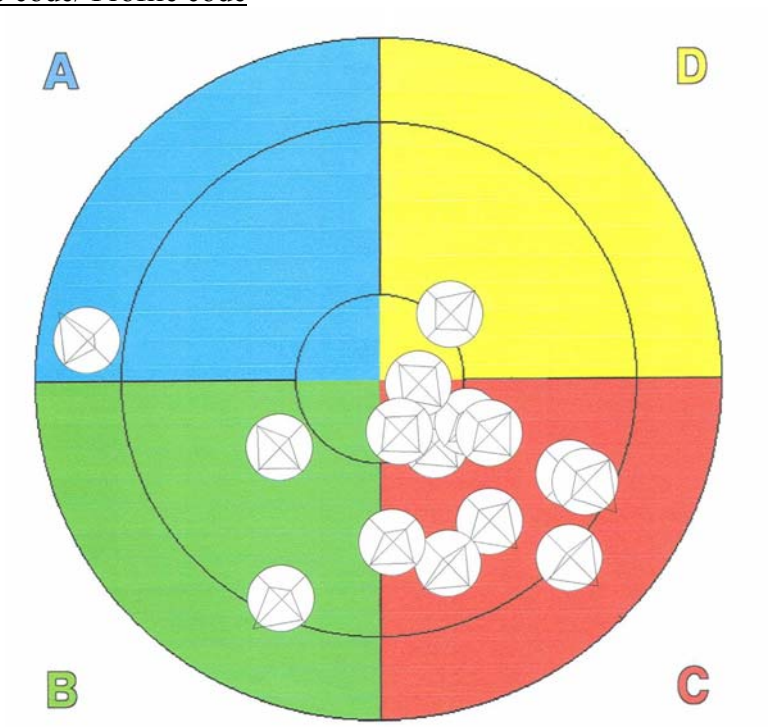
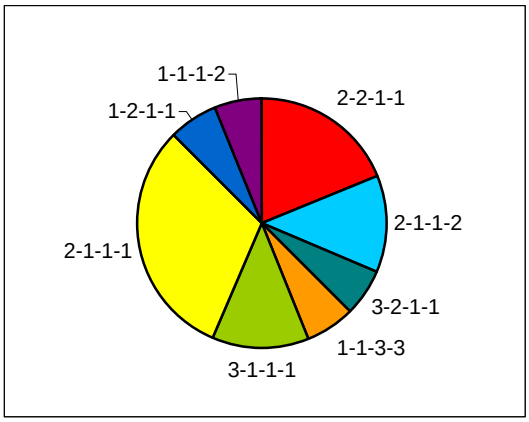
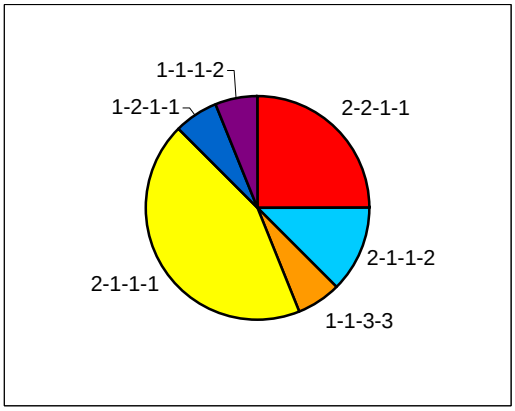


Figure 6.3.1. The generic codes of all the patients plotted onto one graph (the code is plotted in the dominant quadrant). **Figure lables**: Quadrant A – cerebral left; quadrant B – limbic left; quadrant C – limbic right; quadrant D – cerebral right.



A

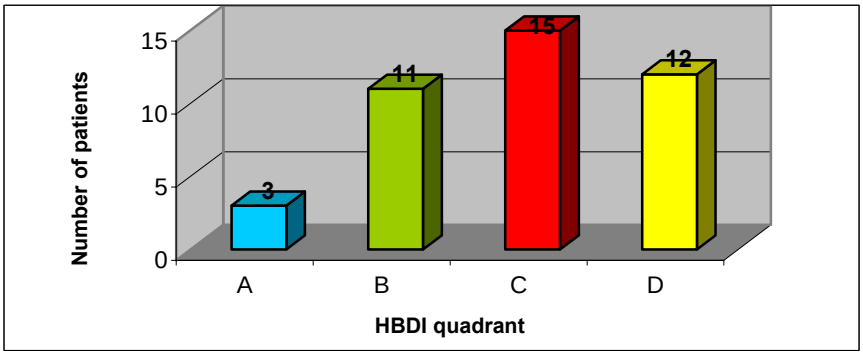
Generic code	Percentage
Code: 2-2-1-1	18.75 %
Code: 2-1-1-2	12.50 %
Code: 3-2-1-1	6.25 %
Code: 1-1-3-3	6.25 %
Code: 3-1-1-1	12.50 %
Code: 2-1-1-1	31.25 %
Code: 1-2-1-1	6.25 %
Code: 1-1-1-2	6.25 %



B

Generic code	Percentage
Code: 2-2-1-1	25.00 %
Code: 2-1-1-2	12.50 %
Code: 1-1-3-3	6.25 %
Code: 2-1-1-1	43.75 %
Code: 1-2-1-1	6.25 %
Code: 1-1-1-2	6.25 %

**Statistics available from population studies:*
Code: 2-1-1-1 – 16% of population at large, 24% of female population
Code: 2-2-1-1 – 14% of population at large, 17% of female population



C

Figure 6.3.2. A A pie graph demonstrating the prevalence of all the generic profile scores relevant to the patient group. **B** A simpler version of graph A, demonstrating the main profile classes patient generic codes can be divided in. Since the control subjects were not assessed with the HBDI, the statistics from population studies relevant to the generic codes observed in the patients are included. **C** Bar graph illustrating the number of patients showing dominance in the respective HBDI quadrants (quadrant A – cerebral left; quadrant B – limbic left; quadrant C – limbic right; quadrant D – cerebral right). Displayed on top of each quadrant bar is the number of patients who showed primary preference in that particular quadrant. * Statistics obtained from *Herrmann, N./ The creative brain – Appendix B. 2 nd ed. Tennessee: Quebecor Printing Book Group; 1994. p. 381-92.*

7. Attachment style – Experiences in close relationships –Revised (ECR-R)

Table 7.1. *The individual anxiety and avoidance score for each patient and control together with the attachment class the respective subject falls into (see Figure 7.1)*

	Patient score		Attachment	Control score		Attachment
	Anxiety	Avoidance	style	Anxiety	Avoidance	style
1	4.78	5.17	Fearful-avoidant	1.50	2.28	Secure
2	3.94	5.33	Dismissing	1.89	3.78	Secure
3	4.72	2.89	Preoccupied	1.00	1.33	Secure
4	4.67	3.28	Preoccupied	2.61	3.33	Secure
5	3.50	4.00	Secure	1.83	1.17	Secure
6	3.94	4.33	Dismissing	2.00	2.33	Secure
7	3.17	3.39	Secure	2.00	1.89	Secure
8	1.56	2.33	Secure	1.56	1.33	Secure
9	5.33	2.67	Preoccupied	1.83	2.22	Secure
10	1.61	1.33	Secure	1.00	1.00	Secure
11	1.56	4.72	Dismissing	1.00	1.17	Secure
12	5.78	6.94	Fearful-avoidant	1.00	1.00	Secure
13	4.50	5.06	Fearful-avoidant	2.06	2.78	Secure
14	1.89	2.67	Secure	1.39	1.72	Secure
15	1.83	1.72	Secure	1.89	3.78	Secure
16	2.50	1.67	Secure			

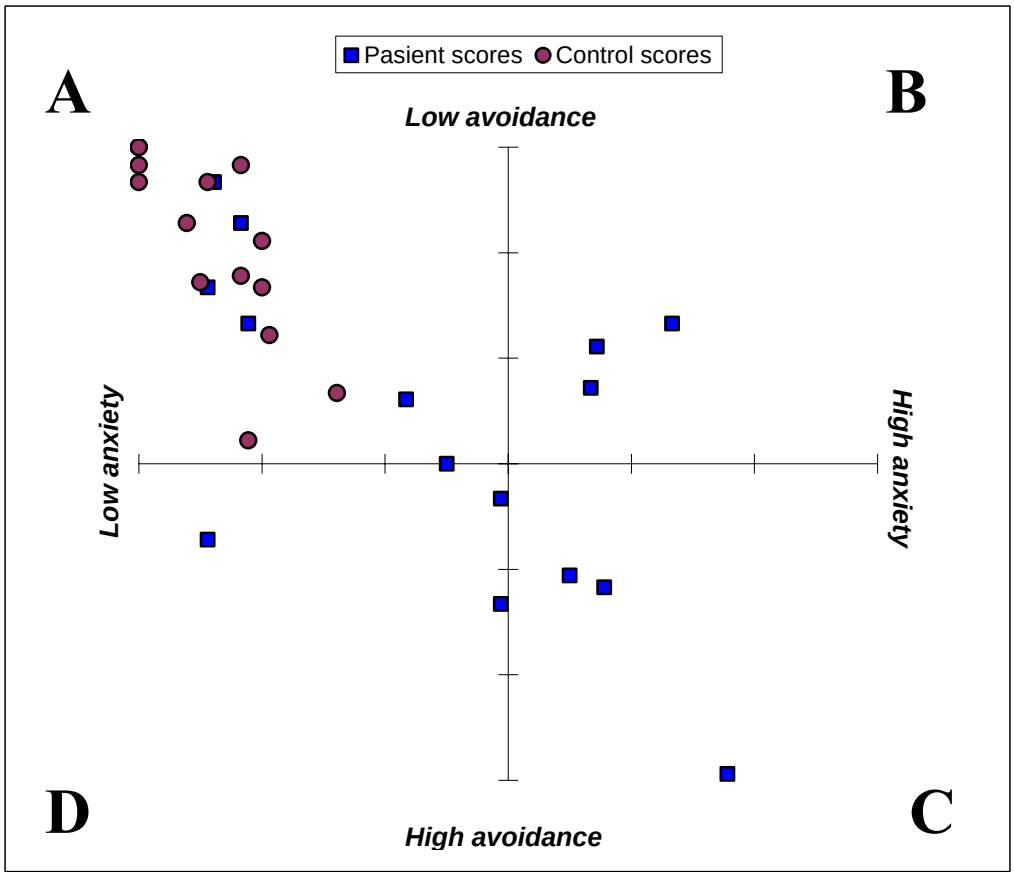


Figure 7.1. The attachment scores (in terms of anxiety and avoidance) plotted onto Barthelomew's two-dimensional graph. **Anxiety axis** (model of self) – individuals with a high score for this variable tend to be concerned about their partners' availability, attentiveness and responsiveness. A low score is associated with security in relationships. **Avoidance axis** (model of others/partner) – individuals on the high end of this dimension, prefer independence. Individuals on the low end tend to be more comfortable with intimacy. **Figure labels:** **A** - secure attachment; **B** – preoccupied attachment; **C** – fearful-avoidant attachment; **D** – dismissing-avoidant attachment.

Patient group (n=16)
Anxiety: 3.45 (SD 1.46)
Avoidance: 3.59 (SD 1.57)

Control group (n=14)
Anxiety: 1.62 (SD 0.49)
Avoidance: 1.95 (SD 0.88)

Statistical difference
Anxiety: p = 0.0001*
Avoidance: p = 0.0015*

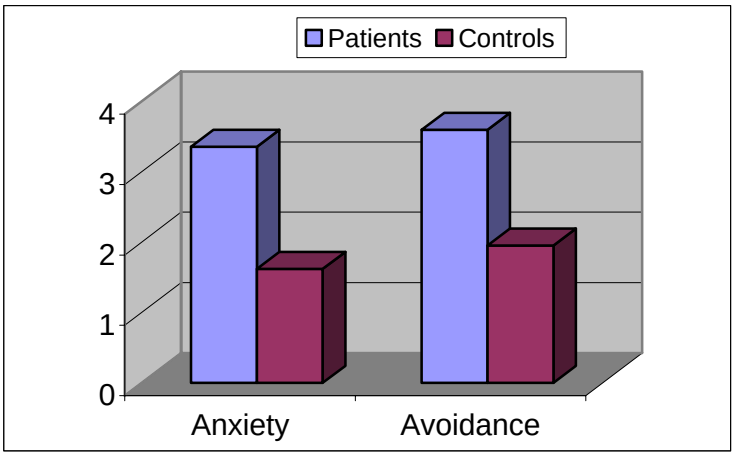


Figure 7.2. Mean anxiety and avoidance scores for patients and controls. P-values obtained with ANOVA test (with age as co-factor).
* indicates a statistical significant difference ($p \leq 0.05$)

Age as co-factor in attachment

Table 7.2. *Correlations between age and attachment variables anxiety and avoidance*

Patient group *(n=16)*			
	Age	**Anxiety**	**Avoidance**
Age p-value	1.00	- 0.12 0.6686	- 0.24 0.3785
Anxiety p-value	- 0.12 0.6686	1.00	0.59 0.0157*
Avoidance p-value	- 0.24 0.3785	0.59 0.0157*	1.00
Control group *(n=14)*			
	Age	**Anxiety**	**Avoidance**
Age p-value	1.00	- 0.46 0.0952	- 0.25 0.3867
Anxiety p-value	- 0.46 0.0952	1.00	0.76 0.0017*
Avoidance p-value	- 0.25 0.3867	0.76 0.0017*	1.00

* indicates a statistical significant difference ($p \leq 0.05$)

C. STATISTICAL CORRELATIONS

In order to compose a psychoneurological profile for the patients, it was necessary develop a model by which connections could be explored between the variables evaluated in the study. In this model (also refer to Figure 1, p. 5.35), the independent variables are possible predictors of fibromyalgia disease status. The dependent variables represent the descriptors of fibromyalgia disease status. Relationships within the independent and

dependent variables respectively are expressed as correlations (Pearson coefficients), and predictive relationships between the dependent and independent variables as model/partial R-squares (calculated through regression analysis). In Table 1.1 and 1.2, only statistically significant correlations ($p \leq 0.05$) are indicated, together with the noteworthy model/partial R-squares. Since there are no HBDI results available for the controls, it was not possible to apply the model to the control group.

Table 1.1. *Pearson coefficient correlations* | r | *and statistical significance within the dependent and independent variables respectively*

Dependent variables	**r-value**	**p-value**
LF/HF ratio and FIQ anxiety	0.62	0.0130
LF/HF ratio and FIQ depression	0.66	0.0079
FIQ anxiety and FIQ pain	0.53	0.0429
FIQ depression and FIQ pain	0.49	0.0607†
FIQ depression and RCS symptoms	0.51	0.0507†
FIQ fatigue and FIQ depression	0.56	0.0312
FIQ anxiety and FIQ stiffness	0.58	0.024
FIQ rested and cortisol	- 0.55	0.0354
Independent variables	**r-value**	**p-value**
Quadrant A and Quadrant C	0.66	0.0077
Quadrant C and traumatic events	0.55	0.0351
Attachment-related avoidance and attachment-related anxiety	0.64	0.0099

Explanation: 'FIQ rested' refers to the scale on the FIQ assessing sleep quality (how rested patient feels after night's sleep); 'RCS symptoms' refer to the total number of symptoms on the RCS (calculated out of a total of 100 symptoms); Quadrant A – cerebral left; Quadrant C – limbic right. **Abbreviations**: LF/HF ratio, low-frequency/ high frequency ratio; RCS, Review of current symptoms questionnaire; FIQ, Fibromyalgia Impact Questionnaire
† indicates noteworthy correlations that is not statistically significant.

Table 1.2. *Predictive relationships (r^2) between the independent and dependent variables calculated through regression analysis*

Dependent variable	**Independent variable**	**Model R-square**
Total power (supine)	Quadrant A	0.5078
Total power (standing)	Quadrant A	0.4852
Low frequency (supine)	Quadrant A	0.5345
Low frequency (standing)	Quadrant A	0.4566
High frequency (supine)	Quadrant A	0.4154†
High frequency (standing)	Quadrant A	0.2164
Salivary cortisol level	Attachment-related avoidance	0.1782
Symptom score	Attachment-related anxiety	0.1467
Allergies	Traumatic events	0.4600
FIQ disability	Traumatic events	0.3435†

Explanation: When a specific independent variable is the only significant predictor of a dependent variable, their relationship is expressed in model R-squares; when there is more than one significant predictor, the relationship with the dependent variable is expressed as partial R-squares; 'symptom score' refer to the total number of symptoms on the RCS (calculated out of a total of 100 symptoms); Quadrant A – cerebral left. **Abbreviations**: RCS, Review of current symptoms questionnaire; FIQ, Fibromyalgia Impact Questionnaire
† indicates partial R-square

D. APPENDIX TO CHAPTER – INDIVIDUAL SUBJECT DATA

I. Patient group

Patient 1

1.1. Patient health questionnaire

1.1.1. Personal information

Marital status: Married
Highest academic qualification: Diploma
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

1.1.2. Anthropometrical data

Gender: Female
Age: 49 yrs
Mass: 68 kg
Height: 1.64 m
Body mass index: 25.28

1.1.3. Medical background

Allergies: Hay fever
Current illnesses (apart from FM): None
Ongoing illnesses (age at which illness started in brackets): hypertension (age 24), thyroid problem (age unknown).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Tonsillectomy Tonsillectomy Bladder neck widening	3 yrs 9 yrs 25 yrs	Difficulty to find correct diagnosis for unexplained symptoms (FM) Because of wrong diagnosis, she only had 1 child. Bitterness towards ignorant doctors	-
Illnesses:			
Eating disorder	17 yrs		

Onset of FM: After a period of overexertion and major stress
Number of years suffering from FM: 31 yrs
FM progress: Improving
Description of pain: Continuous pain spread over whole body. Pain is intensified in joint areas. Pain caused by muscle stiffness.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Moderate exercise Heat Sunlight Sleep	Stress Humidity Caffeine Season

1.1.4. Treatment program

Exercise program
Physiotherapy
Pharmacological medication

Name of medication	Dose	Frequency
Ten Bloka	50 mg	1-2 per day
Topamax	75 mg	1-2 per day
Trepiline	75 mg	1 per day
Alchera	7.5 mg	0.5-1 per day
Tramal	-	-
Tramahexal	-	-
Eltroxin	0.1mg	1 per day
Livifem	-	-
Slow-Mag	-	-
Florinef	0.1 mg	1/ 48 hours

1.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Breast:**		**Joints:**		**Thyroid:**	
fatigue	3	lumps	3	ache/pain	3	cold or heat	
weight change	1	swollen	3	stiff	2	tolerance	1
fever/chills/sweats	1			swelling	1		
appetite change	2	**Lungs:**				**Neuropsychiatric:**	
abnormal thirst	3	cough	1	**G.U. and Hormonal:**		headache (moderate)	2
difficulty sleeping	2	shortness of breath		**(Female)**		depression/apathy	2
light-headed	3	- on exertion	3	severe menstrual		anxiety/irritable	2
		can't get full breath	3	cramps	1	"brain fog"/difficulty	
Skin:		hyperventilation	3	severe premenstrual		concentrating	2
itching	2	phlegm/mucus	1	cramps	1	mood swings	1
flushing	1	chest pain on		menstrual irregularity	1	numbness, tingling	2
rashes	1	exertion	3	yeast or candida			
hives	1	other chest pain or		infection	1	**Gastrointestinal:**	
dry/rough skin	2	distress	3	painful or difficult		blenching, bloating,	
acne	1	palpitations	3	urination	1	or passing gas	3
nail/hair problem	3	ankle swelling	2	pressure/urgency	1	heartburn or	
		sore tender legs	3			stomach pain	3
Eyes:				**Muscles:**		diarrhea	3
vision	3	**Mouth:**		tight/stiff	3	constipation	2
tearing	1	sores/fissures	3	ache-sore-pain		cramps or aches	3
feels heavy	3	herpes or frequent		- neck	3		
		cold sores	2	- shoulder	3	**Nose/Throat:**	
Ears:		gum/tooth problem	3	- upper back	3	sore throat	2
itching	2	tongue problem	3	- low back	3	postnasal drip	2
hearing problem	3			- extremities	2	trouble swallowing	2
blocked ears	3	**Lymph nodes:**		weakness	2		
ringing in ears	2	swollen	2				
dizziness/vertigo	3	sensitive	2				

1.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	5.75	Fatigue:	9.00
Days not feeling good:	7.15	Not rested:	4.00
Work missed:	1.43	Stiffness:	3.00
Inability to perform job tasks:	7.00	Anxiety:	1.00
Pain:	7.00	Depression:	2.00
Total FIQ score:	47.33		

1.4. ELISA

Cortisol level: 11.5 ng/ml

1.5. R-R interval recordings

1.5.1. Heart rate variability data: physical stressor

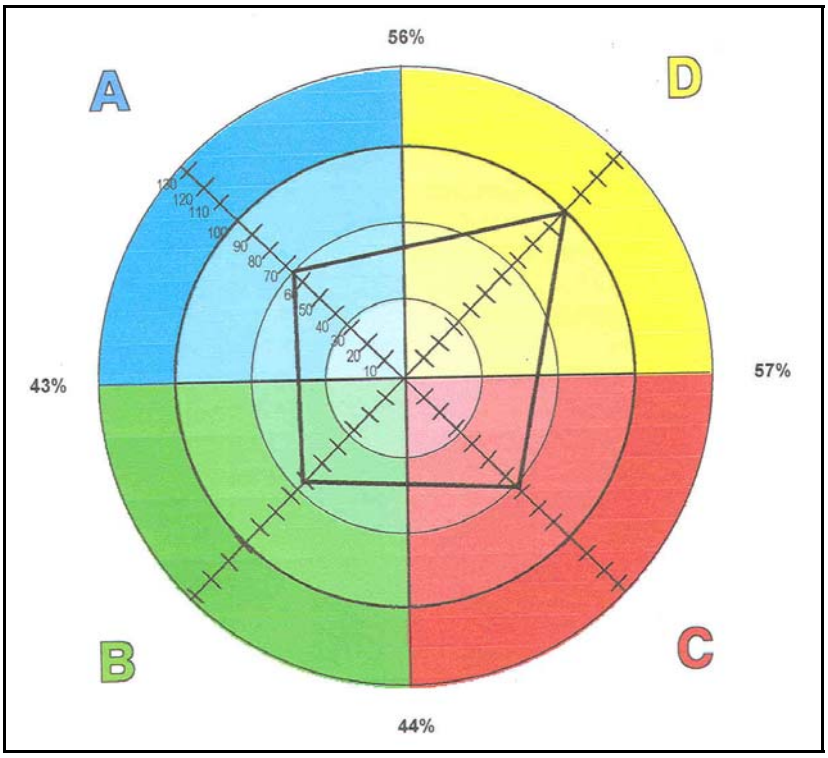
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.82	0.83	0.85
RR standard deviation (s)	0.03	0.01	0.02
Mean HR (1/min)	72.84	72.33	70.87
HR standard deviation (1/min)	2.57	1.31	2.06
Frequency domain results			
LF power (ms^2)	4.97	6.48	13.80
LF power n.u.	2.13	15.89	8.65
HF power (ms^2)	227.79	34.27	145.75
HF power n.u.	97.87	84.11	91.35
LF/HF ratio	0.02	0.19	0.09
Total power (ms^2)	232.99	43.65	161.74

1.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.86	0.86
RR standard deviation (s)	0.01	0.01
Mean HR (1/min)	69.58	70.05
HR standard deviation (1/min)	1.30	1.23
Frequency domain results		
LF power (ms^2)	11.29	24.25
LF power n.u.	23.13	47.58
HF power (ms^2)	37.53	26.72
HF power n.u.	76.87	52.42
LF/HF ratio	0.30	0.91
Total power (ms^2)	51.99	92.49

1.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 66, **B** 62, **C** 68, **D** 99.
Adjective pairs: **A** 5, **B** 3, **C** 10, **D** 6.
Preference code: 2-2-1-1

1.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 4.78
Avoidance score: 5.17
Attachment class: Fearful-avoidant

Patient 2

2.1. Patient health questionnaire

2.1.1. Personal information

Marital status: Married
Highest academic qualification: Grade 12
Work status: Never employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: Full

2.1.2. Anthropometrical data

Gender: Female
Age: 45 yrs
Mass: 60 kg
Height: 1.68 m
Body mass index: 21.3

2.1.3. Medical background

Allergies: Sulphar in antibiotics
Current illnesses (apart from FM): None
Ongoing illnesses (age at which illness started in brackets): Allergies (age 37), migraine headaches (age 23).

Operations and hospitalizations:	Age	Traumatic psychological events:	Age
Hysterectomy Ovarectomy	30 yrs 31 yrs	Traumatic school years (had a hard time to pass) Failed Grade 5 Wet bed Brother died from AIDS Unhappy marriage	7-19 yrs 12 yrs 7-19 yrs 45 yrs 19 +
Illnesses:			
Glandular fever	35 yrs		

Onset of FM: Gradually
Number of years suffering from FM: 20 yrs
FM progress: More painful locations
Description of pain: Indescribable muscle pain.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Food: fresh fruit, vegetables Sleep	Exercise Stress Caffeine Cold Alcohol

2.1.4. Treatment program

Non-allopathic treatment: meditation, acupuncture
Pharmacological medication

Name of medication	Dose	Frequency
Zoloft	50 mg	2 per day
Topamax	75 mg	1 per day
Durogesic	25 µg/h	every 3rd day
Phenergan	25 mg	as needed
Buscopan	10 mg	as needed
Lentogesic	-	as needed

2.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Neuropsychiatric:**		**G.U. and hormonal:**	
fatigue	3	other chest pain or		headache (severe)	3	**(Female)**	
weight change	3	distress	1	depression/apathy	1	yeast or candida	
fever/chills/sweats	3	calf pain on		anxiety/irritable	2	infection	1
difficulty sleeping	2	exercise	3	"brain fog"/difficulty		painful or difficult	
light-headed	1	sore tender legs	2	concentrating	2	sexual problem	3
				numbness, tingling	2		
Eyes:		**Gastrointestinal:**				**Muscles:**	
itching	2	blenching,bloating		**Ears:**		tight/stiff	3
feels heavy	3	or passing gas	2	dizziness/vertigo	2	ache-sore-pain	
		heartburn or				- neck	3
Nose/Throat:		stomach pain	2	**Skin:**		- shoulder	3
stuffed/runny nose	1	diarrhea	2	itching	1	- upper back	3
sore throat	2	constipation	2			- low back	3
tight/swollen throat	1	cramps or aches	2	**Thyroid:**		weakness	1
trouble swallowing	1			tolerance	2		
						Breast:	
						swollen	1

2.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	5.75	Fatigue:	8.00
Days not feeling good:	8.58	Not rested:	8.00
Work missed:	10.01	Stiffness:	8.00
Inability to perform job tasks:	7.00	Anxiety:	6.00
Pain:	8.00	Depression:	4.00
Total FIQ score:	73.34		

2.4. ELISA

Cortisol level: 10.0 ng/ml

2.5. R-R interval recordings

2.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.96	0.89	0.86
RR standard deviation (s)	0.04	0.04	0.03
Mean HR (1/min)	62.68	67.86	69.83
HR standard deviation (1/min)	2.55	3.16	2.86
Frequency domain results			
LF power (ms^2)	255.20	158.15	301.79
LF power n.u.	44.75	21.73	52.39
HF power (ms^2)	315.05	569.76	274.23
HF power n.u.	55.25	78.27	47.61
LF/HF ratio	0.81	0.28	1.10
Total power (ms^2)	589.73	746.97	588.30

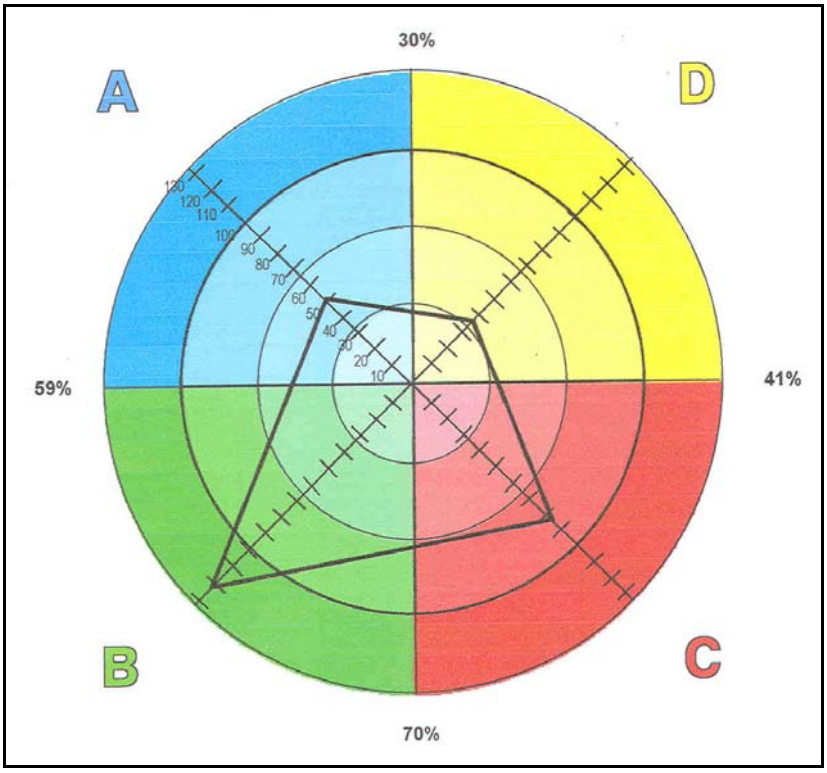
2.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.81	0.76
RR standard deviation (s)	0.03	0.04
Mean HR (1/min)	73.85	79.55
HR standard deviation (1/min)	2.52	3.76
Frequency domain results		
LF power (ms^2)	110.16	226.22
LF power n.u.	31.42	68.42
HF power (ms^2)	240.46	104.42
HF power n.u.	68.58	31.58
LF/HF ratio	0.46	2.17
Total power (ms^2)	358.61	404.07

2.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*

Profile score: **A** 51, **B** 123, **C** 84, **D** 36.
Adjective pairs: **A** 5, **B** 10, **C** 7, **D** 2.
Preference code: 2-1-1-2



2.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 3.94
Avoidance score: 5.33
Attachment class: Dismissing

Patient 3

3.1. Patient health questionnaire

3.1.1. Personal information

Marital status: Widowed
Highest academic qualification: Diploma
Work status: Employed (half day)
Lifestyle: Live with someone who can take care
Disability compensation: None

3.1.2. Anthropometrical data

Gender: Female
Mass: 75 kg
Body mass index: 25.55

Age: 52 yrs
Height: 1.65 m

3.1.3. Medical background

Allergies: Buscopan, Voltaren, Penicillin
Current illnesses (apart from FM): None
Ongoing illnesses (with the age at which illness started in brackets): migraine headaches (age 11).

Hospitalisations and operations:	Age	Traumatic psychological events:	Age
Hysterectomy	23 yrs	36 hours in labour	22 yrs
Blood transfusions	50 yrs	Father died of cancer	22 yrs
3 months in hospital because of wound infection	48 yrs	Mother committed suicide	25 yrs
		Husband died in fire - financial complications	38 yrs
Illnesses:		Hospitalised for depression	44 yrs
Rheumatic fever	7 yrs		
Meningitis	21,23		
Ear infection for 3 months	26 yrs		
Pneumonia	31,49		
Mental illness	34 yrs		
Bleeding disorder	50 yrs		
Tumor on ovaries	52 yrs		

Onset of FM: Gradually
Number of years suffering from FM: 25 yrs
FM progress: Improving
Description of pain: Burning, intense pain.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Heat Sleep	Exercise Stress Humidity Season: winter Cold Time of day Food: sugar

3.1.4. Treatment program

Physiotherapy
Non-allopathic treatment
Pharmacological medication

Name of medication	Dose	Frequency
Tramal	150 mg	3-4 per day
Trepiline	10 mg	1 per day
Effexor	75 mg	1 per day
Duragesic	25 mg	1/96 hours
Magnesit	-	-
CalCVita	-	-
Vitamin B	-	-

3.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Skin:**		**Eyes:**		**Ears:**	
fatigue	3	flushing	2	vision	2	itching	1
weight change	2	dry/rough skin	3	tearing	1	hearing problem	1
fever/chills/sweats	3	acne	3	itching	1	blocked ears	1
appetite change	2	nail/hair problem	3	feels heavy	2	ringing in ears	1
abnormal thirst	2			allergic shiners	1	sensitive to sounds	2
difficulty sleeping	3					dizziness/vertigo	2
light-headed	2						

Lungs:		**Joints:**		**Genital-urinary:**	
cough	1	ache/pain	2	painful or difficult urination	2
wheezes	1	stiff	3		
shortness of breath		swelling	2		
- at rest	1				
- on exertion	1				
can't get full breath	2				
hyperventilation	1				
phlegm/mucus/ bronchitis	2				
chest pain on exertion	1				
other chest pain or distress	1				
palpitations/rapid, slow or irregular heart rate/rhythm	3				
ankle swelling	2				
calf pain on exercise	3				
sore tender legs	3				

Mouth:		**Muscles:**		**Lymph nodes:**		**Nose/Throat:**	
sores/fissures	2	tight/stiff	3	swollen	2	stuffed/runny nose	1
herpes or frequent cold sores	1	ache-sore-pain		sensitive	2	postnasal drip	2
gum/tooth problems	1	- neck	3			sore throat	2
tongue problem	1	- shoulder	3			tight/swollen throat	1
		- upper back	3			hoarse voice	1
		- low back	3			trouble swallowing	2
		weakness	2				

Breasts:	
lumps	1
cystic breasts	2

Thyroid:	
history of x-ray to neck	2

Neuropsychiatric:	
headache (mild/ moderate)	2
headache (severe)	2
depression/apathy	2
anxiety/irritable	2
"brain fog"/difficulty concentrating	3
mood swings	2
suicidal	1
numbness, tingling	2
faints/blackouts	1

Gastrointestinal:	
nausea	2
blenching, bloating, or passing gas	3
heartburn or stomach pain	3
diarrhea	2
constipation	2
cramps or aches	2
rectal pain or itching	1
blood or black stools	1

3.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	5.99	Fatigue:	8.00
Days not feeling good:	7.15	Not rested:	10.00
Work missed:	2.86	Stiffness:	8.00
Inability to perform job tasks:	9.00	Anxiety:	7.00
Pain:	10.00	Depression:	6.00
Total FIQ score:	74.00		

3.4. ELISA

Cortisol level: 10.0 ng/ml

3.5. R-R interval recordings

3.5.1 Heart rate variability data: physical stressor

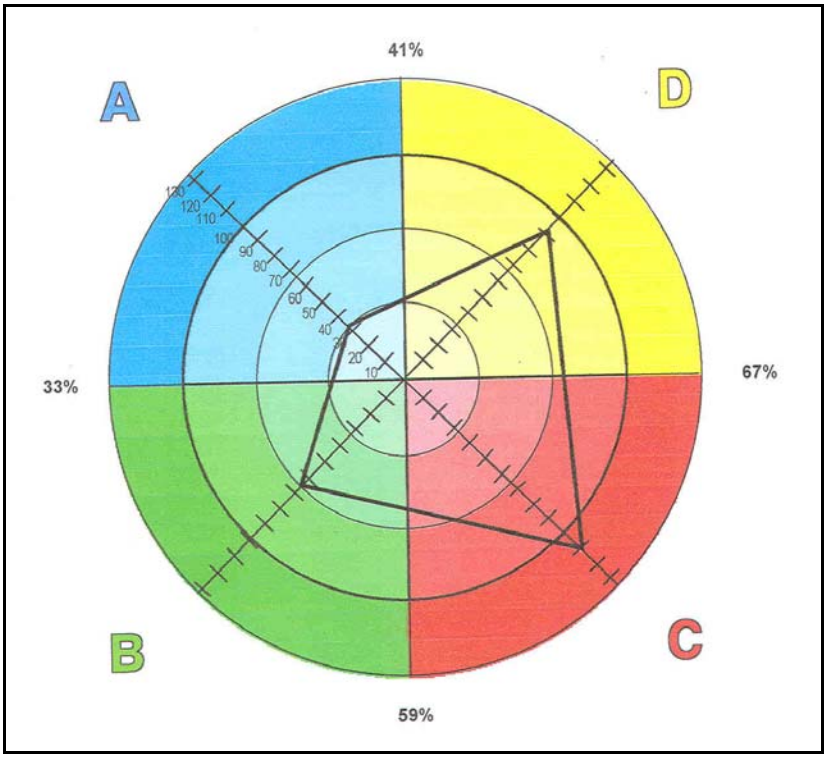
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.76	0.75	0.76
RR standard deviation (s)	0.01	0.02	0.04
Mean HR (1/min)	79.40	80.30	79.41
HR standard deviation (1/min)	1.24	2.16	2.47
Frequency domain results			
LF power (ms²)	38.10	10.58	41.53
LF power n.u.	77.39	27.74	64.62
HF power (ms²)	11.13	27.56	22.74
HF power n.u.	22.61	72.26	35.38
LF/HF ratio	3.42	0.38	1.83
Total power (ms²)	53.11	39.99	70.17

3.5.2. Heart rate variability data: psychological stressor

(recording discarded)

3.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 33, **B** 66, **C** 111, **D** 92.
Adjective pairs: **A** 3, **B** 6, **C** 9, **D** 6.
Preference code: 3-2-1-1

3.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 4.72
Avoidance score: 2.89
Attachment class: Preoccupied

Patient 4

4.1. Patient health questionnaire

4.1.1. Personal information

Marital status: Single
Highest academic qualification: Grade 12
Work status: Never employed
Lifestyle: Smokes 2 cigarettes a day
Occasionally uses alcohol
Disability compensation: None

4.1.2. Anthropometrical data

Gender: Female
Age: 21 yrs
Mass: 64 kg
Height: 1.65 m
Body mass index: 23.50

4.1.3 Medical background

Allergies: None
Current illnesses (apart from FM): diabetes I
Ongoing illnesses from past (age at which illness started in brackets): diabetes (age 15), vaginitis (age 20).

Illnesses:	Age	Traumatic psychological events:	Age
Pneumonia	20 yrs	Diabetes are experienced as emotionally draining	15 +

Onset of FM: After a period of overexertion and psychological stress. FM complaints started gradually.
Number of years suffering from FM: 3 yrs
FM progress: Improving
Description of pain: Continuous aches, cramps and pain. Burning pain in hands and feet.
Fulfillment of Fukuda CFS diagnostic criteria: No

Factors relieving symptoms:	Factors increasing symptoms:
Exercise Sunlight Sleep	Stress Humidity Caffeine Season: winter Barometric pressure Cold Heat Time of day: mornings

4.1.4. Treatment program

Physiotherapy
Non-allopathic treatment
Pharmacological medication

Name of medication	Dose	Frequency
Tramal	100 mg	2 per day
Trepiline	12 mg	when needed

4.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Joints:**		**Neuropsychiatric:**	
fatigue	3	ankle swelling	3	ache/pain	2	headache (mild/ moderate)	1
difficulty sleeping	2	sore tender legs	2	stiff	3	depression/apathy	1
light-headed	1					"brain fog"/difficulty concentrating	1
		Lymph nodes:				mood swings	1
Skin:		swollen	1	**G.U. and hormonal:**			
dry/rough skin	2	sensitive	2	**(Female)**			
nail/hair problem	1			menstrual irregularity	3		
		Gastrointestinal:		frequent vaginal discharge	2	**Eyes:**	
Muscles:		blenching, bloating or passing gas	3	yeast or candida infection	3	feels heavy	2
tight/stiff	3	heartburn or stomach pain	2			**Ears:**	
ache-sore-pain		diarrhea	2			dizziness/vertigo	1
- neck	3						
- shoulder	3						
- upper back	3						
- low back	2						

4.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.33	Fatigue:	8.00
Days not feeling good:	2.86	Not rested:	9.00
Work missed:	1.43	Stiffness:	4.00
Inability to perform job tasks:	3.00	Anxiety:	1.00
Pain:	4.00	Depression:	2.00
Total FIQ score:	35.62		

4.4. ELISA

Cortisol level: 6.5 ng/ml

4.5. R-R interval recordings

4.5.1. Heart rate variability data: physical stressor

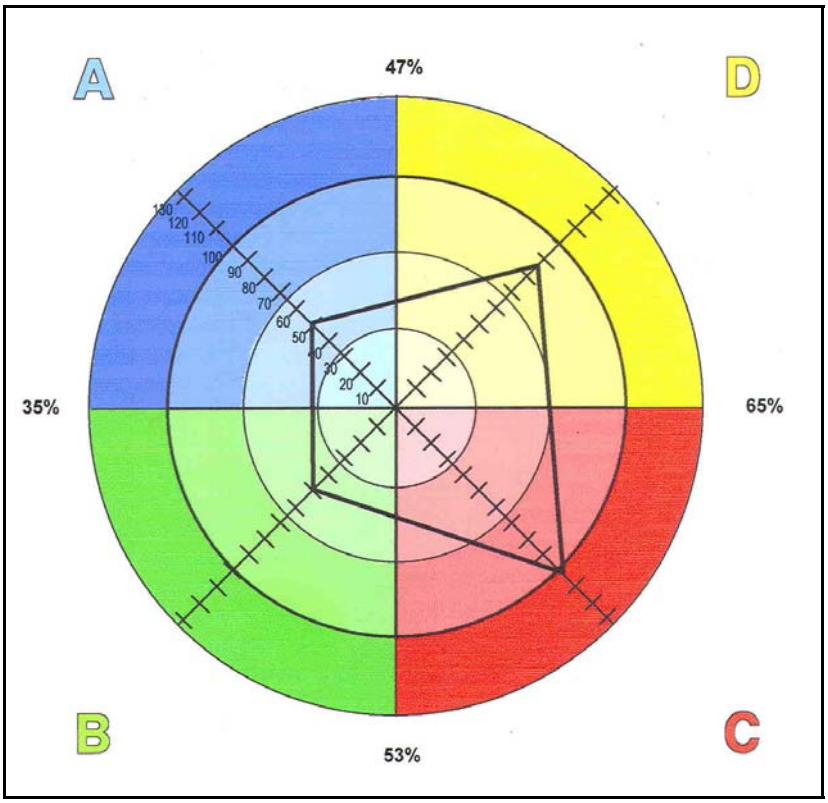
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.62	0.61	0.60
RR standard deviation (s)	0.00	0.00	0.00
Mean HR (1/min)	96.55	98.49	100.79
HR standard deviation (1/min)	0.54	0.70	0.50
Frequency domain results			
LF power (ms^2)	0.92	1.92	0.52
LF power n.u.	33.33	70.78	45.35
HF power (ms^2)	1.83	0.79	0.63
HF power n.u.	66.67	29.22	54.65
LF/HF ratio	0.50	2.42	0.83
Total power (ms^2)	3.38	2.99	1.61

4.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.72	0.71
RR standard deviation (s)	0.01	0.01
Mean HR (1/min)	83.68	84.97
HR standard deviation (1/min)	1.04	0.89
Frequency domain results		
LF power (ms^2)	6.08	7.55
LF power n.u.	48.37	50.53
HF power (ms^2)	6.49	7.39
HF power n.u.	51.63	49.47
LF/HF ratio	0.94	1.02
Total power (ms^2)	15.26	16.60

4.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 51, **B** 50, **C** 102, **D** 86.
Adjective pairs: **A** 5, **B** 4, **C** 9, **D** 5.
Preference code: 2-2-1-1

4.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 4.67
Avoidance score: 3.28
Attachment class: Preoccupied

Patient 5

5.1. Patient health questionnaire

5.1.1. Personal information

Marital status: Married
Highest academic qualification: Honours degree
Work status: Employed (half day)
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

5.1.2. Anthropometrical data

Gender: Male
Age: 35 yrs
Mass: 102 kg
Height: 1.74 m
Body mass index: 33.69

5.1.3 Medical background

Allergies: None
Current illnesses (apart from FM): None
Ongoing illnesses from past (age at which illness started in brackets): allergies (age 5), hypertension (age 11), migraine headaches (age 5).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Hospitalised after rugby match	28 yrs	Psychological stressor (confidentional)	7 yrs
Illnesses:			
Stomach ulcer	27 yrs		

Onset of FM: Gradually
Number of years suffering from FM: 8 yrs
FM progress: Improving
Description of pain: Muscular stiffness leads to headache
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Exercise	Alcohol Stress Humidity Time of day: late afternoon

5.1.4. Treatment program

Exercise program
Physiotherapy
Pharmacological medication

Name of medication	Dose	Frequency
Lantanon	30 mg	1 per day
Cipramil	60 mg	1 per day
Dixarit	-	1 per day
Alluretic	12.5 mg	1 per day

5.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Eyes:**		**Lungs:**		**Nose/Throat:**	
fatigue	2	vision	2	shortness of breath		stuffed/runny nose	3
weight change	1	tearing	2	- on exertion	2	postnasal drip	2
fever/chills/sweats	2	itching	1	phlegm/mucus/		sore throat	1
appetite change	1	feels heavy	2	bronchitis	1	tight/swollen throat	1
abnormal thirst	3			ankle swelling	2		
difficulty sleeping	3	**Ears:**		calf pain on		**Muscles:**	
light-headed	1	itching	2	exercise	3	tight/stiff	3
		hearing problem	1	high blood pressure	3	ache-sore-pain	
Neuropsychiatric:		blocked ears	2			- neck	3
headache (severe)	3	ringing in ears	2	**Gastrointestinal:**		- shoulder	3
depression/apathy	3	sensitive to sounds	3	blenching, bloating,		- low back	3
anxiety/irritable	3	dizziness/vertigo	1	or passing gas	2		
difficulty				heartburn or		**Skin:**	
concentrating	3	**Joints:**		stomach pain	2	rashes	2
mood swings	1	stiff	2			dry/rough skin	2
suicidal	1	swelling	2			acne	1
						nail/hair problem	1

5.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	3.33	Fatigue:	6.00
Days not feeling good:	2.86	Not rested:	10.00
Work missed:	0.00	Stiffness:	8.00
Inability to perform job tasks:	6.00	Anxiety:	7.00
Pain:	7.00	Depression:	4.00
Total FIQ score:	54.19		

5.4. ELISA

Cortisol level: 4.5 ng/ml

5.5. R-R interval recordings

5.5.1. Heart rate variability data: physical stressor

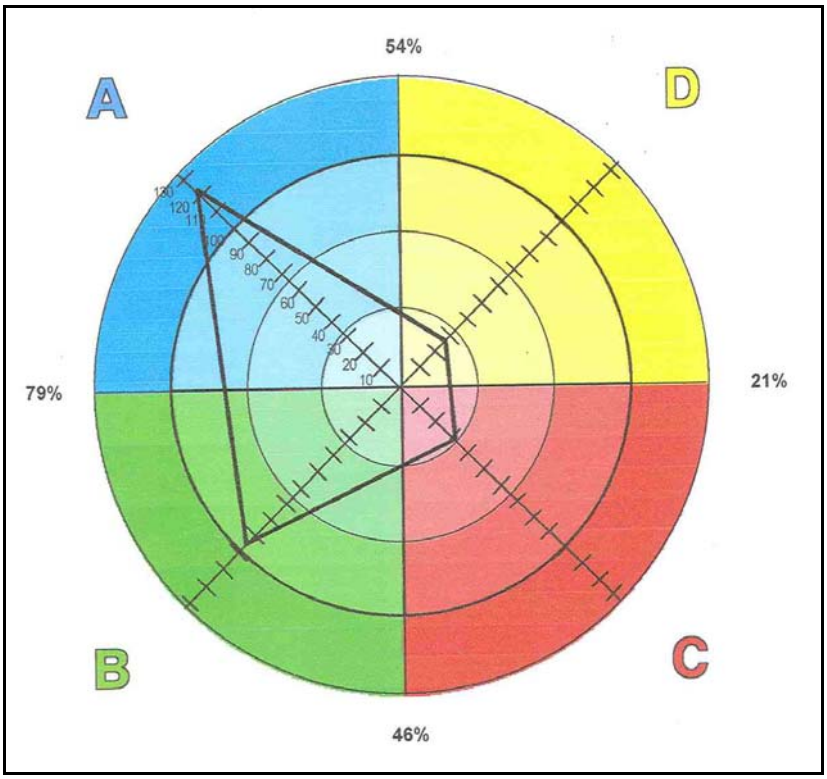
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.09	0.85	0.86
RR standard deviation (s)	0.07	0.04	0.05
Mean HR (1/min)	55.75	70.79	69.89
HR standard deviation (1/min)	4.82	3.30	4.17
Frequency domain results			
LF power (ms²)	1224.40	298.22	891.75
LF power n.u.	46.53	73.50	85.56
HF power (ms²)	1407.30	107.50	150.47
HF power n.u.	53.48	26.50	14.44
LF/HF ratio	0.87	2.77	5.93
Total power (ms²)	2776.54	434.73	1091.71

5.5.2. Heart rate variability data: psychological stressor

(recording discarded)

5.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 123, **B** 95, **C** 32, **D** 26.
Adjective pairs: **A** 11, **B** 9, **C** 3, **D** 1.
Preference code: 1-1-3-3

5.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 3.5
Avoidance score: 4.0
Attachment class: Secure

Patient 6

6.1. Patient health questionnaire

6.1.1. Personal information

Marital status: Divorced
Highest academic qualification: Grade 12
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Disability compensation: None

6.1.2. Anthropometrical data

Gender: Female
Age: 55 yrs
Mass: 74 kg
Height: 1.6 m
Body mass index: 28.9

6.1.3 Medical background

Allergies: Flagyl in antibiotics
Current illnesses (apart from FM): low blood sugar, hypothyroidism
Ongoing illnesses from past (age at which illness started in brackets): allergies (age 50), arthritis (age 25), hypertension (age 43), high cholesterol (age 52), migraine headaches (age 13), thyroid problem (age 53).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Hospitalised for severe headaches	18 yrs	Molested	4 yrs
		Miscarriage	22 yrs
Appendicectomy (emergency)	23 yrs	Unhappy marriage	21-54
Hysterectomy	31 yrs	Son admits homosexuality	51 yrs
Gall bladder removed	35 yrs	Father died of cancer	55 yrs
Knee operation	39 yrs		
Sleep therapy	42 yrs		
Neck operation	47 yrs		
Knee replacement	48 yrs		
Accident	54 yrs		
Illnesses:			
Stomach ulcer	22 yrs		
Non-cancerous breast disease	35 yrs		

Onset of FM: Gradually
Number of years suffering from FM: 41 yrs
FM progress: More painful locations, higher pain intensity.
Description of pain: Feel as if head are crushed/ is going to explode.

Fulfillment of Fukuda CFS diagnostic criteria: Yes

6.1.4. Treatment program

Pharmacological medication

Name of medication	Dose	Frequency
Estrofem	4 mg	1 per day
Eltroxin	1 mg	2 per day
Trepiline	-	-
Prozak	-	-
Rivotril	0.5 mg	1 per day
Oxypan	10 mg	1 per day
Ten Bloka	100 mg	1 per day
Adelat	30 mg	1 per day
Buscopan	10 mg	when needed

6.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Breast:**		**Joints:**		**Thyroid:**	
fatigue	3	lumps	2	ache/pain	3	cold or heat tolerance	3
fever/chills/sweats	3	cystic breasts	2	stiff	3	history of x-ray to neck	3
appetite change	1	discharge	3	swelling	2		
abnormal thirst	3						
difficulty sleeping	3	**Lungs:**		**Genital-urinary:**			
light-headed	2	cough	1	**(Female)**		**Neuropsychiatric:**	
		wheezes	1	yeast or candida infection	2	headache (mild/ moderate)	3
Skin:		shortness of breath		painful or difficult urination	3	headache (severe)	3
itching	2	- at rest	1	pressure/urgency/ itching	1	depression/apathy	2
rashes	2	- on exertion	2			anxiety/irritable	2
dry/rough skin	2	can't get full breath	2	**Muscles:**		hyperactive	2
nail/hair problem	2	phlegm/mucus/ bronchitis	1	tight/stiff	3	"brain fog"/difficulty concentrating	2
Eyes:		chest pain on exertion	1	ache-sore-pain		mood swings	2
vision	2	other chest pain or distress	1	- neck	3	numbness, tingling	2
itching	1	palpitations/rapid, slow or irregular heart rate/rhythm	2	- shoulder	3	faints/blackouts	1
feels heavy	3	ankle swelling	1	- low back	3		
		calf pain on Exercise	3	weakness	3	**Gastrointestinal:**	
Ears:		sore tender legs	1			nausea	2
hearing problem	1	high blood pressure	3	**Mouth:**		blenching, bloating, or passing gas	3
ringing in ears	3			sores/fissures	2	heartburn or stomach pain	3
dizziness/vertigo	2	**Lymph nodes:**		herpes or frequent cold sores	2	constipation	3
		swollen	2	gum/tooth problems	2	cramps or aches	2
Nose/Throat:		sensitive	2			rectal pain or itching	1
stuffed/runny nose	2					blood or black stools	1
postnasal drip	3						
sore throat	1						
hoarse voice	2						

Factors relieving symptoms:	Factors increasing symptoms:
Sleep	Stress Alcohol Humidity Heat Sunlight Food: Sugar Time of day: afternoon

6.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	5.99	Fatigue:	8.00
Days not feeling good:	10.01	Not rested:	8.00
Work missed:	2.86	Stiffness:	8.00
Inability to perform job tasks:	9.00	Anxiety:	6.00
Pain:	9.00	Depression:	6.00
Total FIQ score:	72.86		

6.4. ELISA

Cortisol level: 7.5 ng/ml

6.5. R-R interval recordings

6.5.1. Heart rate variability data: physical stressor

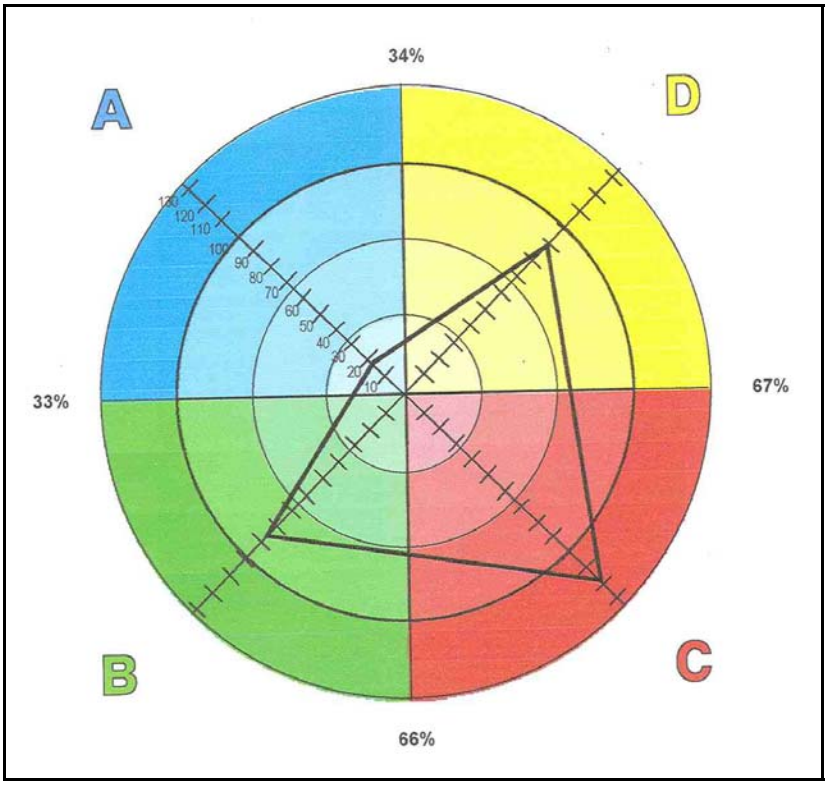
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.88	0.95	0.97
RR standard deviation (s)	0.01	0.02	0.02
Mean HR (1/min)	67.84	63.10	62.19
HR standard deviation (1/min)	1.08	1.53	1.49
Frequency domain results			
LF power (ms^2)	14.46	39.01	27.01
LF power n.u.	18.30	29.79	22.24
HF power (ms^2)	64.55	91.94	94.42
HF power n.u.	81.70	70.21	77.76
LF/HF ratio	0.22	0.42	0.29
Total power (ms^2)	80.48	138.34	126.44

6.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	1.04	0.96
RR standard deviation (s)	0.02	0.02
Mean HR (1/min)	57.50	62.39
HR standard deviation (1/min)	1.54	1.43
Frequency domain results		
LF power (ms²)	37.02	54.41
LF power n.u.	19.46	34.21
HF power (ms²)	153.23	104.64
HF power n.u.	80.54	65.79
LF/HF ratio	0.24	0.52
Total power (ms²)	209.22	176.24

6.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 18, **B** 86, **C** 119, **D** 89.
Adjective pairs: **A** 2, **B** 4, **C** 10, **D** 8.
Preference code: 3-1-1-1

6.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 3.94
Avoidance score: 4.33
Attachment class: Dismissing

Patient 7

7.1. Patient health questionnaire

7.1.1. Personal information

Marital status: Married
Highest academic qualification: Grade 12
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

7.1.2. Anthropometrical data

Gender: Female
Age: 48 yrs
Mass: 78 kg
Height: 1.78 m
Body mass index: 24.61

7.1.3 Medical background

Allergies: Hay fever
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): allergies (age 5), arthritis (age 47), hypertension (age 35), migraine headaches (age 18), mental illness (age 21).

Operations and hospitalisations:	Age	Illnesses:	Age
Shock therapy for depression	29,48	Rheumatic fever Kidney disease	child 19 yrs
Psychological trauma	Age		
Great psychological stressor (confidential)	± 20		

Onset of FM: Following a great psychological stressor
Number of years suffering from FM: 28 yrs
FM progress: Higher pain intensity
Description of pain: Feel as if brain is too big for scull.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Sleep	Stress Exercise Alcohol Humidity Heat Caffeine Season Cold Time of day: late morning/afternoon

7.1.4. Treatment program

Physiotherapy
Non-allopathic treatment
Pharmacological medication

Name of medication	Dose	Frequency
Trepiline	25 mg	4 per day
Aropax	60 mg	3 per day
Zopimed	7.5 mg	1 per day
Alzam	0.5 mg	2 when needed
Mobic	7.5 mg	1 per day

7.2. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	4.54	Fatigue:	9.00
Days not feeling good:	5.72	Not rested:	9.00
Work missed:	7.15	Stiffness:	8.00
Inability to perform job tasks:	5.00	Anxiety:	8.00
Pain:	9.00	Depression:	9.00
Total FIQ score:	74.41		

7.3. ELISA
Cortisol level: 6.5 ng/ml

7.4. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Breast:**		**Joints:**		**Thyroid:**	
fatigue	3	lumps	2	ache/pain	2	mass or lump in neck	1
weight change	2	cystic breasts	1	stiff	2	cold or heat	
fever/chills/sweats	1	discharge	1	swelling	1	tolerance	3
appetite change	2	swollen	3			history of x-ray to	
abnormal thirst	3			**G.U. and hormonal:**		neck	2
difficulty sleeping	3	**Lungs:**		**(Female)**			
light-headed	2	cough	1	herpes	1	**Neuropsychiatric:**	
		wheezes	1	frequent vaginal		headache (mild/	
Skin:		shortness of breath		discharge	1	moderate)	3
itching	1	- at rest	1	yeast or candida		headache (severe)	3
flushing	3	- on exertion	3	infection	2	depression/apathy	3
rashes	1	can't get full breath	1	painful or difficult		anxiety/irritable	3
hives	1	hyperventilation	1	urination	1	hyperactive	1
dry/rough skin	3	phlegm/mucus/		pressure/urgency/		learning disability	1
acne	2	bronchitis	1	itching	1	"brain fog"/difficulty	
nail/hair problem	1	chest pain on		vaginal rash	3	concentrating	3
		exertion	1	sexual problem	3	mood swings	3
Eyes:		other chest pain or				suicidal	2
vision	2	distress	1	**Muscles:**		homicidal	1
tearing	1	palpitations/rapid,		tight/stiff	3	numbness, tingling	3
itching	2	slow or irregular		ache-sore-pain		faints/blackouts	1
feels heavy	3	heart rate/rhythm	2	- neck	3	seizures/convulsions	1
		ankle swelling	1	- shoulder	3		
Ears:		calf pain on		- upper back	3	**Gastrointestinal:**	
itching	1	exercise	1	- low back	3	nausea	1
hearing problem	1	sore tender legs	2	weakness	3	blenching, bloating,	
blocked ears	2	high blood pressure	2			or passing gas	3
ringing in ears	1			**Nose/Throat:**		heartburn or	
sensitive to sounds	2	**Mouth:**		stuffed/runny nose	2	stomach pain	1
dizziness/vertigo	2	sores/fissures	1	postnasal drip	3	diarrhea	1
		herpes or frequent		sore throat	1	constipation	2
Lymph nodes:		cold sores	1	tight/swollen throat	1	cramps or aches	1
swollen	1	gum/tooth problems	1	hoarse voice	3	rectal pain or itching	1
sensitive	1	tongue problem	3	trouble swallowing	1	blood or black stools	1
						worms or parasites	1

7.5. R-R interval recordings

7.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.73	0.70	0.68
RR standard deviation (s)	0.01	0.01	0.01
Mean HR (1/min)	82.51	86.01	88.20
HR standard deviation (1/min)	2.30	2.27	1.26
Frequency domain results			
LF power (ms^2)	32.66	70.72	14.28
LF power n.u.	83.67	85.64	72.23
HF power (ms^2)	6.37	11.86	5.49
HF power n.u.	16.33	14.36	27.77
LF/HF ratio	5.12	5.97	2.60
Total power (ms^2)	49.39	97.99	22.34

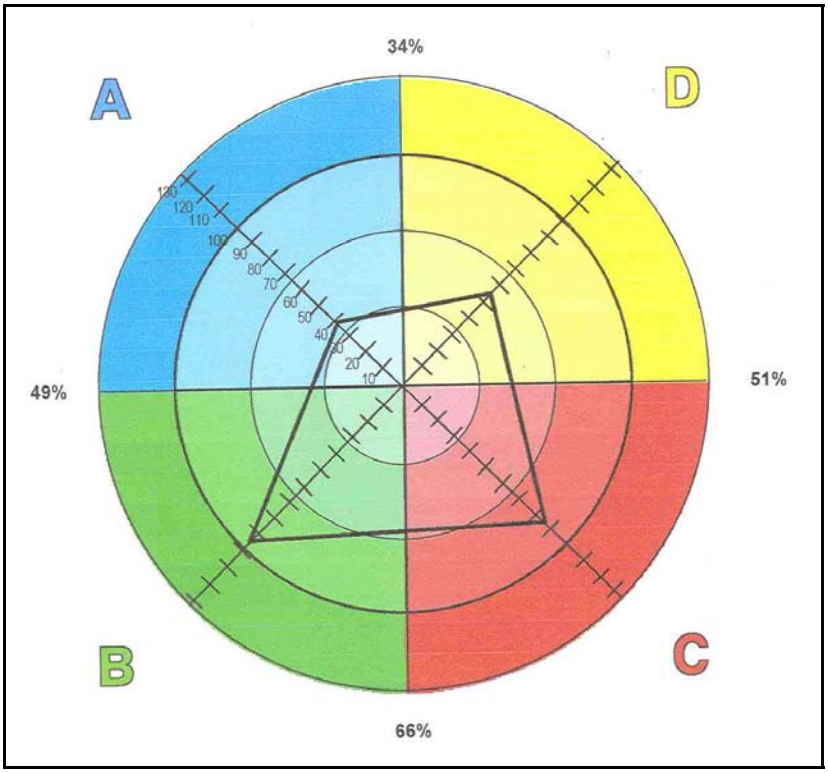
7.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.65	0.65
RR standard deviation (s)	0.01	0.01
Mean HR (1/min)	92.62	92.23
HR standard deviation (1/min)	1.71	1.93
Frequency domain results		
LF power (ms^2)	36.67	33.24
LF power n.u.	90.08	84.45
HF power (ms^2)	4.04	6.12
HF power n.u.	9.92	15.55
LF/HF ratio	9.08	5.43
Total power (ms^2)	48.41	42.44

7.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*

Profile score: **A** 38, **B** 95, **C** 86, **D** 54.
Adjective pairs: **A** 2, **B** 7, **C** 11, **D** 4.
Preference code: 2-1-1-2



7.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 3.17
Avoidance score: 3.39
Attachment class: Secure

Patient 8

8.1. Patient health questionnaire

8.1.1. Personal information

Marital status: Married
Highest academic qualification: Diploma
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

8.1.2. Anthropometrical data

Gender: Female
Mass: 70 kg
Body mass index: 23.67
Age: 33 yrs
Height: 1.72 m

8.1.3 Medical background

Allergies: Hay fever
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): allergies (age 30), migraine headaches (age 31), endometriosis (age 27).

Illnesses:	Age	Traumatic psychological events:	Age
Bilharzia	22 yrs	House burnt down Sister (living with patient) in serious motor car accident Marital problems	22 yrs 22 yrs 23,30

Onset of FM: Following an illness and great psychological stressors occurring in short succession.
Number of years suffering from FM: 12 yrs
FM progress: More painful locations, higher pain intensity
Description of pain: Continuous pain spread over whole body.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Sleep	Stress Exercise Alcohol Humidity Caffeine Time of day: early morning, late afternoon

8.1.4. Treatment program

Exercise program
Physiotherapy
Pharmacological medication

Name of medication	Dose	Frequency
Tramal	-	1 per day

8.2. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	4.24	Fatigue:	0.50
Days not feeling good:	8.58	Not rested:	7.00
Work missed:	2.86	Stiffness:	8.00
Inability to perform job tasks:	4.00	Anxiety:	2.00
Pain:	4.00	Depression:	1.00
Total FIQ score:	42.18		

8.3. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Breast:**		**Joints:**		**Neuropsychiatric:**	
fatigue	1	discharge	2	ache/pain	1	headache (mild/ moderate)	1
weight change	2						
fever/chills/sweats	2	**Lungs:**		**Muscles:**		headache (severe)	3
difficulty sleeping	2	shortness of breath - on exertion	2	tight/stiff	3	anxiety/irritable	2
				ache-sore-pain		"brain fog"/difficulty concentrating	2
Skin:		calf pain on Exercise	2	- neck	3		
itching	2			- shoulder	3	mood swings	2
rashes	2			- upper back	3		
acne	2	**Nose/Throat:**		- low back	3	**Gastrointestinal:**	
nail/hair problem	3	stuffed/runny nose	3			nausea	1
		postnasal drip	2	**Ears:**		heartburn or stomach pain	3
Eyes:				blocked ears	2		
tearing	2	**Mouth:**		ringing in ears	2	constipation	2
feels heavy	3	gum/tooth problems	3	sensitive	2		

8.4. ELISA

Cortisol level: 10.5 ng/ml

8.5. R-R interval recordings

8.5.1. Heart rate variability data: physical stressor

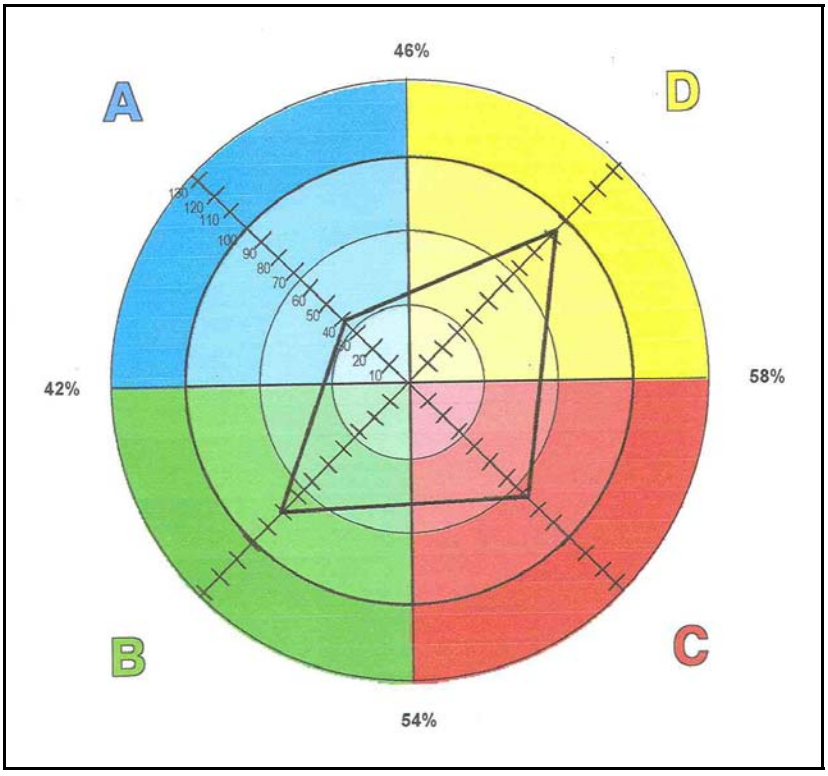
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.77	0.71	0.71
RR standard deviation (s)	0.03	0.05	0.04
Mean HR (1/min)	77.72	84.46	84.78
HR standard deviation (1/min)	3.45	5.82	4.88
Frequency domain results			
LF power (ms^2)	214.10	942.97	306.89
LF power n.u.	36.64	84.31	52.89
HF power (ms^2)	370.31	175.44	273.34
HF power n.u.	63.36	15.69	47.11
LF/HF ratio	0.58	5.38	1.12
Total power (ms^2)	602.99	1158.64	615.73

8.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.84	0.82
RR standard deviation (s)	0.03	0.02
Mean HR (1/min)	71.67	73.46
HR standard deviation (1/min)	3.07	2.66
Frequency domain results		
LF power (ms²)	218.82	72.79
LF power n.u.	62.23	43.47
HF power (ms²)	132.82	94.66
HF power n.u.	37.77	56.53
LF/HF ratio	1.65	0.77
Total power (ms²)	408.77	172.69

8.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 38, **B** 81, **C** 74, **D** 93.
Adjective pairs: **A** 4, **B** 8, **C** 5, **D** 7.
Preference code: 2-1-1-1

8.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.56
Avoidance score: 2.34
Attachment class: Secure

Patient 9

9.1. Patient health questionnaire

9.1.1. Personal information

Marital status: Divorced
Highest academic qualification: Grade 12
Work status: Not employed
Lifestyle: Smoked 2 packs for past 13 yrs
Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

9.1.2. Anthropometrical data

Gender: Male
Age: 40 yrs
Mass: 90 kg
Height: 1.78 m
Body mass index: 28.41

9.1.3 Medical background

Allergies: None
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): migraine headaches (age 20), hypertension (age 24), thyroid problem (age unknown).

Operations and hospitalisations:	Age (yrs)	Traumatic psychological events:	Age (yrs)
Hospitalised in psychiatric hospital for depression	38,39,40	Father alcoholic Father died Psychological trauma (confidential) Divorce Suicide attempt	child child ± 35 39 40
Illnesses:			
Stomach ulcer	38		

Onset of FM: Following a great psychological stressor
Number of years suffering from FM: 5 yrs
FM progress: No change
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Exercise Cold Sleep	Stress Humidity Sunlight Heat

9.1.4. Treatment program

Exercise program
Physiotherapy
Non-allopathic treatment
Pharmacological medication

Name of medication	Dose	Frequency
Nizac	20 mg	2 per day
Xanor	0.5 mg	4 per day
Atarax	25 mg	3 per day

9.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Muscles:**		**Thyroid:**	
fatigue	3	hyperventilation	2	ache-sore-pain		history of x-ray to	
weight change	1	phlegm/mucus/		- upper back	3	neck	3
fever/chills/sweats	2	bronchitis	1	- neck	2		
appetite change	1	chest pain on		- low back	3	**Neuropsychiatric:**	
abnormal thirst	2	exertion	3	weakness	3	depression	3
difficulty sleeping	3	other chest pain or				anxiety/ irritable	3
light-headed	2	distress	2	**Lymph nodes:**		headache (severe)	3
		palpitations/rapid,		swollen	1	learning disability	3
Skin:		slow or irregular		sensitive	1	"brain fog"/difficulty	
itching	1	heart rate/rhythm	1			concentrating	3
flushing	1	ankle swelling	1	**Gastrointestinal:**		mood swings	3
rashes	1	sore tender legs	2	heartburn	3	suicidal	3
hives	1			nausea	3		
dry/rough skin	1	**Eyes:**		rectal pain/itching	3	**Ears:**	
acne	1	vision	1	diarrhea	2	sensitive to sound	1
hair problem	2	feels heavy	1	cramps and aches	2	dizziness/vertigo	3
Nose/Throat:						**Mouth:**	
postnasal drip	3					gum/ tooth problem	1
						tongue problem	1

9.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	5.83	Fatigue:	10.00
Days not feeling good:	10.01	Not rested:	10.00
Work missed:	10.01	Stiffness:	6.00
Inability to perform job tasks:	10.00	Anxiety:	10.00
Pain:	6.00	Depression:	10.00
Total FIQ score:	87.85		

9.4. ELISA
Cortisol level: 9.0 ng/ml

9.5. R-R interval recordings

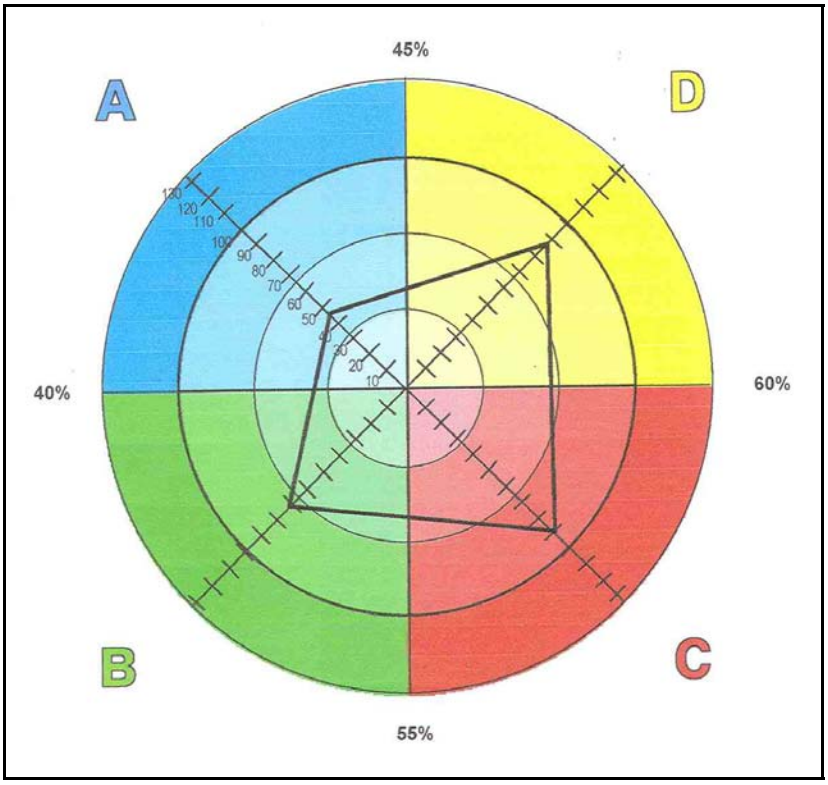
9.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.73	0.70	0.84
RR standard deviation (s)	0.01	0.02	0.03
Mean HR (1/min)	81.81	86.42	71.67
HR standard deviation (1/min)	1.69	2.31	3.07
Frequency domain results			
LF power (ms^2)	44.55	111.15	218.82
LF power n.u.	72.36	84.43	62.23
HF power (ms^2)	17.02	20.50	132.82
HF power n.u.	27.64	15.57	37.77
LF/HF ratio	2.62	5.42	1.65
Total power (ms^2)	63.18	148.15	408.77

9.5.2. Heart rate variability data: psychological stressor
(recording discarded)

9.6. Herrmann Brain Dominance Instrument
*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*

Profile score: **A** 45, **B** 72, **C** 90, **D** 87.
Adjective pairs: **A** 4, **B**5, **C** 9, **D** 6.
Preference code: 2-1-1-1



9.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 5.33
Avoidance score: 2.67
Attachment class: Preoccupied

Patient 10

10.1. Patient health questionnaire

10.1.1. Personal information

Marital status: Married
Highest academic qualification: Grade 12
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

10.1.2. Anthropometrical data

Gender: Female
Age: 63 yrs
Mass: 62 kg
Height: 1.62 m
Body mass index: 23.62

10.1.3 Medical background

Allergies: penicillin, sulphar.
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): arthritis (age 27), high cholesterol (age 45), migraine headaches (age 48).

Operations and hospitalisations:	Age
Hysterectomy	39 yrs
Neck fusion	50,51
Knee replacement	62 yrs

Onset of FM: Gradually
Number of years suffering from FM: 21 yrs
FM progress: More painful locations
Description of pain: Continuous pain spread over whole body.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Exercise	Stress
Heat	Alcohol
Sunlight	Humidity
Sleep	Caffeine
Barometric pressure	Season: winter
	Cold

10.1.4. Treatment program

Exercise program
Non-allopathic treatment
Pharmacological medication

Name of medication	Dose	Frequency
Trepiline	10 mg	1 per day
Zopimed	7.5 mg	1 per day
Slowmag	-	2 per day
Cal-C-Vita	-	1 per day
Caltrate	-	1 per day
Estro-pause	2 mg	1 per day
Lipitor	10 mg	1 per day

10.2. Review of current symptoms – questionnaire
(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Joints:**		**Neuropsychiatric:**	
fatigue	3	palpitations/rapid heart rate/rhythm	2	ache/pain	3	headache (mild/ moderate)	3
weight change	2	calf pain on exercise	2	stiff	3	headache (severe)	3
fever/chills/sweats	1	sore tender legs	2	**Genital-urinary:**		anxiety/irritable	1
appetite change	1	**Ears:**		**(Female)**		difficulty concentrating	2
abnormal thirst	2	itching	2	pressure/urgency/ itching	2	numbness, tingling	3
insomnia	3	hearing problem	1	sexual problem	3	**Gastrointestinal:**	
light-headed	2	dizziness/vertigo	1	**Muscles:**		bloating or passing gas	2
Skin:		**Nose/Throat:**		tight/stiff	3	heartburn or stomach pain	1
itching	1	postnasal drip	1	ache-sore-pain		constipation	3
nail/hair problem	3	sore throat	1	- neck	3		
Eyes:				- shoulder	3		
vision	1			- upper back	3		
itching	1			- low back	2		
				weakness	2		

10.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	3.03	Fatigue:	8.00
Days not feeling good:	7.15	Not rested:	7.00
Work missed:	2.86	Stiffness:	7.00
Inability to perform job tasks:	7.00	Anxiety:	4.00
Pain:	8.00	Depression:	4.00
Total FIQ score:	58.04		

10.4. ELISA
Cortisol level: 16.5 ng/ml

10.5. R-R interval recordings

10.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.06	0.97	0.99
RR standard deviation (s)	0.07	0.03	0.04
Mean HR (1/min)	56.92	62.33	60.70
HR standard deviation (1/min)	3.84	2.96	2.96
Frequency domain results			
LF power (ms^2)	520.86	388.93	200.01
LF power n.u.	21.77	80.72	23.22
HF power (ms^2)	1871.95	92.92	661.41
HF power n.u.	78.23	19.28	76.78
LF/HF ratio	0.28	4.19	0.30
Total power (ms^2)	2408.88	564.76	910.65

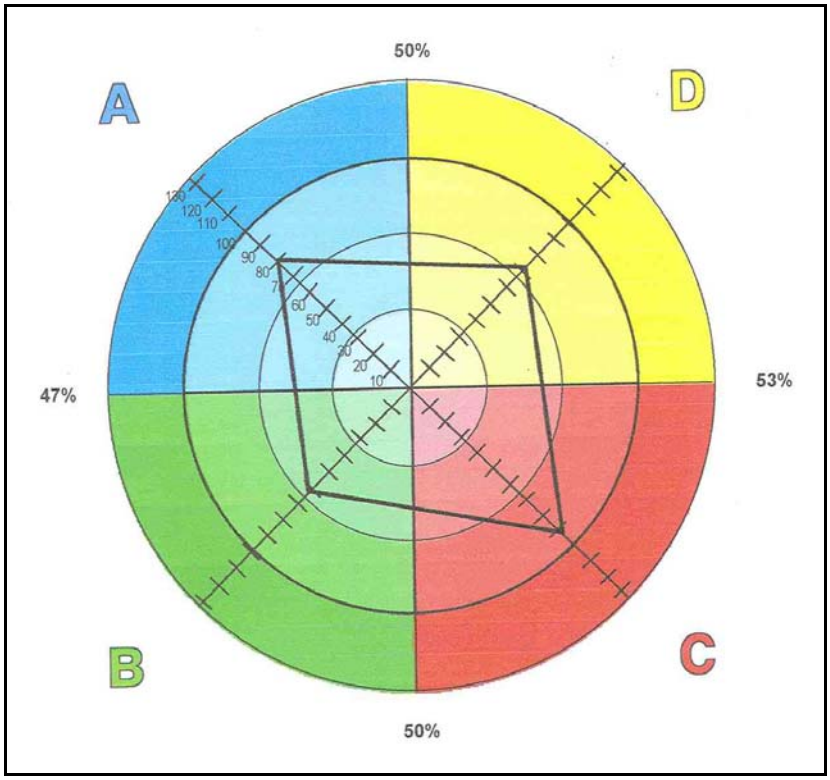
10.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.94	0.89
RR standard deviation (s)	0.03	0.03
Mean HR (1/min)	64.30	67.33
HR standard deviation (1/min)	3.37	2.22
Frequency domain results		
LF power (ms^2)	314.03	138.98
LF power n.u.	75.52	83.50
HF power (ms^2)	101.79	27.47
HF power n.u.	24.48	16.50
LF/HF ratio	3.09	5.06
Total power (ms^2)	469.37	262.93

10.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*

Profile score: **A** 80, **B** 63, **C** 92, **D** 72.
Adjective pairs: **A** 5, **B** 4, **C** 10, **D** 5.
Preference code: 1-2-1-1



10.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.61
Avoidance score: 1.34
Attachment class: Secure

Patient 11

11.1. Patient health questionnaire

11.1.1. Personal information

Marital status: Married
Highest academic qualification: Grade 12
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: Full

11.1.2. Anthropometrical data

Gender: Female
Mass: 68 kg
Body mass index: 24.38

Age: 33 yrs
Height: 1.67 m

11.1.3 Medical background

Allergies: None
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): arthritis (age 29), asthma (age 1, 29,30), mental illness (age 29).

Illnesses:	Age
Polio	1 yr
Stomach ulcer	30 yrs

Onset of FM: Gradually
Number of years suffering from FM: 4 yrs
FM progress: Improving
Description of pain: Flu-like pain
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Exercise Sleep	Stress Exercise Heat Cold

11.1.4. Treatment program

Exercise program
Pharmacological medication

Name of medication	Dose	Frequency
Trepiline	10 mg	1 per day
Arthrotec	-	1 per day
Cipramil	-	1 per day
Lanzor	30 mg	1 per day
Stillnox	-	when needed

11.2. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	4.44	Fatigue:	9.00
Days not feeling good:	7.15	Not rested:	9.00
Work missed:	0.00	Stiffness:	6.00
Inability to perform job tasks:	7.00	Anxiety:	6.00
Pain:	8.00	Depression:	4.00
Total FIQ score:	60.59		

11.3. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Joints:**		**Thyroid:**	
fatigue	3	phlegm/mucus/		ache/pain	3	**Neuropsychiatric:**	
weight change	2	bronchitis	1	stiff	2	headache (severe)	3
fever/chills/sweats	3	other chest pain or		swelling	2	depression/apathy	2
appetite change	2	distress	2			anxiety/irritable	2
difficulty sleeping	3			**Muscles:**		numbness, tingling	2
light-headed	3	calf pain on		tight/stiff	3		
		exercise	2	ache-sore-pain		**Gastrointestinal:**	
Skin:		sore tender legs	3	- neck	3	heartburn or	
flushing	2			- shoulder	3	stomach pain	2
acne	2	**Mouth:**		- upper back	3	cramps or aches	1
nail/hair problem	2	sores/fissures	1	- low back	3		
		herpes or frequent		weakness	3	**Ears:**	
Eyes:						itching	3
vision	2	**Nose/Throat:**		**Lymph nodes:**		dizziness/vertigo	2
		postnasal drip	2	swollen	2		

11.4. ELISA

Cortisol level: 9.0 ng/ml

11.5. R-R interval recordings

11.5.1. Heart rate variability data: physical stressor

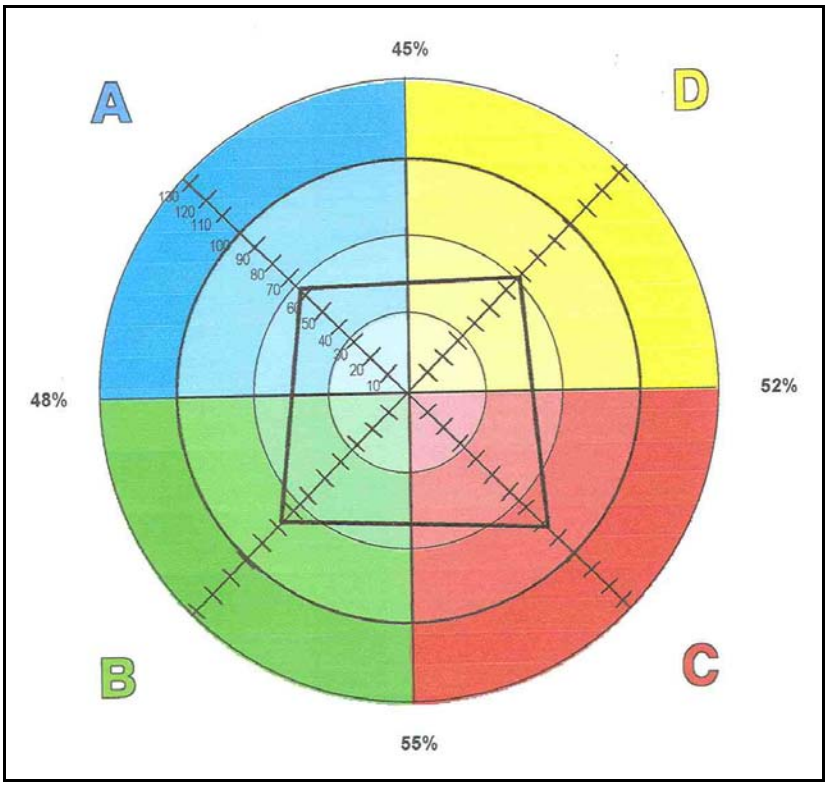
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.67	0.65	0.67
RR standard deviation (s)	0.01	0.03	0.01
Mean HR (1/min)	89.29	92.88	89.31
HR standard deviation (1/min)	2.42	3.50	2.42
Frequency domain results			
LF power (ms^2)	29.98	80.42	30.48
LF power n.u.	59.17	68.38	59.56
HF power (ms^2)	20.68	37.18	20.69
HF power n.u.	40.83	31.62	40.44
LF/HF ratio	1.45	2.16	1.47
Total power (ms^2)	69.18	137.44	70.05

11.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.69	0.67
RR standard deviation (s)	0.02	0.01
Mean HR (1/min)	87.30	89.04
HR standard deviation (1/min)	2.42	2.43
pNN50 (%)	0.00	0.00
Frequency domain results		
Total power (ms²)	138.38	85.11
LF power (ms²)	40.72	39.48
LF power n.u.	32.30	53.07
HF power (ms²)	85.35	34.92
HF power n.u.	67.70	46.93
LF/HF ratio	0.48	1.13

11.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 63, **B** 77, **C** 83, **D** 68.
Adjective pairs: **A** 7, **B** 5, **C** 9, **D** 3.
Preference code: 2-1-1-1

11.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.56
Avoidance score: 4.72
Attachment class: Dismissing

Patient 12

12.1. Patient health questionnaire

12.1.1. Personal information

Marital status: Separated
Highest academic qualification: Honours degree
Work status: Employed
Lifestyle: Occasionally uses alcohol
Lives alone
Disability compensation: None

12.1.2. Anthropometrical data

Gender: Female
Age: 41 yrs
Mass: 59 kg
Height: 1.67 m
Body mass index: 21.16

12.1.3 Medical background

Allergies: None
Current illnesses (apart from FM): Neck injury
Ongoing illnesses from the past (age at which illness started in brackets): endometriosis (age 33), vaginitis (yeast) (constantly).

Illnesses:	Age	Traumatic psychological events:	Age
Glandular fever Seizer/ convulsion Hepatitis	26 yrs 26 yrs 27 yrs	Unhappy marriage	21-41

Onset of FM: Following an operation
Number of years suffering from FM: 15 yrs
FM progress: No change
Description of pain: Pain caused by muscle spasms
Fulfillment of Fukuda CFS diagnostic criteria: No

Factors relieving symptoms:	Factors increasing symptoms:
Sleep	Stress Exercise Caffeine Cold Heat

12.1.4. Treatment program

Exercise program
Physiotherapy
Pharmacological medication

Name of medication	Dose	Frequency
Nuzak	20 mg	1 per day

12.2. Review of current symptoms – questionnaire
(1 – mild, 2 – moderate, 3 – severe)

Constitutional:	
fatigue	2
weight change	2
fever/chills/sweats	1
appetite change	3
abnormal thirst	3
difficulty sleeping	3
light-headed	3

Skin:	
itching	1
flushing	1
rashes	1
hives	1
dry/rough skin	1
acne	1
nail/hair problem	1

Eyes:	
vision	3
tearing	3
itching	2
feels heavy	2
allergic shiners	2

Ears:	
itching	3
hearing problem	2
blocked ears	2
ringing in ears	3
sensitive to sounds	3
dizziness/vertigo	3

Lymph nodes:	
swollen	3
sensitive	3

Breast:	
lumps	1
cystic breasts	1
discharge	1
swollen	1

Lungs:	
cough	1
wheezes	1
shortness of breath	
- at rest	1
- on exertion	1
can't get full breath	1
hyperventilation	1
phlegm/mucus/ bronchitis	2
chest pain on exertion	1
other chest pain or distress	3
palpitations/rapid, slow or irregular heart rate/rhythm	1
ankle swelling	1
calf pain on Exercise	3
sore tender legs	3
high blood pressure	1

Mouth:	
sores/fissures	1
herpes or frequent cold sores	1
gum/tooth problems	1
tongue problem	1

Joints:	
ache/pain	1
stiff	1
swelling	1

G.U. and Hormonal: **(Female)**	
severe menstrual cramps	1
severe premenstrual cramps	1
menstrual irregularity	1
frequent vaginal discharge	3
yeast or candida infection	3
painful or difficult urination	3
pressure/urgency/ itching	2
vaginal rash	1

Muscles:	
tight/stiff	3
ache-sore-pain	
- neck	3
- shoulder	3
- upper back	3
- low back	2
weakness	3

Nose/Throat:	
stuffed/runny nose	1
postnasal drip	1
sore throat	1
tight/swollen throat	1
hoarse voice	3
trouble swallowing	3

Thyroid:	
mass or lump in neck	1
cold or heat tolerance	1
history of x-ray to neck	3

Neuropsychiatric:	
headache (mild/ moderate)	3
headache (severe)	3
depression/apathy	3
anxiety/irritable	2
hyperactive	2
learning disability	1
"brain fog"/difficulty concentrating	2
mood swings	3
suicidal	1
homicidal	1
numbness, tingling	2

Gastrointestinal:	
nausea	1
blenching, bloating, or passing gas	3
heartburn or stomach pain	1
diarrhea	3
constipation	3
cramps or aches	3
rectal pain or itching	1
blood or black stools	1
worms or parasites	1

12.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.00	Fatigue:	7.00
Days not feeling good:	8.58	Not rested:	7.00
Work missed:	0.00	Stiffness:	8.00
Inability to perform job tasks:	3.00	Anxiety:	10.00
Pain:	8.00	Depression:	7.00
Total FIQ score:	58.58		

12.4. ELISA

Cortisol level: 8.0 ng/ml

12.5. R-R interval recordings

12.5.1. Heart rate variability data: physical stressor

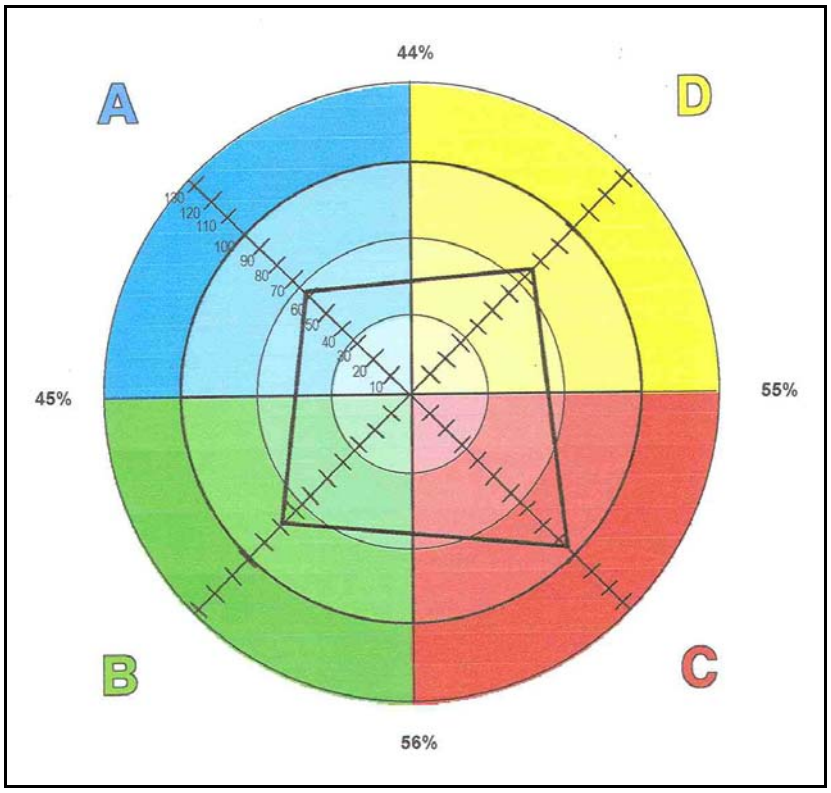
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.88	0.86	0.84
RR standard deviation (s)	0.02	0.03	0.03
Mean HR (1/min)	68.60	70.38	71.63
HR standard deviation (1/min)	2.04	2.80	3.14
Frequency domain results			
LF power (ms^2)	77.90	113.62	137.47
LF power n.u.	63.64	61.86	65.20
HF power (ms^2)	44.51	70.06	73.36
HF power n.u.	36.36	38.14	34.80
LF/HF ratio	1.75	1.62	1.87
Total power (ms^2)	134.62	193.57	258.79

12.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.82	0.78
RR standard deviation (s)	0.02	0.03
Mean HR (1/min)	73.26	77.09
HR standard deviation (1/min)	2.09	4.12
Frequency domain results		
LF power (ms^2)	132.14	324.23
LF power n.u.	58.12	86.20
HF power (ms^2)	95.20	51.91
HF power n.u.	41.88	13.80
LF/HF ratio	1.39	6.25
Total power (ms^2)	238.97	428.79

12.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 62, **B** 78, **C** 95, **D** 75.
Adjective pairs: **A** 6, **B** 7, **C** 8, **D** 3.
Preference code: 2-1-1-1

12.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 5.78
Avoidance score: 6.94
Attachment class: Fearful-avoidant

Patient 13

13.1. Patient health questionnaire

13.1.1. Personal information

Marital status: Single
Highest academic qualification: Postgraduate diploma
Work status: Employed (half day)

Lifestyle: Uses alcohol daily
Live alone
Disability compensation: None

13.1.2. Anthropometrical data

Gender: Female
Age: 46 yrs
Mass: 55 kg
Height: 1.71 m
Body mass index: 18.8

13.1.3 Medical background

Allergies: None
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): anemia (age unknown), hypertension (age 37), high cholesterol (age 40).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Appendicectomy Accident	18 yrs -	Stressful childhood, often unhappy	child

Onset of FM: Following a accident
Number of years suffering from FM: 10 yrs
FM progress: No changes
Description of pain: Continuous pain at tender points.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors increasing symptoms:
Sleep Stress Barometric pressure Time of day: early morning

13.1.4. Treatment program

Exercise program
Physiotherapy
Pharmacological medication

Name of medication	Dose	Frequency
Trepiline	25 mg	1 per day
Anafranil	10 mg	1 per day
Co-diovan	-	1 per day

13.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Joints:**		**Ears:**	
fatigue	3	can't get full breath	1	stiff	1	sensitive to sounds	3
abnormal thirst	2	palpitations/rapid,					
difficulty sleeping	3	heart rate/rhythm	1	**G.U. and Hormonal:**		**Muscles:**	
light-headed	1	high blood pressure	2	**(Female)**		tight/stiff	3
				severe menstrual		ache-sore-pain	
Neuropsychiatric:		**Mouth:**		cramps	2	- neck	2
anxiety/irritable	2	gum/tooth problems	1	severe premenstrual		- shoulder	2
mood swings	1			cramps	1	- upper back	2
		Nose/Throat:		menstrual irregularity	1	- low back	3
		sore throat	1				

13.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.61	Fatigue:	8.00
Days not feeling good:	5.72	Not rested:	8.00
Work missed:	0.00	Stiffness:	7.00
Inability to perform job tasks:	7.00	Anxiety:	7.00
Pain:	7.00	Depression:	3.00
Total FIQ score:	53.33		

13.4. ELISA

Cortisol level: 10.0 ng/ml

13.5. R-R interval recordings

13.5.1. Heart rate variability data: physical stressor

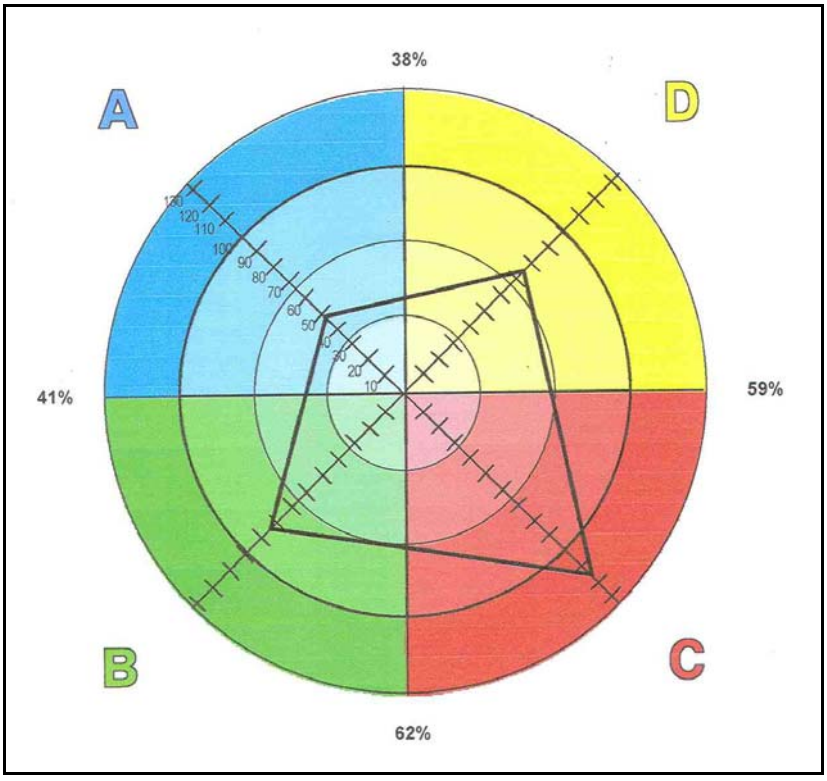
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.81	0.76	0.76
RR standard deviation (s)	0.02	0.02	0.02
Mean HR (1/min)	74.32	78.76	79.23
HR standard deviation (1/min)	2.55	2.40	2.44
Frequency domain results			
LF power (ms^2)	112.35	175.34	149.48
LF power n.u.	65.64	88.73	82.38
HF power (ms^2)	58.80	22.26	31.97
HF power n.u.	34.36	11.27	17.62
LF/HF ratio	1.91	7.88	4.68
Total power (ms^2)	194.52	218.88	187.04

13.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.76	0.70
RR standard deviation (s)	0.02	0.02
Mean HR (1/min)	79.19	85.81
HR standard deviation (1/min)	2.47	3.49
Frequency domain results		
LF power (ms²)	144.56	246.49
LF power n.u.	81.88	91.57
HF power (ms²)	31.99	22.68
HF power n.u.	18.12	8.43
LF/HF ratio	4.52	10.87
Total power (ms²)	181.37	283.62

13.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 47, **B** 84, **C** 116, **D** 75.
Adjective pairs: **A** 3, **B** 7, **C** 10, **D** 4.
Preference code: 2-1-1-1

13.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 4.50
Avoidance score: 5.06
Attachment class: Fearful-avoidant

Patient 14

14.1. Patient health questionnaire

14.1.1. Personal information

Marital status: Married
Highest academic qualification: Degree
Work status: Employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: None

14.1.2. Anthropometrical data

Gender: Female
Age: 38 yrs
Mass: 57 kg
Height: 1.59 m
Body mass index: 22.55

14.1.3 Medical background

Allergies: Flagyl
Current illnesses (apart from FM): None
Ongoing illnesses from the past (age at which illness started in brackets): heart murmur (age 14).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Heart catarisation	14 yrs	1st year on university experienced as traumatic	18 yrs
Illnesses:		Miscarriage	29 yrs
Hepatitis	8 yrs	Difficult pregnancy	32 yrs
Viral infections (Coxsackie, Ebstein Barr, Sito Eliza)	24 yrs	Marital problems and separation	35 yrs
Tumor	32 yrs		
Pneumonia	34 yrs		

Onset of FM: Gradually
Number of years suffering from FM: 4 yrs
FM progress: No change
Description of pain: Continuous sharp, burning pain.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Moderate exercise Sunlight Sleep Season: spring	Stress Caffeine Season: winter Heat Cold Food: sugar, red meat Time of day: early in morning, late at night

14.1.4. Treatment program

Exercise program
Pharmacological medication

Name of medication	Dose	Frequency
Trepiline	5 mg	1 day
Cipramil	10 mg	1 day
Tramahexal	50 mg	2 when needed
Slow-Mag	535 mg	2 per day

14.2. Review of current symptoms – questionnaire
(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Joints:**		**Thyroid:**	
fatigue	2	shortness of breath		ache/pain	2	cold or heat	
weight change	2	- on exertion	2	stiff	2	tolerance	1
fever/chills/sweats	1	can't get full breath	1				
appetite change	1	phlegm/mucus/		**G.U. and Hormonal:**		**Neuropsychiatric:**	
light-headed	2	bronchitis	1	**(Female)**		headache (severe)	3
		chest pain on		frequent vaginal		anxiety/irritable	1
Skin:		exertion	2	discharge	1	"brain fog"/difficulty	
dry/rough skin	1	other chest pain or		yeast or candida		concentrating	1
nail/hair problem	1	distress	2	sexual problem	1	numbness, tingling	1
		calf pain on				faints/blackouts	1
Eyes:		exercise	2	**Muscles:**			
itching	1	sore tender legs	2	tight/stiff	3	**Gastrointestinal:**	
feels heavy	2			ache-sore-pain		blenching, bloating,	
		Mouth:		- neck	3	or passing gas	2
Ears:		gum/tooth problems	1	- shoulder	3	constipation	3
hearing problem	1			- upper back	3	cramps or aches	2
ringing in ears	1	**Nose/Throat:**		- low back	3		
sensitive to sounds	2	stuffed/runny nose	1	weakness	1	**Lymph nodes:**	
dizziness/vertigo	1	sore throat	1			sensitive	1

14.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	1.67	Fatigue:	8.00
Days not feeling good:	8.58	Not rested:	8.00
Work missed:	0.00	Stiffness:	4.00
Inability to perform job tasks:	3.00	Anxiety:	2.00
Pain:	4.00	Depression:	1.00
Total FIQ score:	40.25		

14.4. ELISA

Cortisol level: 12.0 ng/ml

14.5. R-R interval recordings

14.5.1. Heart rate variability data: physical stressor

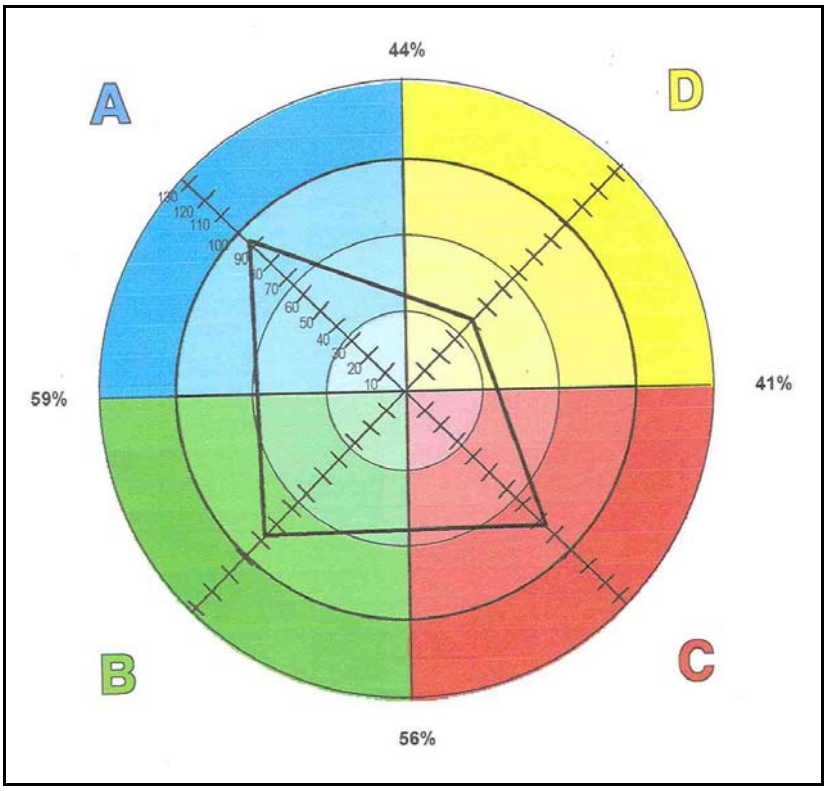
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.79	0.78	0.78
RR standard deviation (s)	0.02	0.03	0.03
Mean HR (1/min)	75.97	77.14	76.75
HR standard deviation (1/min)	2.25	3.28	3.30
Frequency domain results			
LF power (ms^2)	62.65	177.66	118.11
LF power n.u.	28.33	51.43	35.45
HF power (ms^2)	158.47	167.77	215.08
HF power n.u.	71.67	48.57	64.55
LF/HF ratio	0.40	1.06	0.55
Total power (ms^2)	231.81	357.86	365.30

14.5.2 Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.79	0.78
RR standard deviation (s)	0.03	0.03
Mean HR (1/min)	76.33	77.47
HR standard deviation (1/min)	2.89	3.26
Frequency domain results		
LF power (ms^2)	112.22	150.89
LF power n.u.	29.93	35.99
HF power (ms^2)	262.78	268.39
HF power n.u.	70.07	64.01
LF/HF ratio	0.43	0.56
Total power (ms^2)	379.45	422.81

14.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*



Profile score: **A** 93, **B** 87, **C** 84, **D** 41.
Adjective pairs: **A** 6, **B** 9, **C** 7, **D** 2.
Preference code: 1-1-1-2

14.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.89
Avoidance score: 2.67
Attachment class: Secure

Patient 15

15.1. Patient health questionnaire

15.1.1. Personal information

Marital status: Married
Highest academic qualification: Degree
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: Full

15.1.2. Anthropometrical data

Gender: Female
Age: 53 yrs
Mass: 80 kg
Height: 1.55 m
Body mass index: 33.30

15.1.3 Medical background

Allergies: Eczema
Current illnesses (apart from FM): macular degeneration, restless legs.
Ongoing illnesses from the past (age at which illness started in brackets): allergies (age 9), heart murmur (age 9), hypertension (age 49), migraine headaches (age 19), thyroid problem (age 39).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Neck problems 2 neck operations Hysterectomy	48 yrs 48 yrs 29 yrs	Father died (chronic colds and flues started)	30 yrs
Illnesses:			
Diagnosed with MS Macular degeneration	49 yrs 51 yrs		

Onset of FM: Gradually
Number of years suffering from FM: 20 yrs
FM progress: Improving
Description of pain: Continuous pain spread over whole body. Cannot sleep because of pain.
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors relieving symptoms:	Factors increasing symptoms:
Moderate exercise Heat	Stress Humidity Sleep Cold

15.1.4. Treatment program

Name of medication	Dose	Frequency
Estrofem	-	1 per day
Eltroxin	0.1 mg	1 per day
Detrusitol	1 mg	1 per day
Celebrex	200 mg	1 per day
Robaxin	500 mg	2-3 per day
TyLenol ExRl	-	2-3 per day
Calcimight	-	1 per day
Sinemet CR	50/200 mg	1-2 per day

Exercise program
Non-allopathic treatment
Pharmacological medication

15.2. Review of current symptoms – questionnaire
(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Breast:**		**Joints:**		**Thyroid:**	
fatigue	1	lumps	1	ache/pain	3	history of x-ray to	
appetite change	1			stiff	1	neck	3
difficulty sleeping	3	**Lungs:**		swelling	1		
light-headed	1	shortness of breath				**Neuropsychiatric:**	
		- on exertion	1	**Muscles:**		headache (mild/	
Skin:		ankle swelling	2	tight/stiff	3	moderate)	3
itching	1	calf pain on		ache-sore-pain		depression/apathy	1
rashes	1	sore tender legs	1	- neck	3	anxiety/irritable	1
dry/rough skin	3	high blood pressure	2	- shoulder	3	"brain fog"/difficulty	
nail/hair problem	2			- upper back	2	concentrating	1
		Mouth:		- low back	2		
Eyes:		sores/fissures	2	weakness	1	**Gastrointestinal:**	
vision	3	tongue problem	1			nausea	1
				Lymph nodes:		heartburn or	
Ears:		**Nose/Throat:**		swollen	1	stomach pain	1
itching	1	stuffed/runny nose	1	sensitive	1	cramps or aches	1
sensitive to sounds	1	postnasal drip	1				
		sore throat	1				

15.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	1.90	Fatigue:	5.00
Days not feeling good:	2.86	Not rested:	9.00
Work missed:	0.00	Stiffness:	6.00
Inability to perform job tasks:	4.00	Anxiety:	3.00
Pain:	8.00	Depression:	1.00
Total FIQ score:	40.76		

15.4. ELISA
Cortisol level: 10.0 ng/ml

15.5. R-R interval recordings

15.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.75	0.78	0.76
RR standard deviation (s)	0.01	0.02	0.01
Mean HR (1/min)	79.82	76.87	78.85
HR standard deviation (1/min)	0.92	2.08	1.65
Frequency domain results			
LF power (ms^2)	9.96	160.16	22.52
LF power n.u.	50.62	86.67	60.98
HF power (ms^2)	9.72	24.63	14.41
HF power n.u.	49.38	13.33	39.02
LF/HF ratio	1.03	6.50	1.56
Total power (ms^2)	22.42	208.38	47.44

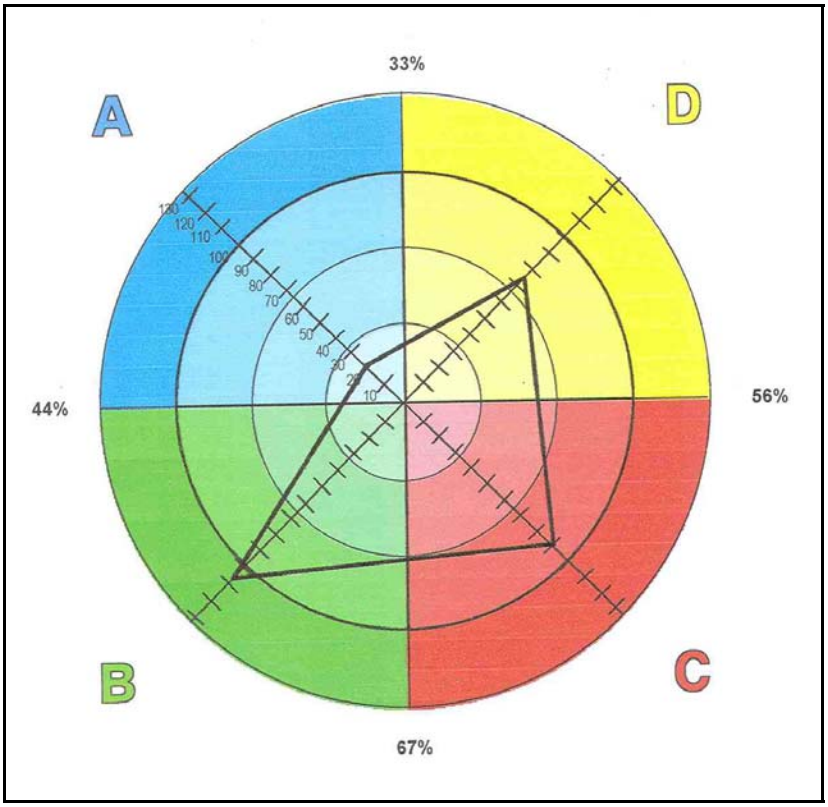
15.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.81	0.79
RR standard deviation (s)	0.01	0.01
Mean HR (1/min)	73.94	76.25
HR standard deviation (1/min)	1.53	1.66
Frequency domain results		
LF power (ms^2)	41.13	26.95
LF power n.u.	73.32	74.29
HF power (ms^2)	14.97	9.33
HF power n.u.	26.68	25.71
LF/HF ratio	2.75	2.89
Total power (ms^2)	64.76	41.37

15.6. Herrmann Brain Dominance Instrument

*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*

Profile score: **A** 21, **B** 107, **C** 90, **D** 75.
Adjective pairs: **A** 0, **B** 8, **C** 9, **D** 7.
Preference code: 3-1-1-1



15.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.83
Avoidance score: 1.72
Attachment class: Secure

Patient 16

16.1. Patient health questionnaire

16.1.1. Personal information

Marital status: Married
Highest academic qualification: Degree
Work status: Not employed
Lifestyle: Occasionally uses alcohol
Live with someone who can take care
Disability compensation: Partial

16.1.2. Anthropometrical data

Gender: Female
Mass: 80 kg
Body mass index: 32.87
Age: 52 yrs
Height: 1.56 m

16.1.3 Medical background

Allergies: voltaren
Current illnesses (apart from FM): problems after back operation
Illnesses of the past: allergies (age 23), anemia (age 26), thyroid problem (age 44), bleeding disorder (age 28), high cholesterol (age 49), migraine headaches (age 7), vaginitis (yeast)(age 21).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age (yrs)
Hysterectomy	37 yrs	Parents divorce – grandparents brought her up	2 yrs
Intestine obstruction operation	40 yrs	Molestation by grandfather	4 yrs
Hospitalised with severe pneumonia	40 yrs	Because of accusations against grandfather, parents rejected her	whole life
Removal of gall bladder	42 yrs	Meets biological father, very traumatic. Relationship with him	
Kidney lithnic	46 yrs	stressful	44 yrs
Removal of ovaries	46 yrs	Death of eldest	42 yrs
Back operation	51 yrs		
Illnesses:			
Hepatitis	7 yrs		
Kidney/ bladder disease	46,47		
Pneumonia	42 yrs		
Stomach ulcer	28 yrs		
Endometriosis	26 yrs		
Cyst of ovaries	46 yrs		
Tumor	47 yrs		

Onset of FM: After an operation and a period of overexertion and major stress (burnout)
Number of years suffering from FM: 18 yrs
FM progress: Improving
Description of pain: Continuous burning pain. Feels as if whole body is bruised
Fulfillment of Fukuda CFS diagnostic criteria: Yes

Factors increasing symptoms:
Stress
Exercise
Alcohol
Humidity
Season: change between seasons
Cold
Food: sugar
Sleep

16.1.4. Treatment program

Exercise program
Physiotherapy
Non-allopathic treatment
Pharmacological medication

Name of medication	Dose	Frequency
Lorrien	10 mg	1 per day
Demetrin	10 mg	2 per day
Trepilene	25 mg	3 per day
Eltroxin	10 mg	1 per day
Celebrex	20 mg	1 per day

16.2. Review of current symptoms – questionnaire

(1 – mild, 2 – moderate, 3 – severe)

Constitutional:		**Lungs:**		**Joints:**		**Ears:**	
fatigue	2	shortness of breath		ache/pain	2	ringing in ears	2
weight change	1	- at rest	2	stiff	3	sensitive to sounds	3
fever/chills/sweats	2	- on exertion	3	swelling	1	dizziness/vertigo	2
appetite change	2	can't get full breath	3				
abnormal thirst	3	hyperventilation	3	**Muscles:**		**Neuropsychiatric:**	
difficulty sleeping	1	phlegm/mucus/		tight/stiff	3	headache (mild/	
light-headed	2	bronchitis	1	ache-sore-pain		moderate)	3
		chest pain on		- neck	2	headache (severe)	2
Gastrointestinal:		exertion	2	- shoulder	3	depression/apathy	1
nausea	1	other chest pain or		- upper back	3	anxiety/irritable	2
blenching, bloating,		distress	1	- low back	3	hyperactive	1
or passing gas	2	palpitations/rapid,		weakness	2	learning disability	2
heartburn or		slow or irregular				"brain fog"/difficulty	
stomach pain	3	heart rate/rhythm	3	**Lymph nodes:**		concentrating	2
constipation	1	ankle swelling	1	sensitive	1	mood swings	1
cramps or aches	1	calf pain on				numbness, tingling	2
		exercise	2	**Nose/Throat:**			
Skin:		sore tender legs	3	postnasal drip	1	**Eyes:**	
itching	1			sore throat	1	vision	2
flushing	2	**Thyroid:**		trouble swallowing	1	tearing	1
dry/rough skin	2	cold or heat				itching	1
		tolerance	2			feels heavy	3
		history of x-ray to				allergic shiners	1
		neck	2				

16.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	6.66	Fatigue:	3.00
Days not feeling good:	5.72	Not rested:	3.00
Work missed:	4.29	Stiffness:	8.00
Inability to perform job tasks:	8.00	Anxiety:	4.00
Pain:	6.00	Depression:	1.00
Total FIQ score:	49.67		

16.4. ELISA
Cortisol level: 12.0 ng/ml

16.5. R-R interval recordings

16.5.1. Heart rate variability data: physical stressor

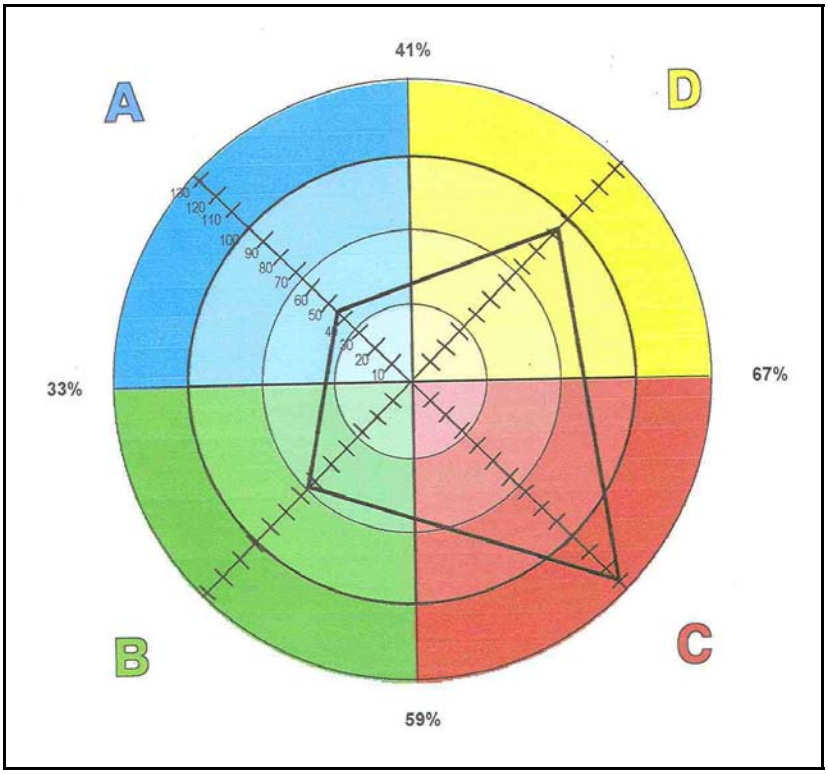
Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.70	0.67	0.67
RR standard deviation (s)	0.01	0.01	0.01
Mean HR (1/min)	85.65	89.87	90.19
HR standard deviation (1/min)	1.90	1.91	1.73
Frequency domain results			
LF power (ms^2)	37.72	38.48	8.32
LF power n.u.	61.42	70.20	28.29
HF power (ms^2)	23.70	16.34	21.10
HF power n.u.	38.58	29.80	71.71
LF/HF ratio	1.59	2.36	0.39
Total power (ms^2)	64.70	58.24	30.35

16.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.59	0.59
RR standard deviation (s)	0.01	0.01
Mean HR (1/min)	102.07	102.48
HR standard deviation (1/min)	2.33	1.80
Frequency domain results		
LF power (ms^2)	14.73	20.86
LF power n.u.	70.57	77.64
HF power (ms^2)	6.14	6.01
HF power n.u.	29.43	22.36
LF/HF ratio	2.40	3.47
Total power (ms^2)	35.50	29.57

16.6. Herrmann Brain Dominance Instrument
*(**A** cerebral left quadrant; **B** limbic left quadrant; **C** limbic right quadrant; **D** cerebral left quadrant)*

Profile score: **A** 44, **B** 65, **C** 129, **D** 93.
Adjective pairs: **A** 5, **B** 3, **C** 12, **D** 4.
Preference code: 2-2-1-1



16.7. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 2.50
Avoidance score: 1.67
Attachment class: Secure

II. Control group

Control 1

1.1. Control health questionnaire

1.1.1. Personal information

Marital status: Married
Highest academic qualification: Grade 12
Work status: Employed (half day)
Lifestyle: Exercise 45 minutes, 5 times a week

1.1.2. Anthropometrical data

Gender: Female
Mass: 79 kg
Body mass index: 27.34

Age: 51 yrs
Height: 1.7 m

1.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Ankle operation	16		

1.1.4. Medication

Name of medication	Dose	Frequency
Activelle	1 mg	1 per day

1.2. Review of current symptoms – questionnaire

No symptoms

1.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.00	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	0.00		

1.4. ELISA

Cortisol level: 6 ng/ml

1.5. R-R interval recordings

1.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.91	0.81	0.83
RR standard deviation (s)	0.03	0.04	0.02
Mean HR (1/min)	66.30	74.19	72.60
HR standard deviation (1/min)	3.04	4.74	2.44
Frequency domain results			
LF power (ms^2)	279.14	394.29	126.09
LF power n.u.	68.20	83.79	61.28
HF power (ms^2)	130.14	76.28	79.67
HF power n.u.	31.80	16.21	38.72
LF/HF ratio	2.14	5.17	1.58
Total power (ms^2)	500.97	542.96	222.64

1.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.81	0.82
RR standard deviation (s)	0.02	0.02
Mean HR (1/min)	73.83	73.45
HR standard deviation (1/min)	2.86	2.34
Frequency domain results		
LF power (ms^2)	113.41	110.30
LF power n.u.	71.73	63.24
HF power (ms^2)	44.69	64.12
HF power n.u.	28.27	36.76
LF/HF ratio	2.54	1.72
Total power (ms^2)	193.50	200.27

1.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.50
Avoidance score: 2.28
Attachment class: Secure

Control 2

2.1. Control health questionnaire

2.1.1. Personal information

Marital status: Married
Highest academic qualification: Diploma
Work status: Employed
Lifestyle: Occasionally uses alcohol

2.1.2. Anthropometrical data

Gender: Female
Age: 44 yrs
Mass: 56 kg
Height: 1.68 m
Body mass index: 19.84

2.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age
Tonsillectomy	4 yrs
Illnesses:	
Anemia	40 yrs

2.1.4. Medication
None

2.2. Review of current symptoms – questionnaire
No symptoms

2.3. Fibromyalgia Impact Questionnaire
Total FIQ score: 0.00

2.4. ELISA
Cortisol level: 2.5 ng/ml

2.5. R-R interval recordings

2.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.77	1.00	0.76
RR standard deviation (s)	0.02	0.03	0.03
Mean HR (1/min)	78.35	60.39	78.75
HR standard deviation (1/min)	1.93	2.93	3.68
Frequency domain results			
LF power (ms^2)	56.22	187.44	336.04
LF power n.u.	48.44	53.77	55.13
HF power (ms^2)	59.84	161.13	273.56
HF power n.u.	51.56	46.23	44.87
LF/HF ratio	0.94	1.16	1.23
Total power (ms^2)	123.43	376.73	651.22

2.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.81	0.83
RR standard deviation (s)	0.06	0.03
Mean HR (1/min)	74.83	72.33
HR standard deviation (1/min)	6.57	2.88
Frequency domain results		
LF power (ms^2)	973.37	173.94
LF power n.u.	89.53	56.03
HF power (ms^2)	113.78	136.52
HF power n.u.	10.47	43.97
LF/HF ratio	8.56	1.27
Total power (ms^2)	1404.17	316.90

2.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.89
Avoidance score: 3.78
Attachment class: Secure

Control 3

3.1. Control health questionnaire

3.1.1. Personal information

Marital status: Married
Highest academic qualification: Diploma
Work status: Employed
Lifestyle: Exercise 30 minutes, 3 times a week

3.1.2. Anthropometrical data

Gender: Female
Age: 55 yrs
Mass: 65 kg
Height: 1.57 m
Body mass index: 26.37

3.1.3 Medical background

Allergies: None
Current illnesses: Epilepsy
Ongoing illnesses from the past: arthritis

Operations and hospitalisations:	Age	Illnesses:	Age
Hysterectomy	43 yrs	Tonsillitis	10 yrs

3.1.4. Medication

Name of medication	Dose	Frequency
Estraderm TTS	50 mg	2 times a week
Lamictin	-	1 per day

3.2. Review of current symptoms – questionnaire
Calf pain on exercise
Mild headaches

3.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	6.05	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	6.05		

3.4. ELISA
Cortisol level: 4 ng/ml

3.5. R-R interval recordings
(recording discarded because ectopic beats exceeds 20% limitation)

3.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.00
Avoidance score: 1.33
Attachment class: Secure

Control 4

4.1. Control health questionnaire

4.1.1. Personal information

Marital status: Single
Highest academic qualification: Honours degree
Work status: Employed
Lifestyle: Occasionally uses alcohol
Exercise 30 minutes, 2 times a week

4.1.2. Anthropometrical data

Gender: Female
Age: 21 yrs
Mass: 62 kg
Height: 1.59 m
Body mass index: 24.52

4.1.3 Medical background

Allergies: Hayfever
Current illnesses: None
Ongoing illnesses from the past: Allergies

Operations and hospitalisations:	Age
Tonsillectomy	7 yrs
Operation on foot	14 yrs

4.1.4. Medication
None

4.2. Review of current symptoms – questionnaire

Fatigue	Weight change
Acne	Postnasal drip
Sore neck and low back muscles	Cough
Menstrual cramps	

4.3. Fibromyalgia Impact Questionnaire
FIQ total score

4.4. ELISA
Cortisol level: 7.0 ng/ml

4.5. R-R interval recordings

4.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.84	0.83	0.84
RR standard deviation (s)	0.06	0.05	0.04
Mean HR (1/min)	72.19	72.46	71.60
HR standard deviation (1/min)	4.81	5.45	4.05
Frequency domain results			
LF power (ms^2)	167.89	1384.39	442.72
LF power n.u.	27.79	77.06	48.43
HF power (ms^2)	436.24	412.07	471.46
HF power n.u.	72.21	22.94	51.57
LF/HF ratio	0.38	3.36	0.94
Total power (ms^2)	616.64	1875.16	947.63

4.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.92	0.91
RR standard deviation (s)	0.06	0.06
Mean HR (1/min)	66.27	66.23
HR standard deviation (1/min)	6.09	5.01
Frequency domain results		
LF power (ms^2)	1532.98	793.56
LF power n.u.	76.70	67.19
HF power (ms^2)	465.66	387.55
HF power n.u.	23.30	32.81
LF/HF ratio	3.29	2.05
Total power (ms^2)	2348.52	1325.11

4.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 2.61
Avoidance score: 3.33
Attachment class: Secure

Control 5

5.1. Control health questionnaire

5.1.1. Personal information

Marital status: Married
Highest academic qualification: Senior certificate
Work status: Employed
Lifestyle: Exercise 120 minutes, 1 time a week

5.1.2. Anthropometrical data

Gender: Male
Age: 27 yrs
Mass: 90 kg
Height: 1.79 m
Body mass index: 28.08

5.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None
Operations and hospitalisations: Appendicectomy at 25 yrs of age

5.1.4. Medication
None

5.2. Review of current symptoms – questionnaire
Hearing problem
Runny nose
Bloating, passing gas

5.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.00	Fatigue:	2.00
Days not feeling good:	0.00	Not rested:	2.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	4.00		

5.4. ELISA

Cortisol level: 5.5 ng/ml

5.5. R-R interval recordings

5.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.09	0.94	0.93
RR standard deviation (s)	0.07	0.08	0.06
Mean HR (1/min)	55.72	64.75	65.16
HR standard deviation (1/min)	4.64	5.82	4.87
Frequency domain results			
LF power (ms^2)	1121.80	1222.43	759.53
LF power n.u.	48.45	52.72	53.85
HF power (ms^2)	1193.75	1096.39	650.82
HF power n.u.	51.55	47.28	46.15
LF/HF ratio	0.94	1.12	1.17
Total power (ms^2)	2466.57	2494.89	1483.73

5.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.88	0.83
RR standard deviation (s)	0.05	0.04
Mean HR (1/min)	68.33	72.49
HR standard deviation (1/min)	4.55	4.49
Frequency domain results		
LF power (ms^2)	363.05	397.17
LF power n.u.	57.82	52.26
HF power (ms^2)	264.82	362.81
HF power n.u.	42.18	47.74
LF/HF ratio	1.37	1.09
Total power (ms^2)	661.68	784.93

5.6. Experiences in Close Relationships questionnaire

Attachment results

Anxiety score: 1.83

Avoidance score: 1.17

Attachment class: Secure

Control 6

6.1. Control health questionnaire

6.1.1. Personal information

Marital status: Married

Highest academic qualification: Diploma

Work status: Employed

Lifestyle: Occasionally uses alcohol
Exercise 30 minutes, 6 times a week

6.1.2. Anthropometrical data

Gender: Female
Age: 55 yrs
Mass: 70 kg
Height: 1.63 m
Body mass index: 26.35

6.1.3 Medical background

Allergies: Sulpher
Ongoing illnesses from the past (age at which illness started in brackets): hypothyroidism (age 52).

Operations and hospitalisations:	Age	Traumatic psychological events:	Age
Caesarean section	29,31	Miscarriage	33 yrs
Hysterectomy	54 yrs		
Illnesses:			
Asthma	6 yrs		
Hepatitis	8 yrs		
Pneumonia	32 yrs		
Endometriosis	53,54		
Non-cancerous breast disease	53,55		

6.1.4. Medication

Name of medication	Dose	Frequency
Eltroxin	0.1 mg	1 per day
Estrofem	1 mg	1 per day

6.2. Review of current symptoms – questionnaire
Problems with vision
Sore neck, back and low back muscles
Mild headaches

6.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.00	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	0.00		

6.4. ELISA

Cortisol level: 3.0 ng/ml

6.5. R-R interval recordings

6.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.03	0.97	0.96
RR standard deviation (s)	0.04	0.04	0.03
Mean HR (1/min)	58.30	62.33	62.35
HR standard deviation (1/min)	2.71	3.99	2.43
Frequency domain results			
LF power (ms^2)	126.13	315.01	295.56
LF power n.u.	26.31	45.07	50.44
HF power (ms^2)	353.22	383.94	290.38
HF power n.u.	73.69	54.93	49.56
Total power (ms^2)	529.03	880.48	635.88

6.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.87	0.89
RR standard deviation (s)	0.04	0.04
Mean HR (1/min)	68.88	67.83
HR standard deviation (1/min)	3.95	3.65
Frequency domain results		
LF power (ms^2)	215.39	359.40
LF power n.u.	38.30	58.41
HF power (ms^2)	347.02	255.96
HF power n.u.	61.70	41.59
LF/HF ratio	0.62	1.40
Total power (ms^2)	619.96	720.23

6.6. Experiences in Close Relationships questionnaire

Attachment results

Anxiety score: 2.00

Avoidance score: 2.33

Attachment class: Secure

Control 7

7.1. Control health questionnaire

7.1.1. Personal information

Marital status: Married

Highest academic qualification: Grade 12

Work status: Employed

Lifestyle: Smoked 1 pack of cigarettes a day for past 25 yrs
Occasionally uses alcohol
Exercise 20 minutes, 2 times a week

7.1.2. Anthropometrical data

Gender: Female
Age: 55 yrs
Mass: 56 kg
Height: 1.56 m
Body mass index: 23.01

7.1.3 Medical background

Allergies: None
Current illnesses: Barlow's syndrome
Ongoing illnesses from the past (age at which illness started in brackets): migraine headaches (age 35)

Operations and hospitalisations:	Age
Hysterectomy Heamaroidectomy	47 yrs 53 yrs
Illnesses:	
Anemia	1 yr

7.1.4. Medication
None

7.2. Review of current symptoms – questionnaire
Light-headedness

7.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	3.03	Fatigue:	7.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	10.03		

7.4. ELISA
Cortisol level: 7.5 ng/ml

7.5. R-R interval recordings

HRV recordings were discarded because of extra systole (Barlow's syndrome)

7.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 2.00
Avoidance score: 1.89
Attachment class: Secure

Control 8

8.1. Control health questionnaire

8.1.1. Personal information

Marital status: Married
Highest academic qualification: Doctoral degree
Work status: Employed
Lifestyle: Occasionally uses alcohol

8.1.2. Anthropometrical data

Gender: Female
Age: 36 yrs
Mass: 56 kg
Height: 1.64 m
Body mass index: 20.82

8.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age
Tonsillectomy	27 yrs
Illnesses:	
Bronchitis	33 yrs

8.1.4. Medication
None

8.2. Review of current symptoms – questionnaire
No symptoms

8.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	3.63	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	3.63		

8.4. ELISA

Cortisol level: 7.5 ng/ml

8.5. R-R interval recordings

8.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.69	0.64	0.64
RR standard deviation (s)	0.01	0.01	0.01
Mean HR (1/min)	87.22	94.00	94.11
HR standard deviation (1/min)	1.62	2.53	2.21
Frequency domain results			
LF power (ms^2)	23.76	56.98	33.35
LF power n.u.	47.45	73.81	75.00
HF power (ms^2)	26.32	20.22	11.12
HF power n.u.	52.55	26.19	25.00
LF/HF ratio	0.90	2.82	3.00
Total power (ms^2)	52.51	88.85	47.32

8.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.58	0.60
RR standard deviation (s)	0.02	0.02
Mean HR (1/min)	104.10	100.72
HR standard deviation (1/min)	3.67	3.36
Frequency domain results		
LF power (ms^2)	97.67	53.82
LF power n.u.	80.25	77.84
HF power (ms^2)	24.04	15.32
HF power n.u.	19.75	22.16
LF/HF ratio	4.06	3.51
Total power (ms^2)	145.61	71.95

8.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.56
Avoidance score: 1.33
Attachment class: Secure

Control 9

9.1. Control health questionnaire

9.1.1. Personal information

Marital status: Married
Highest academic qualification: Degree
Work status: Employed
Lifestyle: Exercise 45 minutes, 5 times a week

9.1.2. Anthropometrical data

Gender: Male
Age: 31 yrs
Mass: 86 kg
Height: 1.72 m
Body mass index: 29.07

9.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None
Operations and hospitalisations: None

9.1.4 Medication
None

9.2. Review of current symptoms – questionnaire

Hearing problem
Tight muscles
Low back pain

9.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.00	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	0.00		

9.4. ELISA

Cortisol level: 5.0 ng/ml

9.5. R-R interval recordings

9.5.1. Heart rate variability data: physical stressor

Variable	Basal	ECR-R stressor	Standing
Statistical measures			
Mean RR (s)	0.58	0.60	1.20
RR standard deviation (s)	0.02	0.02	0.06
Mean HR (1/min)	104.10	100.72	50.71
HR standard deviation (1/min)	3.67	3.36	5.68
Frequency domain results			
LF power (ms^2)	97.67	53.82	812.58
LF power n.u.	80.25	77.84	77.09
HF power (ms^2)	24.04	15.32	241.52
HF power n.u.	19.75	22.16	22.91
LF/HF ratio	4.06	3.51	3.36
Total power (ms^2)	145.61	71.95	1201.33

9.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	1.14	1.13
RR standard deviation (s)	0.05	0.04
Mean HR (1/min)	52.75	53.43
HR standard deviation (1/min)	3.05	3.06
Frequency domain results		
LF power (ms^2)	1225.95	299.63
LF power n.u.	84.67	64.10
HF power (ms^2)	221.90	167.78
HF power n.u.	15.33	35.90
LF/HF ratio	5.52	1.79
Total power (ms^2)	1516.37	578.21

9.6. Experiences in Close Relationships questionnaire

Attachment results

Anxiety score: 1.83

Avoidance score: 2.22

Attachment class: Secure

Control 10

10.1. Control health questionnaire

10.1.1. Personal information

Marital status: Married

Highest academic qualification: Grade 9

Work status: Not employed

Lifestyle: Occasionally uses alcohol

10.1.2. Anthropometrical data

Gender: Female
Age: 60 yrs
Mass: 68 kg
Height: 1.5 m
Body mass index: 30.22

10.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age
Hysterectomy	33 yrs

10.1.4. Medication

Name of medication	Dose	Frequency
Eltroxin	0.05 mg	2 per day

10.2. Review of current symptoms – questionnaire
No symptoms

10.3. Fibromyalgia Impact Questionnaire
FIQ total score: 0.00

10.4. ELISA
Cortisol level: 8.5 ng/ml

10.5. R-R interval recordings

10.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.02	0.98	0.99
RR standard deviation (s)	0.03	0.03	0.02
Mean HR (1/min)	58.96	61.76	60.83
HR standard deviation (1/min)	2.11	4.37	1.88
Frequency domain results			
LF power (ms^2)	116.78	431.72	55.40
LF power n.u.	36.42	83.80	42.49
HF power (ms^2)	203.84	83.45	74.98
HF power n.u.	63.58	16.20	57.51
LF/HF ratio	0.57	5.17	0.74
Total power (ms^2)	339.86	695.23	168.19

10.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.98	0.93
RR standard deviation (s)	0.03	0.03
Mean HR (1/min)	61.06	64.56
HR standard deviation (1/min)	2.25	2.39
Frequency domain results		
LF power (ms^2)	71.61	101.66
LF power n.u.	39.51	69.02
HF power (ms^2)	109.65	45.63
HF power n.u.	60.49	30.98
LF/HF ratio	0.65	2.23
Total power (ms^2)	209.73	168.35

10.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.00
Avoidance score: 1.00
Attachment class: Secure

Control 11

11.1. Control health questionnaire

11.1.1. Personal information

Marital status: Married
Highest academic qualification: Diploma
Work status: Not employed
Lifestyle: Exercise 60 minutes, 6 times a week

11.1.2. Anthropometrical data

Gender: Female
Age: 39 yrs
Mass: 65 kg
Height: 1.71 m
Body mass index: 22.23

11.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: endometriosis (15 yrs)

Operations and hospitalisations:	Age
Remove lump on left lob of thyroid	34 yrs
Hysterectomy	31 yrs

11.1.4. Medication

Name of medication	Dose	Frequency
Eltroxin	0.05 mg	2 per day

11.2. Review of current symptoms – questionnaire

Low back pain

11.3. Fibromyalgia Impact Questionnaire

FIQ total score: 0.00

11.4. ELISA

Cortisol level: 9.0 ng/ml

11.5. R-R interval recordings

11.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.22	1.16	1.11
RR standard deviation (s)	0.06	0.06	0.07
Mean HR (1/min)	49.53	51.80	54.18
HR standard deviation (1/min)	2.53	3.30	4.03
Frequency domain results			
LF power (ms^2)	301.96	1002.74	328.92
LF power n.u.	20.52	45.81	18.52
HF power (ms^2)	1169.68	1186.26	1447.41
HF power n.u.	79.48	54.19	81.48
LF/HF ratio	0.26	0.85	0.23
Total power (ms^2)	1487.19	2270.48	1801.72

11.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	1.08	1.08
RR standard deviation (s)	0.06	0.07
Mean HR (1/min)	55.69	55.88
HR standard deviation (1/min)	3.43	3.95
Frequency domain results		
LF power (ms^2)	710.08	894.29
LF power n.u.	59.55	76.27
HF power (ms^2)	482.24	278.23
HF power n.u.	40.45	23.73
LF/HF ratio	1.47	3.21
Total power (ms^2)	1328.55	1378.03

11.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.00
Avoidance score: 1.17
Attachment class: Secure

Control 12

12.1. Control health questionnaire

12.1.1. Personal information

Marital status: Married
Highest academic qualification: Grade 11
Work status: Never employed
Lifestyle: Exercise 30 minutes, 3 times a week

12.1.2. Anthropometrical data

Gender: Female
Age: 40 yrs
Mass: 57 kg
Height: 1.65 m
Body mass index: 20.93

12.1.3 Medical background
Allergies: Wheat, sugar, preservatives
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age
Accident	36 yrs

12.1.4. Medication

Name of medication	Dose	Frequency
Ativan Trepiline	1 mg 10 mg	1 per day 1 per day

12.2. Review of current symptoms – questionnaire
Fatigue
Difficulty sleeping
Tongue problem
Heart palpitations
Tight muscles causing neck back aches
Menstrual cramps
Mild headaches

12.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	4.33	Fatigue:	2.00
Days not feeling good:	4.29	Not rested:	2.00
Work missed:	2.86	Stiffness:	3.00
Inability to perform job tasks:	6.00	Anxiety:	0.00
Pain:	4.00	Depression:	0.00
Total FIQ score:	28.48		

12.4. ELISA
Cortisol level: 5.5 ng/ml

12.5. R-R interval recordings
(recording discarded because control uses trepiline)

12.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.00
Avoidance score: 1.00
Attachment class: Secure

Control 13

13.1. Control health questionnaire

13.1.1. Personal information

Marital status: Divorced
Highest academic qualification: MSc degree
Work status: Employed
Lifestyle: Exercise 60 minutes, 2 times a week

13.1.2. Anthropometrical data

Gender: Female
Age: 49 yrs
Mass: 62 kg
Height: 1.6 m
Body mass index: 24.22

13.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age
Bunions removed	38 yrs
Hysterectomy	48 yrs

13.1.4. Medication
None

13.2. Review of current symptoms – questionnaire

Fatigue
Weight change
Sweats
Difficulty sleeping
Abnormal thirst
Light-headed
Difficulty concentrating
Vision problem
Tearing/ itching eyes
Shortness of breath on exertion
Tight muscles
Mild headaches
Irritable

13.3. Fibromyalgia Impact Questionnaire
(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	2.72	Fatigue:	1.00
Days not feeling good:	2.86	Not rested:	1.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	1.00	Anxiety:	1.00
Pain:	0.00	Depression:	2.00
Total FIQ score:	11.58		

13.4. ELISA
Cortisol level: 2.0 ng/ml

13.5. R-R interval recordings

13.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.81	0.77	0.76
RR standard deviation (s)	0.02	0.02	0.02
Mean HR (1/min)	74.41	78.12	79.53
HR standard deviation (1/min)	1.84	2.84	1.90
Frequency domain results			
LF power (ms^2)	76.23	122.58	86.27
LF power n.u.	62.64	72.12	69.05
HF power (ms^2)	45.46	47.39	38.66
HF power n.u.	37.36	27.88	30.95
LF/HF ratio	1.68	2.59	2.23
Total power (ms^2)	125.62	196.63	133.75

13.5.2. Heart rate variability data: psychological stressor
(subject preferred not to fill out ECR-R)

13.6. Experiences in Close Relationships questionnaire
Subject preferred not to fill out ECR-R.

Control 14

14.1. Control health questionnaire

14.1.1. Personal information

Marital status: Married
Highest academic qualification: Diploma
Work status: Employed
Lifestyle: Occasionally uses alcohol
Exercise 30 minutes, 5 times a week

14.1.2. Anthropometrical data

Gender: Female
Age: 39 yrs
Mass: 65 kg
Height: 1.63 m
Body mass index: 24.46

14.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: tumor (age 43), endometriosis (age 30)

Operations and hospitalisations:	Age
Appendicectomy	12 yrs
Hysterectomy	38 yrs
Removed melanoma	43 yrs

14.1.4. Medication
None

14.2. Review of current symptoms – questionnaire

Light-headed	Can't get full breath
Rashes	Irregular heart rhythm
Itching ears	Ackle swelling
Hearing problem	Sore neck, shoulders and low
Ringing in ears	back
Dizziness	Numbness and tingling

14.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	0.00	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	1.00
Pain:	6.00	Depression:	0.00
Total FIQ score:	7.00		

14.4. ELISA

Cortisol level: 8.0 ng/ml

14.5. R-R interval recordings

14.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	0.78	0.81	0.77
RR standard deviation (s)	0.03	0.03	0.03
Mean HR (1/min)	77.00	74.77	78.33
HR standard deviation (1/min)	2.78	3.69	2.96
Frequency domain results			
LF power (ms^2)	116.25	189.47	88.54
LF power n.u.	33.20	40.49	33.16
HF power (ms^2)	233.95	278.53	178.46
HF power n.u.	66.80	59.51	66.84
LF/HF ratio	0.50	0.68	0.50
Total power (ms^2)	359.30	493.62	286.39

14.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.75	0.68
RR standard deviation (s)	0.02	0.02
Mean HR (1/min)	80.44	88.61
HR standard deviation (1/min)	2.27	2.88
Frequency domain results		
LF power (ms^2)	25.78	19.58
LF power n.u.	19.93	35.27
HF power (ms^2)	103.58	35.93
HF power n.u.	80.07	64.73
LF/HF ratio	0.25	0.55
Total power (ms^2)	145.28	57.06

14.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 2.06
Avoidance score: 2.78
Attachment class: Secure

Control 15

15.1. Control health questionnaire

15.1.1. Personal information

Marital status: Married
Highest academic qualification: Doctoral degree
Work status: Employed
Lifestyle: Uses alcohol daily
Exercise 60 minutes, 4 times a week

15.1.2. Anthropometrical data

Gender: Female
Age: 52 yrs
Mass: 64 kg
Height: 1.69 m
Body mass index: 22.41

15.1.3 Medical background

Allergies: None
Current illnesses: None
Illnesses of the past: None

Operations and hospitalisations:	Age
Chest operation	20 yrs
Caesarian section	27 yrs
Caesarian section	30 yrs

15.1.4. Medication

Name of medication	Dose	Frequency
Eltroxin	0.1 mg	1 per day

15.2. Review of current symptoms – questionnaire
Low back pain

15.3. Fibromyalgia Impact Questionnaire

(each scale out of 10)

Scale	Score	Scale	Score
Physical impairment:	1.00	Fatigue:	0.00
Days not feeling good:	0.00	Not rested:	0.00
Work missed:	0.00	Stiffness:	0.00
Inability to perform job tasks:	0.00	Anxiety:	0.00
Pain:	0.00	Depression:	0.00
Total FIQ score:	3.33		

15.4. ELISA

Cortisol level: 3.0 ng/ml

15.5. R-R interval recordings

15.5.1. Heart rate variability data: physical stressor

Variable	Supine	Sitting	Standing
Statistical measures			
Mean RR (s)	1.082866	0.996525	0.829136
RR standard deviation (s)	0.030387	0.034701	0.019576
Mean HR (1/min)	55.5161	60.3894	72.4952
HR standard deviation (1/min)	2.114	2.9291	2.1453
Frequency domain results			
LF power (ms^2)	360.2111	187.4427	120.6435
LF power n.u.	76.7845	53.7746	87.77
HF power (ms^2)	108.9087	161.1283	16.8179
HF power n.u.	23.2155	46.2254	12.2346
LF/HF ratio	3.3075	1.1633	7.1735
Total power (ms^2)	514.49	376.73	162.19

15.5.2. Heart rate variability data: psychological stressor

Variable	Basal	ECR-R stressor
Statistical measures		
Mean RR (s)	0.826499	0.847435
RR standard deviation (s)	0.024977	0.025441
Mean HR (1/min)	72.8102	70.8882
HR standard deviation (1/min)	2.9295	2.3346
Frequency domain results		
LF power (ms^2)	233.3989	313.7646
LF power n.u.	80.0804	73.3187
HF power (ms^2)	58.0569	114.1818
HF power n.u.	19.9196	26.6813
LF/HF ratio	4.0202	2.7479
Total power (ms^2)	320.04	442.18

15.6. Experiences in Close Relationships questionnaire

Attachment results
Anxiety score: 1.39
Avoidance score: 1.72
Attachment class: Secure

CHAPTER 5
DISCUSSION

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A. DISCUSSION OF RESULTS

The experimental group for this study consisted of fibromyalgia patients who were on various pharmaceutical drugs and/or alternative treatments such as physiotherapy, non-allopathic treatments and exercise programs. Pharmaceutical drugs used by fibromyalgia patients in general often comprise a wide range of anti-depressive and analgesic medicines (refer to Chapter 4 – Appendix for a medication list for each of the participating patients in the present study). Because of the nature of these patients' therapies, great difficulties arose in the selection of patients and in attaining ethical clearance. Patients not receiving treatment were in the minority, making it impossible to put together a sample of satisfactory size. The alternative, expecting patients to refrain from taking the prescribed medication for the purpose of the study, would have been unethical, as these patients have to cope with unbearable pain daily. Finally, ethical clearance was granted on the condition that no alterations would be made to the patients' current medical treatment program for the purpose of the study.

Although the fact that the patients were not drug free could be considered a confounding factor, the purpose of this study was not to investigate the origin or nature of the disease (in which case it would be necessary to examine the factors without the influence of medication), but rather to study the status quo of their psychoneurology, that is., the state in which they exist within the context of their disease.

1. Sociodemographic results

The study group consisted of 16 patients (diagnosed according to the ACR diagnostic criteria for fibromyalgia) and 15 age- and sex-matched controls. The reason for the smaller control group is that during analysis of the results, it became clear that one of the control subjects met some of the exclusion criteria set up in the protocol for the study. The mean age of the patients was 43.94 years (SD 10.46) and 43.20 years (SD 11.19) for the control group. The youngest participants in the two study groups were both 21 years of age, the oldest patient 63 years, and the oldest control 60 years. Dividing the experimental subjects into age-interval classes, 6.25% fell into the 20 – 29 year range, 25% were between the ages of 30 to 39 years, 37.5% in the 40 – 49 year age interval class, 25% in the 50 – 59 year class, and 6.25% between the ages of 60 and 69 years. The patient group consisted of 14

females and 2 males, and the control group had 13 females and 2 males. In addition to age and sex (as selection criteria for the inclusion of controls), body mass index (BMI) was calculated for prospective controls to see to it that the BMI of the patient and control group did not differ significantly. The mean BMI was 25.84 (SD 4.53) for the patients and 24.64 (SD 3.18) for controls. Statistical differences between the patient and control group for age, gender and BMI were assessed by the Mann-Whitney test (used for small sample sizes) and found to be statistically non-significant.

Despite the small sample size and the random selection, the mean age of this group of fibromyalgia patients was very similar to that described in other publications. In 1994, Yunus reviewed studies with regard to the demographic characteristics of fibromyalgia (5). He combined the demographic outcomes of the studies and presented the following results for a combined sample of 524 participants: the mean age for the joint group was 44 years, exactly the same as in the present study. Four other studies on fibromyalgia calculated the mean age of patients to be 46 years (SD 10.5, n = 19) (1), 41.8 years (SD 6.5, n = 17) (2), 47 years (SD 7, n = 22) (3), and 38.6 years (SD 10.5, n = 30) (4). Furthermore, Yunus reported the most common age at presentation to be between 40 and 50 years (5). According to the descriptive statistics calculated for the age interval classes (in this study), the majority of patients were also in the 40 – 49 year age interval class.

However, not all published studies reflect the above distribution. In October 1997, the Fibromyalgia Network released information derived from fibromyalgia surveys done on 6240 participants. The average age of the fibromyalgia sufferers in this study was 52.6 years (6). A more recent epidemiological study in the United States also confirmed the prevalence of fibromyalgia to increase with age, but added that 1% of the general female population between the ages of 18 to 29 years, and 7% of woman who are 70 to 79 years of age were diagnosed with fibromyalgia (7), suggesting that most fibromyalgia sufferers are much older than what was observed in the present study. These findings are comparable to results obtained from a study on the prevalence and characteristics of fibromyalgia in the general population (8). These authors concluded that the prevalence of fibromyalgia is skewed towards the elderly between the ages of 60 and 79 years. It seems that the present study offered similar results to the studies with comparable sample sizes, but as soon as the study group size increased, the average age of fibromyalgia sufferers increased as well. Fibromyalgia is, however, not confined to middle and older age, but has also been reported

among juveniles (5,7). The same was true for this study – although the study group did not comprise of any children, some of the participants reported onset of fibromyalgia symptoms as early as 14, 17 and 18 years of age (Chapter 4 - Appendix).

The female predominance among fibromyalgia sufferers, as reported by various authors (1,4,7), was also demonstrated in this study by the fact that only two males were available. According to the combined results by Yunus, 90% of fibromyalgia sufferers were female (5). The Fibromyalgia Network found 95% of the 6240 respondents in their study to be female (6). Moreover, studies exploring the difference in disease severity in female and male patients indicated that men with fibromyalgia had fewer symptoms, fewer symptom sites, and fewer tender points. Since this study group only had two male subjects, few conclusions could be made in this regard (9). One of the explanations offered for the phenomenon that most fibromyalgia sufferers are woman, involves sex differences in pain sensitivity. When the pain sensitivity of healthy woman and healthy men were compared in an experimental setting, woman had an increased sensitivity to pain, especially when mechanical pain was induced (10). In an attempt to identify the specific factors causing the higher pain sensitivity in woman, Sorensen *et al.* (1998) observed that muscle nociceptors show a higher sensitivity in woman (11). Therefore, it is possible that the tendency of (healthy) woman to be more responsive to pain may be the very factor that predisposes them to more pathological forms of mechanical hyperalgesia as observed in fibromyalgia.

A noteworthy difference was observed between patients and controls with regard to their marital status. 63% of patients and 86% of controls were married. Of the 37% single patients, 13% had never been married, 6% were divorced, 12% widowed, and another 6% separated. Only 14% of the controls were single, 7% had never been married and 7% were divorced. Noticing the difference between the number of married patients in comparison to married controls, it is tempting to assume that the reason for this difference is the strain put on the family and spouse living with someone suffering from fibromyalgia, which may cause the relationship to deteriorate. The functional disability and mood states associated with fibromyalgia causes physical, financial and emotional complications (especially when the patient is not able to work anymore and does not have either disability compensation or a medical scheme), aggravating the situation. The proportion of divorced and separated patients was double that of the controls, adding value to the speculation that marital problems in fibromyalgia originate, at least in part, from disability and negative mood

states. The lower incidence of married individuals seen in this study is supported by the results obtained by other studies. A study that granted similar results reported 68.8% of the study group being married and 8.4% being divorced (12). Yet another study reported only 56.7% married patients (13). However, one study found no significant difference in marital status between the patients and controls (86% of fibromyalgia patients were married) (3).

The highest qualification obtained by the patients was a postgraduate degree (obtained by three out of the 16 patients). However, most of them (seven patients) only had a high school education. Four had a diploma and two a degree. Four out of 15 controls had a postgraduate qualification, one had a degree, six a diploma, and another four only a high school education. These findings are comparable with a study reporting 39.6% of the patients in their study group only having a primary school education, 25% with a secondary school, and 6.3% with a high school qualification (12), indicating that most of these patients did not have a qualification on tertiary level either. Another study published results showing patients having a lower level of education than control subjects (3). The possibility does however exist that in the present study, selection bias of the control group could have contributed to the difference between the patients and controls.

As expected, the employment status of the patients and the controls differed remarkably. The employment status of the experimental subjects was as follow: Only 31% of the patients were employed in contrast to 73% of the control group. 20% of the control group was not employed at the time of the study and 7% reported not ever occupying a paid job. Of the 69% of the unemployed patients, 13% had never been employed, probably indicating that there is no relation between the disability caused by fibromyalgia and their employment status. However, the other 55% indicated that they were unable to work because of their fibromyalgia complaints. 19% of the employed patients were only employed part time. This proportion of patients also reported that they were unable to maintain a full day's work because of chronic fatigue and pain caused by fibromyalgia-associated functional disability. The outcome in this study with regards to the employment status of the patients was verified by other studies' findings (3,12,13).

According to a study that assessed clinical care utilisation in fibromyalgia, 25% of the recruited subjects received disability assistance or were retired early because of fibromyalgia (13). Because of statistics such as these, physicians are advised to practise

objectivity in diagnosing fibromyalgia and evaluating disability. They are warned against malingering – 'a conscious and voluntary fabrication of physical or psychological symptoms for personal gain' (14). In the present study, 19% of the patients received full disability compensation, 6% partial compensation and 75% no compensation at all. Since disability resources are limited in South Africa, it is unlikely that the patients in the present study exaggerated the degree of functional disability for financial gain.

Several studies exist on the sociodemographic features of fibromyalgia, and although there are many of similarities between those studies, as well as between those studies and the present one, there are also differences between results. The reason for the differences is mainly attributed to different methodologies such as vast differences in sample sizes and diverse study populations. An epidemiological study done by Neumann *et al.* (2003) demonstrated these differences by reviewing clinical features of fibromyalgia in different settings (7). These study groups ranged from patients in the general population to patients from clinics (rheumatology clinics and clinics treating associated conditions) as well as from hospitals and institutions. As expected, the demographic data varied from setting to setting. The sample in this study is representative of the fibromyalgia patients living in suburban areas in South Africa, treated by the same physician and attending the same clinic. Factors such as these could have an influence on the demographic data obtained in this study and could explain differences between this and other studies.

2. Diagnostic criteria and concomitant diseases

As already discussed in Chapter 1, a number of symptoms in fibromyalgia form part of conditions that are diagnostic entities themselves. A study investigating the overlapping features of 13 different syndromes marked by chronic multi-system illness (CMI), showed that fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome and non-ulcer dyspepsia often occur together (15). The same was observed in the present study's patient group. In this study only two of the patients did not fulfil the Fukuda diagnostic criteria for chronic fatigue syndrome in addition to their fibromyalgia diagnosis. Besides the presence of chronic fatigue syndrome features, the patients also presented with symptoms associated with irritable bowel syndrome (50.94% of patient group), premenstrual syndrome (18.75% of patient group) and thyroid problems (35.42% of patients). There was also a high prevalence of headaches (71.88%), anxiety (68.75%) and depression (87.50%) in the patient

group evaluated. According to literature (5), these three symptoms have reached 'disease status'.

The overlapping nature of these diseases brings the diagnostic criteria of fibromyalgia (and all the other disorders in the CMI spectrum) into question. According to Dommerholt & Issa, the tender point count used in the diagnosis of fibromyalgia (American College of Rheumatology, 1990) is not specific enough for distinguishing it from the other disorders (16). Nevertheless, despite the fact that these syndromes all have their own diagnostic criteria and unique features distinguishing them from the rest, the possibility that we are dealing with different aspects of the same disease is undeniable. Naturally, the gaps in the diagnostic criteria of fibromyalgia (assuming it is in fact a distinct diagnostic entity) will have an influence on the psychoneurological profile composed from the results of this study.

3. Course and nature of fibromyalgia complaints

In this study the mean duration of the patients' complaints was 16.56 years (SD 11.03). The mean duration, as reported by other studies, varied from 6.6 (SD 6.4) (1) and 8.0 years (SD 8) (3) to 12.2 years for the Fibromyalgia Network study group (6). Certainly the duration of fibromyalgia in a specific patient (and a patient group) will be dependent on the age at which the complaints started as well as the age of that individual (or the mean age of the patient study group) at the time of the study. The differences in the mean duration between the studies were therefore probably due to variances in these two variables.

In the present study, the duration of complaints for each patient was also expressed as a percentage of his or her lifespan. This way it was possible to compare patients of different ages with one another. One of the patients has been suffering from fibromyalgia-related complaints for most of her life (74.5% of lifetime). Usually, in cases like these, the complaints started before 20 years of age. The duration of complaints (in terms of percentage of lifetime) for the rest of the study group was more than 50% for three of the patients, around 30 to 49% for 43.75% of the group and less than 30% of their lifetime for the rest of the study group.

The onset of fibromyalgia complaints ranged from 14 to 42 years of age for the present study. In this study, 18.75% of the patients' symptoms started to appear from the age of 10

to 19 years. The majority of the patients' complaints started during their twenty's and thirty's, with 43.75% of the patients reporting onset in the 20 to 29 year age interval range and 31.25% during the 30 – 39 year range. Only one patient reported fibromyalgia onset after 40 years of age. Other studies have confirmed fibromyalgia onset after 60 to be very rare (6).

It has been proposed that there is a link between trauma and the development of fibromyalgia. Data about a specific incident prior preceding the onset of the fibromyalgia complaints (as perceived by the patients) signified that 25% of the patients' complaints appeared following a major psychological stressor. In 12.5% of the patients the complaints seemed to be the consequence of a period of overexertion. An operation preceded complaints in 6.25% of the patients. Other events that occurred prior to the onset of complaints were serious illness and a car accident (6.25% respectively). In most of the cases (50%), fibromyalgia symptoms did not appear directly after a traumatic episode, but gradually. It is important to note that in the cases where symptoms worsened progressively, the symptoms were generally preceded by multiple or even a single life drama in the distant past. This phenomenon is clearly demonstrated by two patients in the present study (refer to Chapter 4 – Appendix). According to Patient 6's testimony, she was molested at the age of four. From 13 years of age she started to suffer from severe migraine headaches, for which she was hospitalised for the first time at 18 years of age. Early in her adult life the next traumatic happening took place when she had a miscarriage at the age of 22. At the time of the study (age 55), she had already undergone six surgical operations. Another patient, Patient 16, shared a similar life story. Her parents divorced when she was two years old, after which her grandparents brought her up. At the age of four, she also was molested. Patient 16 reported severe headaches starting at seven years of age. Apart from various illnesses, Patient 16 had already had five operations at the age of 52. Both these cases professed a link between trauma in the distant past and progressive development of fibromyalgia in adult life. In these two cases it started with headaches during childhood, but then circled out to other organ systems.

The results of the present study are in concordance with the outcome of the Fibromyalgia Network survey that showed that 41% of the respondents were not able to identify a specific trigger prior to onset. In the latter study, 39% of the 59% that were able to provide details regarding the foregoing happenings indicated that physical trauma activated their symptoms.

27% stated that their complaints started after a major emotional trauma. 15% reported an infection to have preceded fibromyalgia onset, 9% gave testimony of surgery and 5% of exposure to a chemical agent just before their symptoms began (6). In the light of these findings, as well as the findings obtained in the present study, it is impossible to ignore the role distressing events play in the development of fibromyalgia. The way in which these events are able to impair health and contribute to fibromyalgia symptoms was discussed in Chapter 1.

As far as the natural history of the symptoms is concerned, 37.5% of the patients reported that over the previous 12 months, their symptom status had improved. The same number of patients felt that their condition was worsening. 6.25% of these claimed to experience higher pain intensity, 18.75% more painful locations, and 12.5% had both more painful locations as well as higher pain intensity. 18.75% of the patients reported that no significant changes took place with regard to their symptoms and 6.25% did not have clarity on whether their condition had deteriorated or improved. Reviewing the literature, one study actually reported 0.2% of patients claiming to have recovered fully. 31% of the study group reported that their symptoms had improved, but 40% felt their health status were poorer than before. 20% of the patient group stated that the natural history of their symptoms were unchanged (6). These results were similar to the present study's findings, even though these results were an indication of the natural history of symptoms since diagnosis, and not the history over the previous 12 months like in the present study. The fact that there do not seem to be a difference in the natural history of fibromyalgia symptoms, whether it is assessed over the full duration of the syndrome or whether it is assessed over 12 months, might be indicative of the chronic nature of the disorder.

Although numerous factors influence fibromyalgia symptom status (the number and severity of symptoms), there are a limited number of publications identifying and examining these factors. The factors reported below, were issues mentioned by patients participating in this study during experimental sessions. The primary factor influencing on fibromyalgia symptom status was stress (reported by 100% of patients). 93.75% of patients regarded sleep to have a great influence on their fibromyalgia complaints: 18.8% perceived a full night's sleep as a worsening factor on their symptom status, while 75% reported that sleep actually caused their symptoms to diminish. Exercise was reported to affect 81.25% of the patients' symptoms. Exercise seems to be beneficial to some – 43.75% reported that their

complaints were more controllable when following a light exercise program. However, 37.5% felt that exercise aggravates their symptoms. Cold and heat influenced 75% of the experimental group. These two factors were a major cause of distress in many patients. Cold worsened fibromyalgia symptoms in 68.8% of patients and heat in 56.3%. Only 6.3% benefit from cold, and only 18.8% stated that heat helps to relieve symptoms. Another factor reported to have a negative effect on fibromyalgia symptomology was humidity (this factor increased symptoms in 62.5% of patients). Interestingly, sunlight seemed to improve fibromyalgia symptom status in 25% of patients (12.5% felt that sunlight worsened their symptoms, though). Symptoms seemed to become worse at certain times of day in 56.3% of the patients. This also seemed to be the case with different seasons (37.5% of patients' symptoms increased with specific seasons or season changes). 12.5% of patients felt that changes in barometric pressure (height above sea level) worsened their symptoms, 6.25% felt that it improved symptom status. Alcohol and caffeine intensified complaints in 50% and 43.8% of the patient group respectively. 31.3% claimed that various foods, especially foods that have a high sugar and starch content, also have a negative effect on their symptoms. Eating fresh fruits and vegetables, however, were reported to relieve fibromyalgia complaints in 6.25% of the patient group. It is thus clear that various environmental factors are perceived to have different effects on the patients. There is not one single factor that benefits all the patients, and the only factor that had a negative effect on everyone was stress, a factor that influences healthy individuals as well.

Differences were seen with regard to the treatment programs selected for the patients. The treatment programs of the patients varied according to their current symptoms and complaints and with relation to their unique individual reaction to different therapies. All the patients (100%) made use of pharmaceutical medications to relieve their symptoms. Other treatments utilised by the patients (in addition to drugs) were physiotherapy (62.5%), exercise programs such as stretch exercises, swimming and walking (68.75%) and non-allopathic treatments such as acupuncture and meditation (56.25%). It is generally assumed that successful treatment of fibromyalgia does not exist without the combination of different treatment programs or what can be called an 'integrative treatment strategy'. Most of the patients in this patient group were on some sort of combined therapy for their symptoms: The combination of exercise, physiotherapy, and medication was mostly used by the patients (31.25 %). The second most prevalent combination therapy was the combination of non-allopathic treatment, physiotherapy and medication (18.75% of patients). 12.5% of the

patients were using the combination of exercise and medication; another 12.5% used exercise, medication and non-allopathic treatment simultaneously; and yet another 12.5% made use of combined exercise, physiotherapy, non-allopathic treatment as well as medication. The combination of non-allopathic treatment and medication was used by 6.25 % of the patients. 6.25 % (one patient) only used pharmaceutical medications to treat fibromyalgia complaints.

In order to determine which of these therapies offered the most successful option in treating fibromyalgia, a calculation was done to determine whether the patient's condition improved or whether there was no change/ deterioration using a specific treatment program (Table 1.16, p. 4.19). According to this table not one of the therapies could confidently be associated with improvement of fibromyalgia. For instance: 25% showed improvement on pharmaceutical drugs, but 43.75% did not show any improvement at all. This does not necessarily mean that allopathic medicine does not work, but it confirms the complexity of the symptoms and that there is an altered functional interaction between various bodily systems in fibromyalgia. According to a study assessing different treatment strategies, 40.9% of patients that exercised showed improvement compared to 31.8% that did not. The percentage of patients that showed improvement with physiotherapy was similar to the number of patients that did not show any progress at all (37.5% and 31.5% respectively). Analgesic drugs failed to relieve pain in 46.3% of the patients in the study and only seemed to help 31.3% of the participants (17). These findings serve as a further motivation to use a combination of therapies in treating fibromyalgia. Therapies that offer positive results in conjunction with other therapies include methods helping sleeping patterns, thermal treatment, hydrotherapy, and antidepressant medication (6). Some of the patients in the present study also confirmed sleep medication and antidepressant drugs to improve symptom status. However, alternative therapies that have been shown to be quite successful on their own are cardiovascular fitness training, EMG-biofeedback, hypnotherapy, regional sympathetic blockade and cognitive behavioural therapy (17). Unfortunately, only a few of the subjects in this study used any of these therapies.

4. Current symptom presentation

The symptom presentation of the patients as reviewed by means of a questionnaire that included symptoms commonly associated with both fibromyalgia and chronic fatigue

syndrome. The control group was screened for the same symptoms to serve as a comparative measure for the symptomology of fibromyalgia. All the symptoms were allocated to different symptom-categories (Table 2.2, p. 4.19). The means (for responses ranging from 0 = absent, to 3 = severe) for these categories were as follow: constitutional symptoms were 1.77 (SD 0.56) for patients, 0.13 (SD 0.3) for controls; symptoms relating to the skin were 0.89 (SD 0.52) for patients, 0.02 (SD 0.05) for controls; symptoms relating to the eyes were 0.99 (SD 0.63) for the patients, 0.08 (SD 0.21) for the controls; symptoms relating to the ears were 1.06 (SD 0.70) for the patients, 0.18 (SD 0.60) for the controls; symptoms associated with the nose and throat were 0.80 (SD 0.56) for patients and 0.02 (SD 0.06) for controls; symptoms of the mouth were 0.64 (SD 0.79) for the patient group, 0.02 (SD 0.06) for the controls; problems associated with the lymph nodes were 0.97 (SD 0.92) for patients and 0.03 (SD 0.13) for controls; problems with breasts were 0.48 (SD 0.66) for the patient group, 0.0 (SD 0.0) for the controls; respiratory symptoms were 0.92 (SD 0.57) for the patients and 0.03 (SD 0.06) for the controls; gastrointestinal symptoms were 0.94 (SD 0.56) for patients, 0.01 (SD 0.06) for controls; symptoms relating to muscle groups were 2.53 (SD 0.38) for the patients, 0.22 (SD 0.32) for the controls; symptoms of the joints were 1.52 (SD 0.77) for the patient group, 0.0 (SD 0.0) for the control group; symptoms associated with the genital-urinary tract were 0.41 (SD 0.46) for the patients, 0.01 (SD 0.04) for the control group; thyroid problems 0.71 (SD 0.75) for the patients and 0.0 (SD 0.0) for the controls; and neuropsychiatric symptoms were 0.99 (SD 0.52) for the patient group and 0.04 (SD 0.07) for the control group. The ANOVA test was used to calculate the statistical difference between the patient and control group. The p-values obtained for all the symptom-categories were highly significant ($p = 0.0001$). The mean total number of symptoms for the patient group was 51.69 (SD 23.29) with the minimum total number of symptoms 21, and the maximum total number of symptoms in a patient 95. The control group had a mean total number of symptoms of 4.33 (SD 5.33) with the minimum total number of symptoms nought, and the maximum number of total symptoms 15. A p-value was also calculated for the total number of symptoms for each study group ($p < 0.0001$). This data serves as additional evidence that fibromyalgia is characterised by multiple symptoms involving various organ systems.

A mean response (ranging from 0 – 3) was calculated for each of the individual symptoms as well. Symptoms that had a mean response of ≥ 2 were regarded as most severe in this particular fibromyalgia group and included fatigue, sleep abnormalities, tight or stiff

muscles, neck pain, shoulder pain, upper and lower back pain and severe headaches. Figure 2.3 (p. 4.21) illustrates the responses to the questions enquiring about these symptoms for the patients and controls. The mean response for patients to 'fatigue' was 2.5 (SD 0.73), compared to the mean control response of 0.3 (SD 0.59). Patients responded to 'sleep abnormalities' with a mean of 2.4 (SD 0.89), and controls with a mean of 0.1 (SD 0.35). The mean patient response to symptoms relating to muscle pain and stiffness, was 2.9, SD 0.25 for tight/ stiff muscles (controls: 0.2, SD 0.41); 2.8, SD 0.4 for neck pain (controls: 0.3, SD 0.62); 2.8, SD 0.77 for shoulder pain (controls: 0.2, SD 0.56); 2.3, SD 1.2 for upper back pain (controls: 0.1, SD 0.26); 2.8, SD 0.45 for lower back pain (controls: 0.5, SD 0.83); and 2.1, SD 1.31 for severe headaches (controls: 0.0, SD 0.0). Since these mean responses were out of a total of three, it is clear that these symptoms were quite severe and are strongly related to fibromyalgia symptom status in this study group. In point of fact, according to Table 2.3 (p. 4.20) these symptoms were not only the most severe in this group but also the most common. The prevalence of these symptoms ranged from 75-100% in the patient group, with 100% of the experimental subjects presenting with general fatigue, tight or stiff muscles, and neck and lower back pain (this explains why fibromyalgia is described as a musculoskeletal disorder, even in the absence of evidence of anatomical abnormalities of the muscles). Sleep disturbances were present in 93.75% of patients. 0-40% of the controls also presented with some of these problems, as neck and low back pain were relatively common in the control group as well (26% and 40% of controls respectively). 20% of the control group also reported general fatigue and tight muscles to be a regular problem. These results for the control group are in accordance with a study (mentioned in the first chapter) which stated that a minimum of 75% of the population report at least one complaint (like fatigue, tiredness, dizziness and headaches) during a 30-day period (18). According to the data obtained in the present study, it seems that the symptoms that healthy individuals commonly present with was neck and low back pain, fatigue and tight muscles. Only when these minor symptoms are aggravated to a point where it becomes unbearable, as in the fibromyalgia patient group, will these symptoms reach 'syndrome' status.

Some work has been published on the connection between the presence of different types of allergies and muscle pain. To explore the matter, the patients and controls were asked to indicate whether they suffer from any type of allergy. In this study, 62.5% of the patient group reported to have some kind of allergy, a significant higher prevalence than in the control group (20.0%). In other words, 37.5% of the patients and 80% of the controls did

not have any allergies at all. Despite the clear lower prevalence of allergies in the control group, the main difference between the patients and controls seemed to be in the number of allergies per person. The majority of subjects that reported to suffer from allergies had one allergy, i.e., 43.75% of the patient group and 13.3% of the control group. 12.5% of the patients and 0.07% of the controls suffered from two types of allergy. None of the controls had more than two allergies. In the patient group, however, one had three types if allergy. The mean number of allergies per patient was 0.88 (SD 0.8) and 0.27 (SD 0.59) for the controls. The statistical difference calculated for the two groups with the Mann-Whitney test, gave a statistical significant p-value of 0.0224 ($p \leq 0.05$). The higher prevalence of allergies in the patient group is significant because of the symptoms commonly associated with a systemic allergic manifestation: fatigue, muscle pain, joint pain, digestive symptoms, chest pain, mild depression, and racing pulse (19). The main culprits in the systemic allergic response are cytokines, regulatory proteins responsible for the intensity and duration of immune responses. Wallace *et al.* (2001) identified specific cytokines with relevance to fibromyalgia (20): IL-8, which intensifies pain, was shown to be twice normal levels in fibromyalgia. IL-1 receptor antagonist (IL-1ra) was also found to be double normal quantities. IL-1ra is known to increase the response to stress and counter-balance the effects of IL-8 (19). The most interesting finding made by Wallace *et al.* (2001), was that IL-6 (which increases pain, fatigue, alters mood and increases the response to stress) was produced at vastly increased levels when fibromyalgia patients' white blood cells were stimulated (20). This could explain why some individuals would develop fibromyalgia after an illness or infection.

Results from the Fibromyalgia Impact Questionnaire (FIQ) also provided useful information to set up a symptom-profile for the patients. The questionnaire comprised of ten scales (each scale ranged from 0 – 10) specifically associated with the symptoms causing distress in fibromyalgia patients. The scales were 'physical impairment' (mean patient score: 3.75 (SD 2.26), mean control score: 1.44 (SD 2.08)); 'do not feel good' (mean patient score: 6.79 (SD 2.36), mean control score: 0.45 (SD 1.29)); 'work missed' (mean patient score: 2.86 (SD 3.42), mean control score: 0.18 (SD 0.74)); 'could not do job' (mean patient score: 6.19 (SD 2.29), mean control score: 0.44 (SD 1.55)); 'pain' (mean patient score: 7.06 (SD 1.84), mean control score: 0.63 (SD 1.8)); 'fatigue' (mean patient score: 7.16 (SD 2.46), mean control score: 0.75 (SD 1.86)); 'not rested' (mean patient score: 7.88 (SD 2.0), mean control score: 0.31 (SD 0.72)); 'stiffness' (mean patient score: 6.69 (SD 1.7), mean control

score: 0.19 (SD 0.77)); 'anxiety' (mean patient score: 5.25 (SD 2.93), mean control score: 0.13 (SD 0.35)); and 'depression' (mean patient score: 4.06 (SD 2.86), mean control score: 0.13 (SD 0.52)). The statistical difference between the patient and control group for each one of the ten individual scales was highly significant with $p < 0.0001$. The FIQ total score also differed significantly ($p < 0.0001$) between the groups with the mean total FIQ score 57.69 (SD 15.19) for the patients and 4.94 (SD 7.59) for the controls.

Another study also used the FIQ to assess disability in 180 participating fibromyalgia patients and found a mean total FIQ score of 57.74 (13), exactly the same as in this study. According to Burchardt *et al.* (1991), the authors that validated the FIQ, the average fibromyalgia patient scores about 50 on the FIQ, whilst severely afflicted patients obtain scores of 70 and higher (21). Four of the patients (Patient 2,3,6 and 7) in this study had scores higher than 70. Their FIQ scores corresponded to the outcome on their 'Review of current symptoms' – questionnaire, since these patients also presented with more symptoms and greater symptom severity (refer to Chapter 4 – Appendix).

As far as the subscales of the FIQ are concerned, the pain, fatigue, stiffness, sleep quality (assessed by 'not rested'-scale), anxiety and depression scales were of particular interest. A couple of studies granted similar type of information by assessing these important aspects of the FIQ on visual analogue scales out of ten (just as the FIQ does). A study done by Cohen, *et al.* (2000) indicated that the fibromyalgia patients had a mean score of 8.2 (SD 1.6) for pain and 7.9 (SD 1.9) for fatigue (3). These values are slightly higher than the values obtained in the present study. Another study recorded a lower value of 6.1 (SD 2.0) for pain and 7.5 (SD 2.2) for fatigue (4). Values documented for stiffness was 6.6, SD 2.7 (3); 5.7, SD 3.5 (4) and 4.7, SD 2.8 (1). It seems that the patient group in the present study gave the highest values for stiffness. Another aspect commonly assessed by other researchers, seems to be sleep disturbances or sleep quality. The FIQ evaluates this aspect by asking patients to indicate on a scale from zero (not rested at all) to ten (well rested), how rested they feel after a nights' sleep. Scores published by other authors are 5.8, SD 2.4 (4) and 6.2, SD 2.9 (1). These scores are lower than the scores obtained in this study, indicating a more severely afflicted patient group in the present study.

Note that, in the present study, the patient scores for depression and anxiety were lower (4.06 and 5.25 out of ten respectively) than the scores obtained for pain, fatigue, sleep

disturbances and stiffness. This also seemed to be true for Cohen's study, which recorded a score of 4.9, SD 3.2 for anxiety and 3.4, SD 3.4 for depression, much lower than the scores for pain and fatigue mentioned previously (3). Firstly, this could simply be an indication that anxiety and depression are not one of the major symptoms associated with fibromyalgia. On the other hand, the lower depression and anxiety scores are more likely to be due to the use of anti-depressive medications by the patients in the present study. Contradicting this possibility is the fact that similar results were obtained in Cohen's study, where patients refrained from taking their anti-depressant drugs for the purpose of the study (3).

An alternative way to evaluate anxiety and depression in the patients was to look at prevalence rather than the severity of these two conditions within the patient group. 68.75% of the present patient group reported self-assessed global anxiety whereas 87.50% had self-assessed global depression. A study that found similar values for the prevalence of anxiety in their patient group reported 63% of the patients to have anxiety (4) as opposed to another study that reported a prevalence of 31% (1). Interestingly, a study that compared the lifetime prevalence of anxiety disorders in fibromyalgia, rheumatoid arthritis and major depression patients, found that 26% of the fibromyalgia group had anxiety disorders such as panic disorder and/or agoraphobia. None of the rheumatoid arthritis patients reported the presence of an anxiety disorder at any stage in their lifetime (22).

The prevalence of self-assessed global depression in the present study's patient group was 87.50%, which provides a different picture on depression in fibromyalgia than the severity score of 4.06 out of ten. The reported measures of the prevalence of depression show great variation from study to study. The most obvious reason for these differences is probably that the prevalence-measures of depression differ when patients report self-assessed depression as opposed to studies where patients were evaluated by a qualified psychiatrist for clinical major depression according to the criteria set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Examples of these differences were demonstrated by two studies that found the frequency of major depression (assessed according to criteria set out by the American Psychiatric Association) in the fibromyalgia patient group to be 43% (23) and 20% (24) respectively. These were significantly higher than the control groups in these studies that comprised of patients with other pain conditions.

Accordingly it can be said that depression and anxiety in fibromyalgia do not present a problem of the same magnitude as the pain, stiffness, fatigue and sleeping problems associated with the condition, but definitely forms part of a profile for fibromyalgia. This profile is distinctly higher than that of other pain conditions such as rheumatoid arthritis (22,23). In fact, depression and anxiety play such an important role in conditions characterised by medically unexplained symptoms, that recommendations had been made to remove the category somatoform disorders in the DSM-V since depression and anxiety characterises patients with medically unexplained symptoms better (25). In the latter study they found that 44.7% of the 206 patients with unexplained symptoms had full anxiety diagnoses, 45.6% had either full of minor depression diagnoses and only 4.4% had a full DSM-IV somatoform diagnosis or abridged somatisation disorder (18.9%) (25).

Another study evaluated the prevalence and predictors of psychiatric disorders in fibromyalgia specifically (26). In this specific study, 115 fibromyalgia patients were evaluated with the Structured Clinical Interview for DSM-IV after they were grouped into one of three psychosocial subgroups (dysfunctional, interpersonally distressed and adaptive copers). Axis I diagnoses were present in 74.8% of the participants, with the 'dysfunctional' subgroup mainly reporting anxiety, and the 'interpersonally distressed' subgroup, mainly mood disorders. Axis II diagnosis were present only in 8.7% of the participants. The authors concluded that fibromyalgia is not a homogeneous diagnosis, but has varying proportions of comorbid anxiety and depression depending on of the psychosocial features of the patients (26).

5. Hypothalamic-pituitary-adrenal (HPA)-axis function

The malfunctioning of the HPA-axis has been linked with depressive illnesses and chronic pain as part of a physiological stress response that generates a loss of affective and cognitive flexibility, anxiety, sleep disturbances and activates the autonomic nervous system (27). Reviewing previous publications exploring HPA-axis function in fibromyalgia (Chapter 1, p. 1.41-1.42), conflicting results have been published. As a result, there is a lack of agreement as to the overall state of HPA-axis activity in fibromyalgia. Findings from studies assessing HPA-axis function in fibromyalgia point in the direction of altered activation at both the pituitary and adrenal level. Fibromyalgia seems to be associated with a hyperactive HPA-axis function during restful conditions (evident in elevated basal cortisol

levels), an exaggerated reaction of the pituitary gland to stress (evident in higher than normal ACTH levels in response to CRH), accompanied by reduced sensitivity of the adrenal gland to ACTH (28). It is hypothesised that the inability of the adrenal glands to respond to elevated ACTH levels might be an adaptive mechanism of the adrenal cortex to chronic stress (29).

In the present study, HPA-axis function was evaluated by analysis of the salivary cortisol by means of ELISA. Patients showed elevated cortisol levels in comparison to control subjects. The patients had a mean salivary cortisol level of 9.59 ng/ml (SD 2.79), statistically significantly higher that the control mean cortisol level of 5.60 ng/ml (SD 2.3). A p-value of 0.0003 was obtained with the Mann-Whitney test for the statistical difference between the two study groups. The pattern of elevated cortisol levels, together with symptoms of fatigue and cognitive impairment, is similar to that observed in burnout syndrome, which is believed to be the result of ineffective coping with enduring stress (30). In point of fact, HPA-axis activity has directly been correlated with passive coping where CRH – ACTH – cortisol levels increase when feelings of hopelessness arise (31). What is more, elevated CRH levels have been linked with anxiety (32), and could be the pathophysiological mechanism underlying the high prevalence of anxiety disorders amongst fibromyalgia sufferers.

Hemispheric laterality is said to play a major role in the stress-induced activation of the HPA-axis, with the right prefrontal cortex predominantly exerting stimulatory effects and the left prefrontal cortex inhibitory effects (33). In other words, cortisol secretion is predominantly controlled by the right hemisphere in healthy individuals (31). When the right hemisphere is unable to perform this task, it is possible that the left hemisphere could adopt this function. However, left hemisphere driven cortisol regulation (as seen in PSTD patients), is said to be associated with a significantly higher incidence of physical complaints, recurrent illness, affective and behavioural abnormalities (just as observed in fibromyalgia) (31). The question that arises is whether cortisol function could, as a result of early life trauma to the right brain, be regulated by the left hemisphere in fibromyalgia. This possibility is explored further in the discussion on hemisphere dominance.

6. Autonomic nervous system function

In this study, autonomic nervous system function was assessed by exposing the experimental subjects to both a physical and a psychological stressor. To access the response of the autonomic nervous system to physical stress, an orthostatic test was performed during which subjects were expected to lie in the supine bodily position for 10 minutes, sit upright for 10 minutes and then stand against a wall for 10 minutes. The heart rate variability recordings obtained during each of these bodily positions were analysed in 5-minute segments, so that the first five minutes of each section (bodily position) could be used as an indication of how the autonomic nervous system compensates to the new bodily position, and the second five minutes for the description of the status of the autonomic nervous system in that specific position. To access the effect of a psychological stressor on the autonomic nervous system, a baseline recording was performed in the sitting position, after which heart rate variability was recorded while the subjects were filling out the Experiences in Close Relationships-questionnaire (ECR-R).

As discussed in Chapter 3, a wide variety of analytical techniques are available for analysis of heart rate variability, the most common measures being descriptive statistical and frequency domain measures. In the analysis of the present study's data, the only statistical measure utilized is the mean heart rate, since the other statistical measures have limited application in basic psychophysiological research (34). Analysing the heart rate variability results obtained, both similarities and differences were noticed between the patients and controls. There was a tendency towards faster heart rate in the subjects with fibromyalgia during supine (patients – 75.48 bpm, SD 11.19; controls – 65.12 bpm, SD 12.59), sitting (patients – 77.76 bpm, SD 10.84; controls – 69.01 bpm, SD 12.38), and standing (patients – 93.29 bpm, SD 14.65; controls – 82.53 bpm, SD 13.79). These differences between the patients' and the controls' mean heart rate was significant for the supine position (supine: $p = 0.0299$; sitting: $p = 0.0594$; standing: $p = 0.0630$). Both groups showed notable increases in heart rate upon sitting up from supine (patients: $p = 0.0113$; controls: $p = 0.0597$) as well as on standing from sitting (patients: $p = 0.0002$; controls: $p = 0.0060$). However, with each manoeuvre, the patients' mean heart rate showed greater increases (the difference in change between the patients and the controls was not significant). Since a racing pulse is associated with anxiety and allergies (19), the increased heart rate in the patient group is noteworthy.

Power spectral density analysis provided the basic information on how variance (in terms of power) distributes as a function of frequency and allows the study of the frequency specific oscillations that correspond to the influences of the sympathetic and parasympathetic branches of the autonomic nervous system respectively (35). By means of this technique it was also possible to instantaneously detect alteration of the autonomic tone in response to changes in posture (during the orthostatic test) or psychological stress. In the frequency domain, the power spectral density of the low frequency band (0.05 - 0.15 Hz) describes the activity of the sympathetic nervous system function, whereas the power spectral density of the high frequencies (0.15 - 0.35 Hz) is indicative of vagal (parasympathetic) activity. Autonomic tone (sympathetic-parasympathetic balance) is described by the ratio between these two frequency bands (LF/HF), indicating which branch of the autonomic nervous system is dominant with physiological compensation, or during a specific bodily position. The amount of variability is demonstrated by the total power in the frequency domain (the sum of the very low, low and high frequency components).

While power spectral densities did not differ significantly between the patients and controls in the supine and sitting positions, there was a significant difference ($p = 0.0188$) in both the low and the high frequencies in the standing position (patients - LF (n.u.): 72.61 (SD 17.96), HF (n.u.): 27.39 (SD 17.96); controls - LF (n.u.): 86.12 (SD 8.97), HF (n.u.): 13.88 (SD 8.97). Patients exhibited lower sympathetic and higher parasympathetic activity in comparison to controls while standing. Chronic corticosterone treatment is one of the factors known to reduce the low frequency component of HRV (36). One can therefore expect high psychological or physiological stress induced cortisol levels to have a similar effect on the sympathetic nervous system. The lower sympathetic activity in the patient group can therefore possibly be contributed to the elevated cortisol levels observed in this group. These differences in parasympathetic and sympathetic activity between the patients and controls were also demonstrated by the sympathetic-parasympathetic balance in the standing position: the LF/HF ratio of the controls was double that of the patients (patients: 5.42, SD 5.36; controls: 10.98, SD 10.11; $p = 0.1046$). This implies that although the sympathetic nervous system is dominant in the standing position in the patients (as seen in the healthy controls), the relative amount of vagal activity in relation to sympathetic activity is higher than in the controls. The lower LF/HF ratio in the patients is also caused by lower than normal sympathetic activity in the standing bodily position.

As far as the physiological compensation to the new bodily position is concerned, notable differences were observed between the patients and controls in the delta value (change from supine to sitting and from sitting to standing) of the spectral densities (Figure 5.1.3., p. 4.26). First of all, the delta values for the change within a group were noteworthy for both the low and high frequency component, but these changes were not all statistically significant because of the great standard deviation calculated for the means. For the change from supine to sitting, the delta value for the low frequency component in the patient group was much smaller than the value for the control group (patients: Δ = 5.81 ms², SD 312.6); controls: Δ = 246.01 ms², SD 369.31; p = 0.0739). Conversely, the delta value for the high frequency component was greater in the patient group (patients: Δ = - 196.15 ms², SD 540.54); controls: Δ = - 6.92 ms², SD 63.19; p = 0.1848). These results imply that upon sitting upright from the supine position, the patients' autonomic nervous system did compensate by increasing sympathetic activity (as expected), but to a much smaller extent than the controls. In addition to the relative lack of sympathetic activity in response to postural change, the parasympathetic nervous system seems to overcompensate by reacting much more strongly to the postural change than did the parasympathetic nervous system of the controls. For the change from sitting to standing, the delta value for the low frequency component in the patient group was similar to that of the control group (patients: Δ = 103.65 ms², SD 353.97); controls: Δ = 125.61 ms², SD 439.21; p = 0.8867). But, the delta value for the high frequency component was significantly lower in the patient group (patients: Δ = - 5.19 ms², SD 259.89; controls: Δ = - 264.12 ms², SD 352.60; p = 0.0374). These results imply that upon standing from the sitting position, the patients' autonomic nervous system did compensate by increasing sympathetic activity, almost as happened with the healthy controls. However, it seems as if the parasympathetic nervous system of the patients is unable to compensate for the standing position as happened with the controls. The p-values calculated for the difference in change (delta values) between the two groups was non-significant for both the spectral components (LF and HF).

The patient group also had diminished variability in heart rate (in all three bodily positions), as evident in the lowered total power in the frequency domain. The difference in total power between the patients and controls was significant for the sitting and standing positions (p = 0.0355 and p = 0.0437 respectively). Although the overall suppression of the autonomic nervous system is probably partially the consequence of the anti-depressive drugs the patients use (as seen in Chapter 3, p.3.38.), lowered heart rate variability still

forms part of the status quo of their neurological profile. As far as the physiological compensation to postural change is concerned, the patients and controls seem to respond oppositely from each other in terms of total power. Upon sitting from supine, the total power (heart rate variability) of the patients decreased while that of the controls increased significantly (patients: Δ = - 189.21 ms², SD 763.92; controls: Δ = 273.68 ms², SD 389.66; p = 0.0666). Upon standing up from the sitting position, the total power (heart rate variability) of the patients increased while that of the controls decreased (patients: Δ = 106.05 ms², SD 506.44; controls: Δ = - 143.59 ms², SD 541.33; p = 0.2285). The p-values calculated for the difference in change (delta values) between the two groups was non-significant.

An interesting difference was observed between the patients and controls in response to the psychological stressor. First of all, the patients' mean heart rate increased significantly (p = 0.0005) while filling out the ECR-questionnaire, while the control's heart rate remained the same. In addition, the patients' autonomic nervous system did not seem to respond to the psychological stressor with a decrease in heart rate variability as expected. Figure 5.2.2 (p. 4.28) shows how the total power of the controls decreased while they filled out the ECR-R questionnaire, while the total power of the patients remained the same (patients: Δ = 10.87 ms², SD 113.07; controls: Δ = 259.11 ms², SD 492.82; p = 0.1307). As far as the autonomic balance is concerned, both groups showed sympathetic dominance during the baseline (patients: 2.13, SD 2.47; controls: 2.92, SD 2.4) and stressor recording (patients: 3.16, SD 3.06; controls: 1.89, SD 0.9). However, according to the LF/HF ratio, the patients' autonomic nervous system compensated for the psychological stressor with increased dominance of the sympathetic nervous system (through diminished parasympathetic activity). The controls' autonomic condition shifted to a state of decreased sympathetic dominance by mainly decreasing the sympathetic activity (Figure 5.2.1.B, p. 4.27). Interestingly, a study exploring the relationship between depressed mood and parasympathetic control of heart rate during psychological stress (challenging speech tasks), found depressive mood to be correlated with a greater decrease in vagal activity during stress (37). The patients' depressed mood state could therefore have a relationship with their decrease in parasympathetic activity when exposed to a psychological stressor.

In summary it can be said that, in this study, the fibromyalgia patients' autonomic nervous system activity during a stabilised bodily position was marked by faster mean heart rates,

lower sympathetic and higher parasympathetic activity in the standing position (in comparison to controls), a weakened shift towards sympathetic dominance during the standing position and lowered overall heart rate variability. Upon compensation for a new bodily position, their mean heart rates showed greater increase than in the control group. During the second change from sitting to standing, the patients' sympathetic and parasympathetic nervous system showed a similar response to what was observed during the controls' physiological compensation to the first change from supine to sitting. This observation was also made for the total power (amount of heart rate variability). When exposed to the psychological stressor, the patients' autonomic nervous system failed to respond with lowered heart rate variability as seen in the healthy controls. These findings suggest that the patients' autonomic nervous system is reluctant to respond to both physical and psychological stress. It has been shown that an inability to activate the sympathetic nervous system during stress may be a feature of avoidant attachments (38). What is more, the sympathetic nervous system contributes to positive emotions (38). The lowered sympathetic activity of the fibromyalgia patients in comparison to controls might therefore have a relationship with their psychological profile in terms of their mood state and attachment styles. The autonomic perturbations in fibromyalgia may also contribute to the pain experienced by patients (54). Cortelli & Pierangeli (2003) proposed that, since the nociceptive and the autonomic nervous system interact at the levels of the periphery, spinal cord, brainstem and forebrain; it is possible that brainstem pain modulating systems forming part of the central autonomic network may play an important role in the pathophysiology of chronic pain (54).

7. Hemisphere dominance

In this study, the Herrmann Brain Dominance Instrument (HBDI) was used to assess lateralisation in the patient group. The control group was not evaluated for hemisphere dominance because of insufficient funds, but a bank of normal values is available against which findings can be compared. Although Ned Herrmann, the founder of the instrument, claims to have based it on physiology (the instrument was validated against EEG recordings), there are some concerns pertaining to the instrument's division of the brain into limbic and cerebral (cortical) structures as well as the interpretation of the results in neurophysiological terms. For instance, according to the HBDI, a person who tends to be emotional and enjoys being in the company of others, 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. Moreover, it is important to recognise that though referred to as hemispheric dominance, the HBDI in fact measures an individual's preferred way of thinking or 'thinking style'. Despite the criticism of the HBDI, several doctoral degrees were conducted using the instrument. Owing 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 (regardless of what the founder may claim). For the purpose of this study the focus will thus be on preferred way of thinking as a psychological phenomenon and although HBDI analytical terms are, it is not presumed that thinking is performed by specific quadrants.

Thinking styles is in the context of HBDI terminology named after so-called brain quadrants, e.g. the *cerebral left* (quadrant A), which is associated with mathematical, logical and analytical thinking, as well as a preference towards autonomy; *limbic left* (quadrant B), associated with the need to be in control (leadership), structured tasks and attention to detail; the *cerebral right* (quadrant D), responsible for the ability to take risks, selling ideas, integrating and inventing solutions; and the *limbic right* (quadrant C), involved in working with people, building relationships, teaching, and intuition about other people's intentions and emotional states.

For the purpose of this study, the results obtained by the HBDI were displayed in different ways, each way providing information in a unique manner. First of all, the brain profiles of the patients were plotted onto the two-dimensional graph set out by Herrmann in 'The Creative Brain' (39), called the 'group composite graph' (Figure 6.1.1., p. 4.28). However, it is rather difficult to distinguish the different patient profiles on this graph. For this reason the generic codes for each one of the patients were plotted on another (similar) graph, displaying the generic code of each patient in the quadrant dominant for that specific patient ('generic code' refers to the 27 different types of profiles described by the HBDI, p.2.19; 'dominance' are defined as the quadrant in which peak scores were obtained). In this graph (Figure 6.3.1., p. 4.30) 12 of the 16 patients' generic codes fell in the C quadrant, suggesting that 75% of the patient group is dominant for the limbic right brain quadrant. In other words, the majority of the patients show thinking patterns influenced by input from the right limbic structures in the brain. As a result these patients are very emotional. Two patients'

generic codes fell in the B quadrant, showing dominance in the limbic left quadrant. Therefore, during decision-making processes, these individuals will be punctual, organised, and would like to be in control of each situation (the drawback to the need to be in control is that a much anxiety can arise when the person feels that the situation is beyond control). Only one patient's generic code fell into each of the remaining cerebral quadrants (A and D). Although these two patients seem to be an exception to the rest of the patients, their generic codes were still presented very close to the dividing margin between the cerebral and limbic quadrants on the two-dimensional graph. Since the HBDI does not intent to classify subjects into distinct classes, and aims to present the results on this specific graph on a continuum from left to right, and limbic to cerebral, these two patients' thinking styles also seem to have relatively strong influence from the limbic brain structures.

The second way in which the patients' brain profiles were described, were by means of profile code-classes (Figure 6.3.2. A and B, p. 4.31). These classes are groupings of generic codes with common characteristics. Generic codes (e.g. 2-1-3-1, 2-1-1-1 or 3-2-1-1) describe unique combinations representative of the four HBDI quadrants in the following arrangement: A-B-C-D. In these combinations, a '1' indicates a primary (very strong) preference, '2' a secondary preference (intermediate), and '3' a tertiary (low) preference. Therefore, the generic code 3-2-1-1 actually means: cerebral left quadrant A (low preference) – limbic left quadrant B (intermediate preference) – limbic right quadrant C (very strong preference) – cerebral right quadrant D (very strong preference).

In the present study, the patients' brain profiles corresponded to the following profile code-classes:

2-1-1-1: This profile is a triple dominant profile with the three most preferred quadrants being both the cerebral and limbic right quadrants as well as the limbic left quadrant. The highest percentage (43.75%) of the patient group showed this generic code to be their preference as far as thinking styles is concerned. The dominance in three different quadrants is associated with a reasonable amount of integration between organised and structured processing from the left hemisphere (limbic left quadrant), and holistic, synthesising and creative modes of thinking from the right hemisphere. This multi-dominant array of preferences is said to be characterised by a 'generalised' nature, able to utilise most of the brain structures in problem solving. A subgroup of the 2-1-1-1 generic code, is the 3-1-1-1 code. Individuals with this profile function in a similar manner as the 2-

1-1-1 individuals, just more to the extreme. 12.5% of the patients had the 3-1-1-1 profile. What may be problematic about this type of thinking processes (both the 2-1-1-1 and 3-1-1-1 codes) is the lack of preference (or even avoidance in the case of the 3-1-1-1 generic code) of logical, rational and analytical thinking of the left cerebral quadrant. The avoidance of the mode of thinking of this quadrant tends to reinforce the use of the dominant structures, in this case, making the use of the dominant structure more visible (40).

2-2-1-1: The 25% of patients showing this generic profile were mainly right brain orientated (with primaries in both the right hemisphere quadrants). This profile is thus associated with a strong preference for so-called right brain thinking, i.e. visualising, creativity, communication, working with people and being emotional and intuitive. Though all the left-brain functions are available to the individual in problem solving, using the left hemisphere is a secondary preference. One of the patients had the 3-2-1-1 profile (a subgroup of the 2-2-1-1 profile code). To this individual, the use of the cerebral left quadrant is a tertiary preference. As with the 2-1-1-1 profile, it is possible that the functions of the left cerebral quadrant is in point of fact avoided in problem solving (especially in the case of the 3-2-1-1 generic profile).

2-1-1-2: 12.5% of the patients had 2-1-1-2 generic profiles. This profile shows dominance in thought processes influenced by the limbic structures, with two primaries, the limbic left as well as the limbic right quadrant. This profile is characterised by strong preferences towards conservative thinking and controlled behaviour, with a need for organization and structure as well as detail and accuracy. These desires and preferences are due to influence from the limbic left brain structures and cause the individual with primary dominance in this quadrant to worry about details. In addition to, and opposing these thought processes are the emotional and interpersonal preferences from the limbic right quadrant. A primary dominance in this quadrant is associated with high emotionality, intuitive ‘feelings’, an interest in music and a sense of spirituality. These diverse qualities of the two limbic quadrants can lead to internal conflict since both these thinking styles are primary within the same individual (40).

The last three patients did not seem to show similar thinking patterns to the rest of the patient group. Their thinking style preferences were as follows: **1-2-1-1:** This profile is also an example of a triple dominant profile, exhibiting primaries in both the right

hemisphere quadrants as well as in the cerebral left quadrant. This individual will be more experimental than organised and more emotional than controlled. **1-1-3-3:** This profile is double dominant in the left hemisphere (cerebral and limbic left quadrants). This profile clearly exhibits an avoidance of the right hemisphere thinking processes. The left-brain characteristics would therefore be even more profound in this profile as it is reinforced by the extreme lack of right-brain thinking. **1-1-1-2:** One of the patients showed this triple dominant profile. Characteristic of this profile is dominant features of both the left hemisphere quadrants and the limbic right quadrant. What was interesting about these patients, was that they were three of the five patients that did not have insecure attachment styles. This may be indicative of the relationship between early life experiences and the development of preference for the utilisation of specific brain quadrants in thinking.

Figure 6.3.2 C (p. 4.31) demonstrated the dominance in the respective HBDI quadrants in yet another way. In this bar graph, the number of patients that showed primary preference in the thinking style associated with each respective quadrant were displayed. (Primary preference is indicated by a score higher than 67 for the quadrant). Only 18.75% of the patients primarily preferred cerebral left quadrant (quadrant A) thinking. The limbic left and cerebral right quadrant styles (B and D) were primarily preferred by 68.75% and 75% of the patients, respectively. The vast majority of the patients (93.75%) showed that the limbic right structure thinking style (quadrant C) was their primary choice in thinking style. In other words, these patients show relatively strong preferences for all the brain quadrants except for the cerebral left quadrant, which is associated with mathematical, logical and rational thinking. The findings summarised on this graph accentuate the avoidance of the cerebral left quadrant in thinking styles as already indicated by the profile code-classes.

Figure 6.1.2. (p. 4.29) illustrates the mean profile for the patients evaluated in this study. In other words, the mean score for each one of the individual quadrants was calculated from the patient scores, and illustrated on a graph to show the 'average' fibromyalgia patient's brain profile for this study. The mean score for the cerebral left quadrant was 54.46 (SD 26.87), 80.69 (SD 18.5) for the limbic left quadrant, 90.94 (SD 22.92) for the limbic right quadrant and 72.56 (SD 22.29) for the cerebral right quadrant. Combining these quadrant scores over the two brain halves, a mean score of 54.38 (SD 11.99) was obtained for the right hemisphere and 45.63 (SD 11.99) for the left hemisphere. The mean score for the cerebral structures was 42.63 (7.46) as opposed to 57.4 (SD 7.46) for the so-called limbic

structures. From this graph, and the data presented in the previous paragraphs, it is thus clear that that there is a strong preference for thinking styles associated with activity in the right brain structures as well as the limbic structures. Most of the patients seem to be very emotional, a characteristic of the quadrant where the limbic and right brain structures overlap (limbic right quadrant).

The HBDI has an interesting and valuable feature in that it, at a certain stage, forces the subject to choose between self-descriptive adjective pairs. Apparently the adjective pair score reveals the thinking style preference that is most instinctive to that person. Therefore, the quadrant with the highest adjective pair score (among the four quadrants) is the thinking style preference that is favoured in stressful situations (39). In the present study, the limbic right quadrant's mean score was notably higher than all the other quadrants (8.63, SD 2.25). This implies that during problem solving activities in stressful situations, most of the patients in this group will exhibit thinking patterns strongly influenced by emotionality. The limbic left quadrant had the second highest score with 6.19, SD 2.26. The mean adjective pair scores for the two cerebral quadrants (left and right) were rather similar with 4.63 (SD 2.5) and 4.56 (SD 2.0) respectively. According to these results, the patients strongly prefer the emotional right limbic quadrant and the organising (or sequential) left limbic quadrant to the two cerebral quadrants in thought processes during stress. Comparing the mean profile scores (which is an indication of thinking styles exhibited in every day life) to the mean adjective pair scores, an interesting shift was observed in the preference of one quadrant to another. Figure 6.2 (p. 4.30) illustrates the mean profile scores in relation to the mean adjective pair scores. There were no remarkable shifts in the scores in the left hemisphere quadrants. Conversely, the mean adjective pair scores for the right limbic quadrant increased notably. Furthermore, the mean adjective pair score for the cerebral right quadrant were noticeably decreased (in relation to the profile score). Thus, in addition to the strong preference for right limbic structure thinking during restful conditions, thinking style preferences for most of the patients in this study group will shift even more to this quadrant during stressful situations. This implies that, during stress, these patients are predisposed to use emotional coping mechanisms, probably because of the loss of the ability to utilise so-called cortical processing for problem solving.

In summary it can be said that the majority of the fibromyalgia patients evaluated in this study appear to use right-brain processing in daily functioning, together with decision

making processes strongly influenced by the limbic structures. In HBDI terminology, this type of thinking is characteristic of the 2-1-1-1 generic profile code. According to population studies, the 2-1-1-1-profile code is the most common brain profile, with 16% of the population displaying this generic profile. Moreover, there is a clear female predominance in this profile, with 24% of the female population exhibiting this pattern of thinking processes (40). The second most common generic profile in this present study group, the 2-2-1-1-profile, is the third most common profile in the population (14%) with relatively small differences in the male and female population (11% and 17% respectively). Thus it seems that these profiles are not specific to the fibromyalgia patients, but are representative of the general (healthy) female population. The implication of these findings is perhaps that these specific profiles codes, may not be the cause of firomyalgia symptoms, but rather a predisposing factor in the development of fibromyalgia, explaining the higher prevalence of fibromyalgia among woman. However, there has been no indication that the emotional reaction to stress (as indicated by the adjective pairs in this study) is unique to the 2-1-1-1 and 2-2-1-1-profile. Therefore, emotional coping seems to be typical to this specific fibromyalgia patient group.

In spite of the criticism of the interpretation of the results obtained by the HBDI (especially the strange neurological terminology) there are cerebral perfusion studies confirming the HBDI results mentioned above (41,42,43). Regional blood flow abnormalities detected in fibromyalgia included a decreased flow in the frontal, temporal and parietal areas (cortical structures). In some cases, this hypoperfusion was restricted to the left hemisphere (41). Another study found an 8% reduction in the total cortex perfusion of fibromyalgia patients (42). Therefore, the HBDI results indicating a lower preference for cerebral thinking, especially that of the cerebral left quadrant, are verified by cerebral perfusion results. As far as the strong preference for the right hemisphere is concerned, research has shown that relative greater right frontal EEG activation in adults may be a marker for negative affect, dysphoric mood state, and depression (43). Additionally, greater right frontal EEG activity (influenced by the right amygdala) has been noted in infants and young children with behaviours marked by fearfulness (anxiety) (44). Right brain dominance has also been associated with heightened HPA responsitivity (45). According to these findings, the anxiety, depression and hypercortisolism of fibromyalgia could perhaps be associated with their right hemisphere dominance. This would insinuate that cortisol function could not be regulated by the left hemisphere as speculated at the end of Section 5 (p. 5.17).

Nevertheless, whether the natural emotion-based style of thinking predisposes to the development of fibromyalgia, or whether early life experiences with the development of insecure attachment predisposes to both emotion-based thinking and the development of fibromyalgia, is yet to be investigated by future studies.

8. Attachment

Attachment is an inborn characteristic that motivates an infant to seek proximity to parents and establish communication with them. This system essentially evolves in response to early childhood experiences. The attachment system organises motivational, emotional and memory processes with respect to the mother (or significant caregiving figures) (46). Repeated interpersonal experiences will therefore become encoded in implicit memory as expectations, which will be transformed to mental working models of attachment on what to expect from the caregiver in times of need. In adult life, when confronted with a stress situation, the cognitive schema that predicted the likely behaviour of the attachment figure in threatening circumstances during infancy will allocate appropriate behavioural actions during adulthood (47). The attachment system/ style developed during childhood will thus manifest throughout the lifespan of the individual (48). During times of stress, the adult is likely to seek 'attachment figures' as sources of comfort. For adults, such figures may be close friends or, as assessed in this study, romantic partners (46).

In this discussion, the attachment patterns of the patients and controls are described by Bartholomew's two-dimensional, four-category conceptual scheme of individual differences in adult attachment (refer to Chapter 2, p.2.7). The two dimensions are labeled 'model of self' (relating to anxiety) and 'model of others' (relating to avoidance) (49). Bartholomew's illustration enables researchers to view the subject's attachment styles on a continuum, but defines the diverse ends of the continuum, simplifying the interpretation of results. The four categories described are *securely* attached individuals, who are comfortable with intimacy and autonomy; *preoccupied* individuals, constantly worried about their relationships; *fearful* people, who are fearful of intimacy and socially avoidant; and *dismissing* people, who dismiss intimacy and prefer to be independent (49,50).

The four attachment categories are described in terms of anxiety and avoidance. In this study, the mean anxiety score was 3.45 (SD 1.46) for the patient group and 1.62 (SD 0.49)

for the control group. Mean avoidance scores were 3.59 (SD 1.57) for patients and 1.95 (SD 0.88) for controls. The statistical difference (calculated with ANOVA) between the two study groups was highly significant with $p = 0.0001$ for anxiety and $p = 0.0015$ for avoidance. The anxiety and avoidance score of each subject was plotted onto Bartholomew's two-dimensional graph, organising all the subjects into the four attachment classes (Figure 7.1., p.4.32).

Reviewing Bartholomew's graph of the subjects in this study, clear differences in the attachment styles of patients and controls can be observed. According to Figure 7.1 and Table 7.1. (p. 4.32.), all the control subjects (100 %) had secure attachment styles (low anxiety and low avoidance). Secure people tend to have relatively enduring and satisfying relationships marked by mutual sharing and a collaborative give-and-take between the members (46). They are comfortable expressing their emotions (50), and tend not to suffer from depression and other psychological/ psychosomatic disorders. The patients, on the other hand, were scattered among all the attachment classes. Only 31.25 % of the patients were secure in their adult romantic relationships. The other 68.75 % of the patient group had insecure attachment styles. 18.75 % showed preoccupied attachment (high anxiety, low avoidance): In general these people tend to have highly conflictual relationships (46). Although they are comfortable expressing their emotions, preoccupied individuals often experience a lot of negative emotions, which can often interfere with their relationships. These individuals can be preoccupied with the past, struggling to forget distressing experiences (46). Another 18.75 % of the patients had fearful-avoidant attachment (high anxiety, high avoidance): Fearful people tend to have much difficulty in their relationships. They tend to avoid becoming emotionally attached to others, and, when they do enter a committed relationship, the relationship may be characterized by mistrust or a lack of confidence (50). Dismissing attachment (low anxiety, high avoidance) was present in yet another 18.75 % of the patient group: Generally, people in this quadrant tend to prefer their own autonomy – oftentimes at the expense of their close relationships. Although these people often have high self-confidence, they sometimes come across as hostile or competitive by others, and this interferes with their close relationships (50). One of the patients (6.25 %) was right between the dismissing-avoidant and secure quadrant. Note that these groupings are general patterns, and that a given individual may reveal elements of more than one attachment classification (46). Additionally, it should be remembered that the grouping of subjects on the two-dimensional graph is not a strict classification of

attachment classes, but should be viewed as a continuum ranging from low anxiety and avoidance to high anxiety and avoidance (49).

The question to be asked is: what is the cause of the high anxiety and avoidance amongst the fibromyalgia patient group? Although previous studies on fibromyalgia and attachment could not be found, other studies may throw some light on the question. According to a basic survey with 280 participants diagnosed with fibromyalgia, 62% of the patients reported physical and/ or emotional trauma before fibromyalgia onset (6). In the present study, the patients' medical and psychological pasts with regards to specific traumatic incidents (whether it was previous hospitalisations, surgeries or accidents, or a major psychological distressing happening) were reviewed. It was notable that these patients' histories were often marked by one trauma after the other. The mean number of traumatic events that occurred in the patient group (throughout their lives) was 5.5 events (SD 4.44). Two of the patients reported a total of 14 events that they felt were particularly distressing. In contrast to the patients, the control subjects experienced a mean total number of traumatic events of 2.07 events (SD 0.96) with the highest number of events in the group being four. The statistical difference calculated for the two groups (by means of the Mann-Whitney test) were highly significant ($p = 0.0071$). Further studies are necessary to ascertain whether differences in perception of trauma between normal and fibromyalgia individuals may contribute to the higher incidence of traumatic events reported in the patient group.

Despite the possibility that the testimonies of trauma by the patient group could be exaggerated, ample research findings have confirmed the effect trauma has on the development of the attachment system of an individual (refer to Chapter 1, Section 3.1.). It has already been discussed how interactive experience during early life (transmitted to the infant through its relationship with its primary caregiver) is of prime importance in the maturation of the infant brain. The significance of this relationship explains why relational trauma such as abuse and neglect during early life can have permanent effects on personality organization (51). In this study, patients reported sexual abuse, parental divorce, alcoholic parents, the loss of one or both parents and stressful family environments as early childhood trauma (refer to Chapter 4 – Appendix). When a traumatic event is experienced and the caregiver provides a sense of security, the child is helped to cope by a process called 'interactive repair'. Conversely, with abusive, inattentive or absent parents, extreme levels of stimulation and arousal are induced (or not removed through interactive repair), leaving

the child in an extremely disturbed psychobiological state that is beyond his/her immature coping mechanisms (52). Because the attachment system is instinctive to humans, infants will become attached to the primary caregiver, even if the caregiver is psychologically or physically abusive (46). In such cases, insecure attachment is likely to develop, marked by a representational working model of distrust of others (avoidance) and self-doubt (anxiety) (53). If the child experiences 'fright without solution', he will most likely resort to a state of dissociation in order to survive the overwhelming levels of distress (51).

According to Maunder and Hunter (2001) attachment subtypes tend to persist over an individual's lifespan (47). In order to see if age-dependent differences exists in attachment over the lifecycle, statistical correlations were calculated between age and attachment-related anxiety and avoidance. Although no correlations were statistically significant, the direction of the correlations yielded interesting indications and a larger study population may show a more significant trend. The correlation between age and anxiety in the patients was – 0. 12 ($p = 0.6686$), and – 0.24 ($p = 0.3785$) for avoidance. In the control group the correlation between age and anxiety was – 0.46 ($p = 0.0952$) and – 0.25 ($p = 0.3867$) for avoidance. Although the following speculation is not really warranted by the results, it is tempting to argue along the following lines. Firstly, both anxiety and avoidance is negatively related (although non-significant) to age, which means that the patients' as well as the controls' attachment styles seem to become more secure over time. Secondly, in the control group, the r-value (correlation) between age and anxiety was almost twice the r-value for the patient group, signifying that although patient anxiety also decreases with advancing age, the healthy subjects seem to be twice as secure as far as anxiety is concerned as they age. This leads to the speculation that in the fibromyalgia study group, there is resistance to change (becoming more secure in adult relationships), and that attachment behaviour is more likely to stay the same through their lifecycle. Insecurely attached individuals tend to have long-lasting, less complex autoregulatory modes because of underdeveloped subcortical-limbic connections (51). For the purpose of a larger follow-up study it can therefore be hypothesised that, because of the more primitive strategies for survival, these patients lack the ability to incorporate new, positive experiences into their working model of attachment in order to become more secure in romantic relationships as healthy individuals are able to do. However, research is needed on the proposed rigid nature of fibromyalgia patients' attachment styles in comparison to controls. A much larger, longitudinal study might yield interesting results.

In summary, it can be said that the attachment style that developed during childhood is likely to manifest in adult relationships. In this study, the majority of patients were shown to be insecurely attached with higher anxiety and avoidance scores than observed in the control group. According to Bowlby's theory, secure attachment is an "inner resource" that may help the individual to cope successfully with life adversities (55). These individuals deal with distress by acknowledging it, endorsing constructive actions, and turning to others for emotional and instrumental support (56). Without this "secure base", anxious individuals tend to deal with stressful events by relying on passive, ruminative, emotion-focused strategies (56). An anxious attachment style could therefore be associated with the high emotionality of the patients under stress, as indicated by the adjective pairs of the HBDI (refer to Section 7, p. 5.29). Avoidant individuals, on the other hand, might deal with distress by relying on distancing withdrawal strategies (56). The exaggerated activity of the parasympathetic nervous system during stress in this patient group (Section 6, p. 5.19) could have a relationship with the tendency of avoidant individuals to withdraw from stressful situations. The higher incidence of adverse traumatic events during the patients' early lives might be a contributing factor in the development of the insecure attachment styles of the patients.

B. CORRELATIONS

The question to be asked is whether a specific psychoneurological profile could be discerned in the limited group of fibromyalgia patients investigated in this study. This question is answered by reviewing the results discussed in Section A of this chapter in the light of correlations (Pearson coefficients) and predictive relationships (model R-square) calculated through regression analysis (Figure 1). When interpreting these associations, it is to be remembered that the independent variables are possible predictors of fibromyalgia disease status. The dependent variables represent the descriptors of fibromyalgia disease status. When a specific independent variable is the only significant predictor of a dependent variable, their relationship is expressed in model R-squares (reported as r^2 or a percentage). When there is more than one significant predictor, the relationship with the dependent variable is expressed as partial R-squares (reported as r^2 or a percentage). The relationships within the independent variable group and within the dependent variable group were calculated as correlations (only significant r-values are cited).

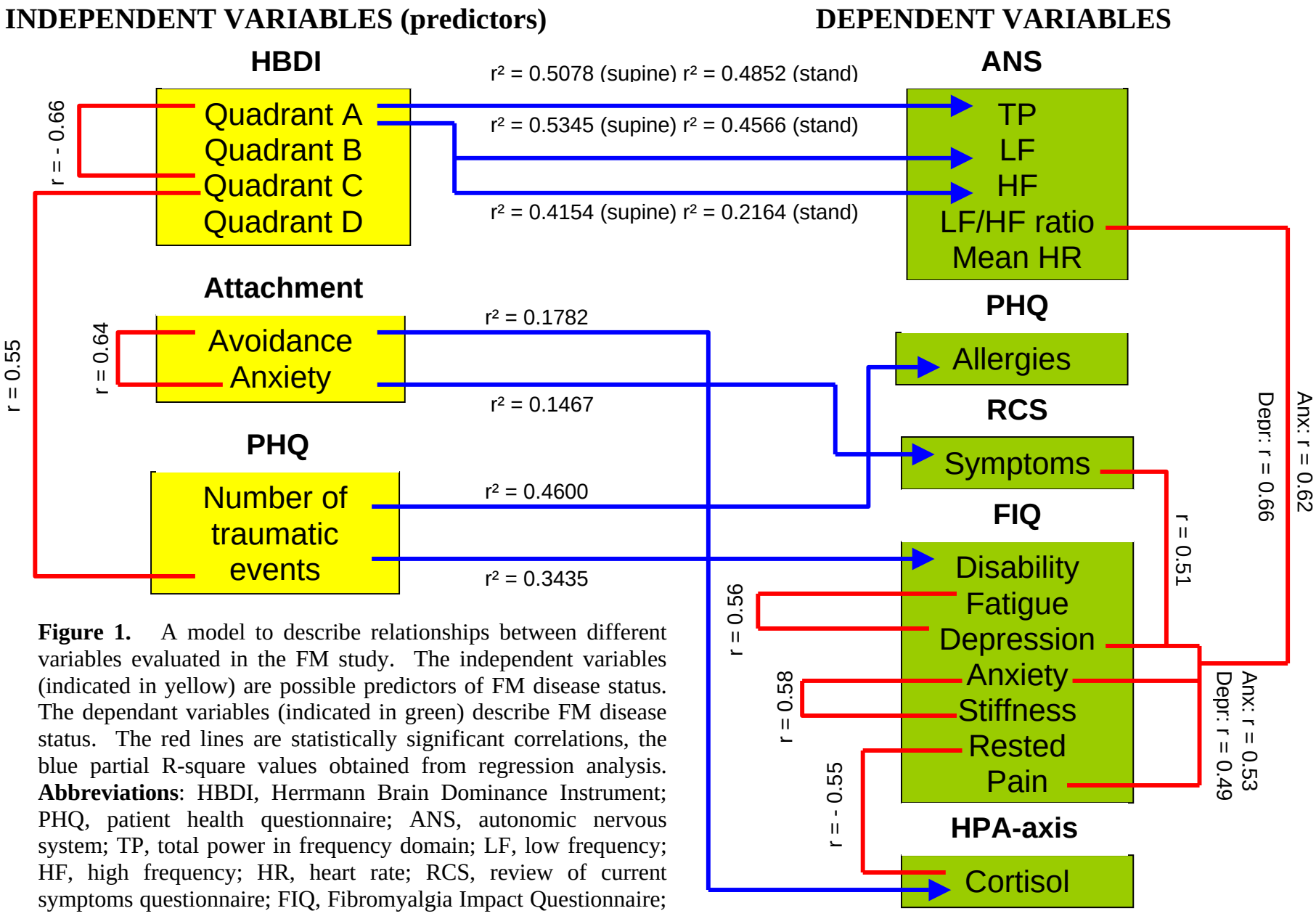

Figure 1. A model to describe relationships between different variables evaluated in the FM study. The independent variables (indicated in yellow) are possible predictors of FM disease status. The dependant variables (indicated in green) describe FM disease status. The red lines are statistically significant correlations, the blue partial R-square values obtained from regression analysis. **Abbreviations**: HBDI, Herrmann Brain Dominance Instrument; PHQ, patient health questionnaire; ANS, autonomic nervous system; TP, total power in frequency domain; LF, low frequency; HF, high frequency; HR, heart rate; RCS, review of current symptoms questionnaire; FIQ, Fibromyalgia Impact Questionnaire; HPA-axis, hypothalamus-pituitary-adrenal axis.

There can be no doubt that the patient group fully met the diagnostic criteria for fibromyalgia (set out by the American College of Rheumatology) and that their reported pain and physical discomfort levels (as seen from the FIQ) were significantly higher than normal (<0.0001). The patients also presented with a significantly higher number of symptoms (<0.0001). Regression analysis showed anxiety to be the best predictive factor in the number of symptoms a patient developed (model R-square = 14.67%). As would be expected, anxiety and depressive symptoms correlated positively with their degree of pain ($r = 0.53$, $p = 0.0429$ and $r = 0.49$, $p = 0.0607$ respectively). Anxiety also correlated with muscle stiffness ($r = 0.58$, $p = 0.0240$), confirming the 'pain-anxiety-muscle tension hypothesis' (discussed in Chapter 1, p.1.8) which states that 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. Depression had a positive correlation with the total number of symptoms the patients presented with ($r = 0.51$, $p = 0.0507$). It was also seen that most (87.5%) of the patients met the diagnostic requirements for chronic fatigue syndrome. In this study, fatigue did not correlate significantly with the degree of pain experienced by the patient group, though ($r = 0.37$, $p = 0.1744$). Nevertheless, fatigue did seem to have a relatively strong relationship with depression ($r = 0.56$, $p = 0.0312$).

When attachment styles were considered, the majority of patients showed insecure attachment styles. The two dimensions of attachment, i.e. anxiety and avoidance, had a strong positive correlation ($r = 0.64$, $p = 0.0099$), indicating that a high score in the one dimension is usually associated with a high score in the other. In contrast to the control group, the older portion of the patients did not seem to be any more secure than the younger group, illustrating the inflexible nature of their attachment styles. As attachment style is considered dependent on early life experiences, especially the interaction with primary caregivers, it was considered useful to evaluate both experimental groups for the prevalence of traumatic events during childhood. Of interest is the fact that the perceived or rather reported prevalence of significant adverse events in the patients' adult lives were also significantly higher (than that of the control group) and may show these events as contributing factors to the development of their symptoms. Another point of interest is that according to the partial R-square calculated through regression analysis, the number of adverse events that occurred throughout the individual's lifetime accounts for 34.35% of fibromyalgia impairment and 46.0% of the number of allergies the individual suffer from.

According to the HBDI results, the majority of patients exhibit thinking patterns strongly influenced by the right limbic brain structures, a tendency which seems to be exacerbated under stress. The strong emotionality of their preferred way of thinking correlated significantly with the number of adverse events ($r = 0.55$, $p = 0.0351$). The model R-square indicated that the preference for left cerebral thinking predicts 50.78% of the of heart rate variability at rest and 48.52% during physical stress. It also accounted for 53.45% of the sympathetic activity during rest and 45.66% of the sympathetic activity during physical stress. The partial R-square for the relationship between vagal activity during rest and analytical thinking patterns was 0.4154. The implication is that their avoidance of logical, rational thinking accounts (at least in part) for the overall lowered heart rate variability observed in the patient group.

Some deviations from the norm were noted in their neuroendocrine profile. Firstly, the cortisol levels were significantly higher than normal ($p = 0.0003$). 17.82% of the cortisol level seems to be predicted by attachment-related avoidance ($r^2 = 0.1782$). The elevated cortisol levels in the patient group were negatively correlated ($r = - 0.55$, $p = 0.0354$) with how rested the patients felt following a night's sleep. In other words, the higher the cortisol level, the less the patients could maintain a full night's sleep, and the less they felt rested in the morning. What is of great importance is the fact that the heart rate variability of these patients, which is a reflection of the autonomic nervous system function, was significantly lower than normal ($p = 0.0437$). Decreased heart rate variability during rest is generally seen as an indication of physical and psychological illness, which confirms that fibromyalgia disease state is accompanied by psychological and physiological abnormalities. The patients' autonomic nervous systems were also reluctant to respond to both physical and psychological stress. In the standing position, patients seemed to have lower sympathetic and higher parasympathetic activity. With regard to sympathetic-parasympathetic balance, they exhibited a weakened shift towards sympathetic dominance upon physical stress. The autonomic balance of the patients correlated with depression ($r = 0.66$, $p = 0.0079$) and anxiety ($r = 0.62$, $p = 0.0130$) as determined by the FIQ.

C. PSYCHONEUROLOGICAL PROFILE OF FIBROMYALGIA PATIENTS ACCORDING TO RESULTS FROM THIS STUDY

It can be said that the patient group in this study were characterised by a high prevalence of adverse events, insecure attachment styles, thinking styles marked by high emotionality in the absence of rationality, multiple somatic symptoms (apart from chronic pain), and altered stress-axes activity reflected in low heart rate variability, poor autonomic responses to acute stressors and elevated basal cortisol levels. In most cases, these results differed significantly from the age- and sex-matched control group. Therefore it can be concluded with confidence that this specific group of fibromyalgia patients have a distinct psychoneurological profile.

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CHAPTER 6
CONCLUSIONS

It can be said that the results found in this study for individual symptoms of fibromyalgia largely conform to that of other published findings. Although early fibromyalgia onset (such as in late teens) is known to occur, and some surveys have shown cases where fibromyalgia has first been diagnosed in patients in their seventies, it would seem fair to describe fibromyalgia as a disease which predominates in middle age (40-49 yrs of age). Although the present study is too small to make any assumptions to this effect, and the patients' ages were largely determined by availability through a fibromyalgia clinic, the mean age of the study group is in agreement with the idea of fibromyalgia as a disease of middle age. It is generally known that a strong female predominance exists in fibromyalgia and that the symptoms of male fibromyalgia sufferers, in general, do not have a good fit with the typical profile generally associated with fibromyalgia. This is supported by the results of this study where only two men were available with one of them exhibiting a completely atypical psychoneurological profile. As would be expected, many of the patients were unable to hold down full time work. In virtually all patients, co-morbidity was found between fibromyalgia and other syndromes.

The majority of fibromyalgia sufferers in this study perceive their lives to be riddled by adverse events and some associate traumatic events with the onset of their disease. High frequency of reported traumatic events coincides with a high prevalence of allergies. Stress vulnerability appear to be high and most individuals claim to be particularly sensitive to a wide range of environmental factors. These factors were alleged to either worsen or ameliorate their fibromyalgia symptoms, but no pattern could be distinguished as to the specific effects of individual factors on fibromyalgia symptoms. Depression and anxiety formed part of the overall profile of the fibromyalgia sufferers and correlated with the severity of the fibromyalgia symptoms.

The functioning of both major stress axes would appear to be abnormal, with high cortisol levels and an inability to respond with the appropriate autonomic nervous system stress reaction to either orthostatic or emotional stress. Heart rate variability, which can be suppressed in the case of either physical or serious psychological disorders, was

significantly lower than normal, but the use of antidepressants could have contributed to this. Nevertheless, whether lower heart rate variability resulted from physical disability, psychological factors, medication, or a combination of these factors, it is present, and in turn has negative implications for the physical well-being of the patients.

The so-called right-brain thinking is the style preferred by the majority of patients and it would appear that most of them prefer emotion-based coping mechanisms and emotion-based decision taking. Stress causes a further shift towards emotion-based thinking in these patients. Almost all fibromyalgia patients in this study display insecure attachment styles, a fact that is compatible with their perception of early lives riddled with adverse events, and perhaps with a strongly emotion-influenced, rather than logical/analytical preferred way of thinking.

In summary it can be said that this work presents a psychoneurological profile of the typical fibromyalgia patient – a preliminary profile that should be further investigated and refined on larger study groups. In addition, it provides pointers for further study. For example, correlations between early experiences, adverse incidents and the psychoneurological profile derived from this study give some indications of possible causes-and-effects but should at this stage perhaps only be seen as indicators for further studies on larger population groups. It can, for instance, be speculated whether the natural emotion-based style of thinking predispose one to the development of fibromyalgia or whether early life experiences with the development of insecure attachment predispose one to both emotion-based thinking and the development of fibromyalgia. Pointers for further research can also be found in the model of probable contributors to specific aspects of the syndrome status (dependent variables versus independent variables). Another question derived from this work that may be of interest to study, is whether fibromyalgia patients have a lowered ability than the general population to grow into secure attachment behaviour.

In view of the psychological influences on heart rate variability, autonomic function and HPA-axis functioning on the one hand, and the influence of these factors on pain sensitivity and general well-being on the other, it is tempting to speculate that psychotherapy aimed at adjusting coping mechanisms, and improving attachment behaviour, could perhaps have a positive influence on the well-being of fibromylagia sufferers.