Preface and acknowledgement

This master's thesis is the result of a collaboration between the Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital in Trondheim. Our project, supervised by Stig Arvid Hollup, is part of a larger fibromyalgia project supervised by Egil Fors.

Fibromyalgia is a condition highly debilitating for the individual and highly misunderstood by the public. The labelling of the illness as psychological is degrading and cause despair among the individuals afflicted. The diagnosis is controversial due to the lack of objective measures of the symptoms. As there are no objective measures, and hence no effective treatments for fibromyalgia, the diagnosis entails a life in suffering. This leads to economic, social and psychological problems. Adding to the suffering is the classification by the public of fibromyalgia as a low status illness. While men get heart attacks, women get fibromyalgia.

To us, the motivation behind writing this thesis lay in refuting the current understanding of fibromyalgia as merely a psychological, low status diagnosis. It is time for a change, and we believe that this thesis is a contribution to this belated change by investigating a possible underlying cause. An objective measure of the illness is sorely needed to improve the understanding of the illness itself, the treatment options available and the status of the illness.

After completing this project, there are 20 individuals we would like to thank, and they are the fibromyalgia patients contributing to this project with both their time and their effort. We are sincerely grateful.

Abstract

Fibromyalgia is a highly disabling condition that causes widespread muscle pain and fatigue. Core symptoms are often accompanied by poor sleep, memory deficits and depressive symptoms. The unknown aetiology of fibromyalgia makes it difficult to diagnose and give proper treatment. The extensive overlap with other syndromes characterized as unexplained points toward a possible common underlying mechanism, which has been suggested to be central sensitization. A possible sensitization of the central nervous system should be reflected in the neural activity of the brain. In this study, this was assessed with qEEG and ERPs in a VCPT. The aim of the study was twofold. The first objective was to investigate whether fibromyalgia patients could be differentiated from chronic pain and chronic fatigue patients based on ERPs. The second objective of this study was investigating whether Slow Cortical Potentials neurofeedback is effective in normalizing ERPs in fibromyalgia patients and whether it can lead to symptom relief. A MANOVA analysis showed significant differences between the three patient groups, and a discriminant analysis revealed two functions separating the groups, in combination. The two functions may represent two core symptoms of the illnesses; pain and fatigue. Multiple t-test revealed three significant improvements of ERPs due to neurofeedback. Limitations and interpretations of results are discussed.

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Chapter 1: Introduction

Fibromyalgia

Fibromyalgia is an illness characterized by chronic, widespread, unexplained pain without pathology or disease. The most common coexisting symptoms of fibromyalgia are fatigue, impaired cognition and sleep disturbances. In addition, patients can suffer from mood disorders (depression, anxiety), restless leg syndrome (RLS) (30%), chronic headache (50-60%), stiffness and leg cramps, dysesthesias (65%), poor balance, dizziness and vertigo, hypersensitivity to noise, odours, light, chemicals including medication, extreme heat and/or cold, irritable bowl and bladder, temporomandibular joint syndrome (TMJ) and exhaustion post exertion (Sumpton & Moulin, 2013). Even though the diagnosis is relatively new, fibromyalgia-like symptoms have been reported since the 1800s, then by the name ”neurasthenia” (Sumpton & Moulin, 2013). In 1904 the syndrome was renamed ”fibrositis”, indicating an infection. After discovering that the aetiology of the illness may lay in the central nervous system, fibromyalgia syndrome got it its current name (P. Mease, 2005).

Diagnositc criteria

In 1990, the American College of Rheumatology (ACR) developed diagnostic criteria for fibromyalgia. The criteria demand that the pain is widespread and long lasting (for more than three months), affecting both sides of the body, above and below the waist. The pain is measured with 4 kg pressure on something called tender points. To be diagnosed with fibromyalgia, pain must be present on at least 11 of the 18 tender points (Marcus, 2009). Before diagnosing a patient with fibromyalgia, several other diseases must be eliminated: ankylosing spondylitis, diabetes, hepatitis C, HIV/AIDS, hyperparathyroidism, hypothyroidism, Lyme disease, metastatic cancer, multiple rheumatica, rheumatoid arthritis, scleroderma, Sjögren´s syndrome and systemic lupus erythematous.

As the ACR 1990 criteria was primarily developed for researchers and not suited for clinical practise, it was later revised in 2010. The 1990 criteria focused on pain and missed 46% of the patient population (Boomershine & Crofford, 2009). The

ACR 2010 classification system downgraded the examination of tender points and in addition included assessment of fatigue, cognition and other somatic symptoms. According to Wolfe (2010), the 2010 criteria are not intended to replace the 1990 criteria. The criteria is meant to be used as a supplement in giving a diagnosis in a general practice setting where tender point examination is not routinely done (Wolfe et al., 2010). The 2010 classification criteria use a Widespread Pain Index (WPI) and a symptom severity score (SS-Score). The diagnosis of fibromyalgia is, according to the 2010 criteria, not given by a physical examination. It is diagnosis is given using information provided about the patient and is therefore suited for primary health care. The new diagnostic criteria correctly classifies the majority of cases, and does not solely focus on pain, but includes fatigue, sleep disturbance and other symptoms. Additionally, the criteria enables the physician to diagnose the patient on a continuum, and not solely as an "all or nothing" phenomenon. The 2010 criteria can find concomitant depression and detect fibromyalgia in patients with other diseases (Moyano, Kilstein, & de Miguel, 2014).

Demographics and comorbidity

Fibromyalgia syndrome (FMS) affects 2-4%/0.5-5% of the western population (Fitzcharles & Yunus, 2011; Moyano et al., 2014). Fibromyalgia mainly affects women (Katz, Mamyrova, Guzhva, & Furmark, 2010; Wolfe et al., 2010).

Aggarwal, McBeth, Zakrzewska, Lunt, and Macfarlane (2006) studied the comorbidity between chronic syndromes such as fibromyalgia, chronic fatigue, and chronic pain in 2299 subjects. The results showed that 27% subjects reported one or more symptoms. There was also a greater prevalence of subjects having multiple syndromes than expected by chance. The chronic syndromes shared several features; predominance in women, higher levels of health related anxiety, confirmation-seeking behaviour, and negative life events together with other somatic symptoms. However, it should be noted that some of the factors might be a consequence rather than a risk factor for developing a syndrome. The literature does not clearly indicate whether the syndromes are discrete separate units or if they comprise a continuum of syndromes with shared risk factors (Aggarwal et al., 2006). The symptom overlap and the prevalent comorbidity between the syndromes strengthen the assumption that there are both a common mechanism and a hereditary component (Woolf, 2011). The age distribution between the syndromes is a point of interest. Aggarwal et al. (2006) found

that the prevalence of chronic pain syndromes appears to increase with age, whilst the prevalence of CFS decreases with age. It is questionable whether some syndromes are risk factors for others.

Treatment: What are the options today and how to they work?

Pregabalin, duloxetine, and milnacipran have been approved for fibromyalgia patients in some countries (Boomershine & Crofford, 2009). Pregabalin is a gamma aminobutyric acid (GABA) inhibitor primarily used to reduce neuropathic pain by modulating calcium influx in nerve terminals. Duloxetine and milnacapran are serotonine-norepenephrine reuptake inhibitors (SNRI) used in the treatment of fibromyalgia, generalized anxiety disorder and depression (Arnold, 2006). In addition to medication, a tailored exercise program, water therapy, physiotherapy, relaxation, cognitive behavioural training, and psychological support can relieve symptoms (Häuser, Thieme, & Turk, 2010). Due to the heterogeneity of fibromyalgia patients and unknown cause of the illness, there is no treatment that will help all; each patient needs a tailored program. Most importantly, there is no existing treatment that relieves all symptoms; the treatments available today only reduce them. Research focusing on the heterogeneity of the patients has indicated that there are subgroups of fibromyalgia patients. Further research differentiating the patients might help individualize the treatment, especially if one underlying cause is not present. If, however, an underlying cause is identified, this might lead to a general treatment that reduces symptoms for all patients.

Chronic pain cannot solely be explained by sensory processing, and the pain's subjective nature makes it difficult to treat (Loeser, 2000; de Vries et al, 2013). When treating pain, self-report from the patient should be supplied with objective measures to secure correct diagnosis and treatment. Currently, many chronic pain conditions do not have objective measures (bio-markers) to accompany self-report from the patients, this includes fibromyalgia syndrome. Together with wide diagnostic criteria, this constitutes the core problem surrounding diagnosing and treating chronic pain conditions.

Theories about cause and effect – clinical findings and causes

After the diagnostic criteria was made by the American College of Rheumatology in 1990, a vast variation of research has been conducted. The clinical findings are many and diverse like the patient group, but there seems to be a consensus in the field that genetic predisposition, neurophysiological changes, and abnormal stress responses may explain and consequently be causes of the syndrome (Fitzcharles & Yunus, 2011).

Genetic predisposition

Studies looking at first-degree relatives of fibromyalgia patients have shown that fibromyalgia and fibromyalgia symptoms run in families. This proposes a genetic influence in the development of fibromyalgia (Arnold et al., 2004). According to Buskila (2007) polymorphisms of genes in serotonergic, dopaminergic and catecholaminergic systems might play a role in fibromyalgia and related conditions (Buskila, 2007). Genetic factors may explain a significant amount of the variance in the perception of pain, sensitivity to painful stimuli and development of chronic pain (Mogil, 1999). There is in particular one genetic polymorphism linked to fibromyalgia called catecholamine o-methyltransferase (COMT). COMT Val158Met polymorphism influences the subjective experience of pain (Zubieta et al., 2003). The gene is thought to affect descending inhibitory pain pathways by the deactivating biogenic amines (Williams & Clauw, 2009). Particularly the COMT Met/Met genotype is associated with fibromyalgia. The genotype is possibly also linked to emotional factors of the disorder (Jules Desmeules et al., 2014). Diatchenko et al (2005) identified three haplotypes of the COMT gene that influence sensitivity to experimental pain (Diatchenko et al., 2005). Low pain sensitivity (LPS), average pain sensitivity (APS) and high pain sensitivity (HPS). The presence of a single LPS haplotype increases the risk of developing temporomandibular joint disorder (TJD). In addition to COMT, MicroRNA studies show promising results (Ablin & Buskila, 2015). MicroRNA are modulators of gene expression and may play a role in the development and stress response of the central nervous system (CNS). According to Bai an colleagues (Bai, Ren, & Dubner, 2015) epigenetic regulation may play a role in the transition from acute pain to chronic pain.

Neurophysiological changes

The efferent pathway responsible for downregulating pain is named the diffuse noxious inhibitory control (DNIC). Research clearly indicate that patients suffering from fibromyalgia, have an abnormally functioning DNIC (Sumpton & Moulin, 2013). Fibromyalgia patients show increased substance P and glutamate levels in the cerebrospinal fluid (CSF) (Evengard et al., 1998; Harris et al., 2009). Substance P is a neuromodulator causing sensitization of excitatory neurotransmitters involved in nociception. Glutamate is an excitatory neurotransmitter (Sumpton & Moulin, 2013). A lower blood level of L-tryptophan (serotonin precursor) and serotonin is also registered (Clauw & Crofford, 2003). This denotes a defective synthesis and metabolism of the neurotransmitters, which may contribute to the disorder.

As well as an imbalance in levels of neurotransmitters in CSF, there has also been registered elevated levels of cytokines and tumour necrosis factor α (TNF α)(Salemi et al., 2003). Increased measures of interleukin-8 (IL-8), a cytokine, in CSF in fibromyalgia patients is an indication of central inflammation (Kadetoff, Lampa, Westman, Andersson, & Kosek, 2012). TNF α is also a cytokine involved in inflammation. Elevated levels of cytokines in the CSF indicate inflammation of the CNS because cytokines cannot enter the CSF because of the blood brain barrier.

Mease (2005) reported reduced levels of insulin-like growth factor-1 (IGF-1) in fibromyalgia patients (P. Mease, 2005). IGF-1 is a mediator of growth hormone (GH), a hormone involved in muscle repair. Low levels of IGF-1, and subsequent low levels of GH, is associated with low energy levels, dysphoria, impaired cognition, poor health, reduced exercise capacity, muscle weakness and cold intolerance (R. Cuneo, Salomon, McGauley, & Sönksen, 1992; R. C. Cuneo, Salomon, Wiles, Hesp, & Sonksen, 1991; Florini, 1987; McGauley, Cuneo, Salomon, & Sönksen, 1990; Rutherford, Beshyah, Schott, Watkins, & Johnston, 1995; Salomon, Cuneo, Hesp, & Sönksen, 1989; Wallymahmed, Baker, Humphris, Dewey, & MacFarlane, 1996).

Hormones

Fibromyalgia, like depression, is overrepresented in the female population. The reason for this is unclear. Sex hormones may play a role in gender differences because it modulates pain perception and response to treatment. Neonatal exposure to testosterone is believed to reduce pain sensitivity in male patients (Marcus, 2009).

Estrogen also modulates pain sensitivity in adults, and cycling estradiol is linked to cyclic changes in pain response. There may also exist gender differences in the pain threshold. When checking tender points on healthy men and women, there Marcus (2009) found discrepancy between the sexes. Women reported higher levels of pain than men did. With this natural difference in pain threshold, it raises the question that men might not be adequately diagnosed (at least with the ACR 1990 classification system) (Marcus, 2009).

Abnormal stress response. An abnormal stress reaction is considered an important pathophysiological mechanism in the disorder (Crofford et al., 2004). The hypothalamic-pituitary-adrenal (HPA) axis functions abnormally in fibromyalgia patients, who showing a decreased cortisol response, and increased levels of adrenocorticosterid hormone (Parker, Wessely, & Cleare, 2001). One possible explanation for the alterations in the HPA axis is prenatal exposure to maternal psychosocial stress. Entringer et al (2009) compared healthy young adults whose mothers experienced severe stress during pregnancy (major negative life events such as the death of a close relative) with an age-matched control group while performing the Trier Social Stress Test (TSST) (Entringer, Kumsta, Hellhammer, Wadhwa, & Wüst, 2009). The group exposed to prenatal stress showed lower cortisol levels before the test than the control group, and higher increase in cortisol as a response to the TSST, proving that prenatal stress exposure can alter HPA axis regulation. Thieme and colleagues (2015) identified four subgroups of fibromyalgia based on stress response indicating heterogeneity within the patient group (Thieme, Turk, Gracely, Maixner, & Flor, 2015).

These findings demonstrate that fibromyalgia affect patients in a variety of ways. However, they do not point in a specific direction or give rise to an assumption of a single cause. Although there have been various theories, there has been very little consensus within the copious volume of literature.

A model that unifies genetic predisposition, neurophysiological changes and abnormal stress responses is the biopsychosocial model of sickness (Engel, 1989). The model states that diseases have a biological contribution, as well as a psychological and a social contribution. The biological factors of fibromyalgia consist of the genetic predisposition and neurophysiological changes that decide to some extent the way pain is processed, how the body responds to stress and the chemical

balance in the brain to mention some. The psychological contribution to the syndrome can be the effect of an altered HPA axis and the depression and anxiety that follow chronic unexplained pain. The social factors can be negative life events that trigger the disease or the condescending looks from sceptical individuals who question the diagnosis and illness. Another social aspect is the diagnostic overrepresentation of fibromyalgia in women. Social factors may also be an indicator as to why there is a diagnostic overrepresentation of fibromyalgia in women.

Measures of fibromyalgia

As there are no known bio-markers for fibromyalgia, clinicians must rely on the patient's self-report to assess the severity of the illness. There are several questionnaires rating fibromyalgia symptoms. The Medical Outcome Study (MOS), the Brief Pain Inventory (BPI), and the Multidimensional Fatigue Inventory (MFI-20) are all applicable, but the Fibromyalgia Impact Questionnaire (FIQ) is the only questionnaire made specifically for fibromyalgia syndrome (Williams & Arnold, 2011). The FIQ measures the impact the condition has had on an individual during the last week on a scale from 0 to 100. An average fibromyalgia patient scores 50 and severely afflicted score 70 and above. The questionnaire has been extensively used to measure therapeutic efficacy, and is specifically designed to capture the total spectrum of fibromyalgia related symptoms, not only pain (Bennett, 2005). The diagnostic criteria focus on the development of the illness and location and severity of pain. This separates it from the FIQ, which takes into account the fluctuations of the illness, not only the general impact. The 1991 version measures function (question 1), overall impact (question 2 and 3) and symptoms (question 4-10) over the previous week. Since the FIQ was first published in 1991, it has been modified twice (1997 and 2002) and revised (FIQR, 2009) (Williams & Arnold, 2011). The questionnaire has been criticized for having a gender bias favouring women since it focus on stereotypically female activities like cleaning, but the FIQR 2009 made alterations reducing the bias. In the revised edition, question one concerning physical function was altered to better represent the large muscle groups in both the upper and lower extremities. The overall impact section was completely revised to involve the overall impact on functionality and perception of reduced functionality due to fibromyalgia. Four items were added to the symptom part now involving tenderness, memory, balance and environmental sensitivity.

Pain

Chronic pain

Pain is divided into three groups: acute, lasting/persistent and chronic. Acute pain is necessary to survive because it helps us avoid harmful stimuli. Acute pain is stimuli dependent, which means that painful sensations experienced stops when the stimuli disappears. This is not the case with chronic pain. In experiencing chronic pain, the pain experienced does not stop when the stimuli disappears. Arguably, this makes chronic pain useless for the individuals who experience it, as pain loses its protective function when it becomes chronic.

Neural processing of pain

To understand pain, it is necessary to look at the neural processes that cause it. In the skin, the tissue under the skin, in the joints and in the muscles we have specialized receptors, called nociceptors. The nociceptors process information about pain (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2014). Activation of these nociceptors, this results in nociceptive pain or nociception. According to Kandel (2014), there are three different types of nociceptors. The three different nociceptors have different qualities. Thermal nociceptors are activated by extreme cold and heat, and are the periphery ending of myelinated Aδ-axons. Mechanic nociceptors are activated by strong pressure against the skin and are also the periphery ending of Aδ-axons. Polymodal nociceptors can be activated by mechanic, chemic and thermal stimuli, but these receptors exist only in the ending of unmyelinated c-axons. This makes the information travel slower. A sudden experience of pain is caused by Aδ-fibre activation, and the lingering discomfort is caused by c-fibre activation. In addition to these receptor types, we have silent nociceptors that are activated by inflammation and chemicals.

Unexplained chronic pain

Chronic pain is divided into explained and unexplained chronic pain. Unexplained chronic pain is a long lasting pain without function and known cause. It differs from neuropathic pain, which can be attributed to damage in the peripheral and central nervous system (Kandel et al., 2014). Many chronic pain conditions are caused by neuropathic pain, but they are often to some extent explained. Unexplained chronic pain also differs from acute pain as acute pain is dependent upon a sensory component, while motivational and evaluative systems play a larger role in chronic unexplained pain (Bourke, Langford, & White, 2015).

Pain matrix

The pain matrix (PM) consists of more than just nociceptively activated brain regions. The pain matrix is context dependent and consists of emotional processing of pain and attention. The perception of pain is not only a sensory experience, it is also emotional and subjective (Kandel, 2012). Many factors affect pain perception. It is not a direct expression of a sensory experience, but the result of complicated processing in the brain.

The PM consists of the brain areas that are activated by painful stimuli, and include sensory, cognitive and affective dimensions of pain (Garcia-Larrea & Peyron). According to Koberda (2014), the PM consists of the anterior cingulate cortex, the insula, the parietal operculum, including second somatosensory cortex, and the thalamus (Koberda, 2014). Isnard et al. (2011) concluded, after studying a man with epileptic seizures centred in the insula, that the insula plays an important role in triggering the PM and the subsequent subjective experience of pain (Isnard, Magnin, Jung, Mauguière, & Garcia-Larrea, 2011). There is currently no consensus about which areas the PM consists of. Some scientists view the PM as a bio-marker for pain, while others view it as a non-specific system for threat detection, also called a salience detection system. Legrain et al. (2011) belong to the latter group and have three reasons for their belief in the salience detection system. They claim that the definition of the pain matrix as a matrix that represents intensity and unpleasantness of nociceptive stimuli is incorrect. Rather, they believe that because intensity of pain is not necessarily associated with the magnitude of response in the PM (i), the context strongly influences the response of the PM (ii), and they argue that stimuli other than

pain also can elicit neural activation similar to that of the PM (iii). Due to this, Legrain et al. propose the alternative view that this network is a system involved in detecting, orienting attention towards, and reacting to the occurrence of salient sensory events. The information that should be emphasized in this alternative view, is that they propose the idea that the sensory channel previously thought to activate the PM, nociception, might in fact not be the only way to activate this system. Garcia-Larrea and Peyron (2013) stress that the PM can be activated with and without painful stimuli. Anterior cingulate cortex, anterior insula and prefrontal and posterior parietal areas show increased activity in experiments not related to pain, but related to emotion and cognition (Garcia-Larrea & Peyron, 2013).

Legrain et al. (2011) redefines the PM as a system that alerts the body of potential danger, which consequently involve calculating an appropriate action to the perceived danger. When defining the PM as a salience detection system, pain and other potentially dangerous stimuli is linked to the body's ability to detect and orient attention to events in the sensory environment that may or may not be threatening to the individual. The hypothesis about the salience detection system suggests that patients suffering from chronic pain syndromes have altered attentional mechanisms that can lead to bias or amplification of pain perception. Legrain et al. (2011) interprets this over-responsiveness as a result of an increased attentional sensitivity to stimuli in the surroundings. It is possible to keep nociceptive stimuli from capturing attention. This is done by controlling the content of working memory with pain-unrelated information. The challenge with fibromyalgia patients is their over-attentiveness to threat sensations, making it impossible to keep body-related information out of the working memory (Legrain, Iannetti, Plaghki, & Mouraux, 2011).

One could argue that distracting patients with an irregular working attentional system could reduce pain experienced. However, research shows that that is not the case. Attempts to distract health anxious people resulted in greater affective pain and worry. Distraction was a better strategy for non-health anxious patients (Hadjistavropoulos, Hadjistavropoulos, & Quine, 2000). Only highly demanding tasks might distract the patient's attention away from the pain experienced. This is not a practical long-term solution.

Eccleston & Crombez (1999) made a model of the interruptive function of pain on attention (Eccleston & Crombez, 1999). They see chronic pain as chronic

interruption. Attention is seen as a filter of information where noise is ignored and important information is given access to further processing. They refer to capacity models of attention, which understand attention as a capacity that can be divided between tasks. When the amount of tasks exceeds the resource limit, behaviour and cognition is disrupted and flawed. Continuity of attention is necessary to complete tasks, but the organism must also be open to information from the surroundings. The latter leads to intrusion. They hypothesize that pain captures attention due to the superior goal of self-protection and the need to be aware of possible threats in the surroundings.

Attention – default mode network

Many fibromyalgia patients have long-term and working memory deficits (Glass, 2006). This cognitive dysfunction is often called "fibro-fog" and can be seen in association with attentive problems (Glass, 2008). Legrain et al. (2011) claim that chronic pain patients attentional system is not working properly. Other scientists have also made the connection between pain and attention, claiming that pain, and chronic pain in particular, affects attention.

Dynamic pain connectome

Kucyi and Davis (2015) take a closer look at the subjective perception of pain and explained it through the interaction between pain and attention. They propose that the connections between networks in the brain, called functional connectivity, that participate in the dynamic pain connectome (salience network, default mode network and antinociceptive system) are in constant, dynamic change. The salience network is known for its ability to trace to which extent external stimuli catch attention. The default mode network is the salience network's counterpart, and is activated when you do not think about anything specific, or something not related to the external world. This network is deactivated when an individual think about pain. The antinociceptive system is associated with pain modulation. Kucyi and Davis (2015) propose that individuals differ in their connectivity between networks, and that this is manifested in the structure and function of the individual brain networks. They see this difference in connectivity as the reason why people differ in their attention to painful stimuli, and consequently, how they experience and handle the pain. Functional connectivity

between periaqueductal grey (PAG) (a part of the antinociceptive system) and default mode network increases when an individual spontaneously focuses on something other than pain. This indicates that this connectivity induces the spontaneous fluctuation of attention when experiencing pain. The authors claim that the networks relevant for spontaneous fluctuation of attention is disturbed in individuals suffering from chronic pain.

Baliki et al. (2008) were the first to demonstrate that the functional connectivity in the DMN in chronic back pain (CBP) patients was disrupted (Baliki, Geha, Apkarian, & Chialvo, 2008). They claimed that this unbalance might lead to a plastic reorganization of the brain. They found a significant deactivation failure in medial prefrontal cortex (mPFC) during an attention task. Normally, the left intraparietal sulcus (LIPS) activates and the mPFC deactivates when performing attention tasks. CBP patients showed less deactivation than healthy subjects mainly in the mPFC, amygdala and posterior cingulate cortex (PCC). It was concluded that the brain of CBP patients does not process pain as normal persons and that this leads to cognitive and behavioural changes. This research enables the understanding of how pain can alter cognitive areas not related (directly) to pain.

Central sensitization

Sensitization and habituation

Habituation and sensitization are the simplest forms of learning in the nervous system, and are caused by repeated stimulation. Habituation is a decreased response as a result of non-harmful repeated stimulation, while sensitization is an increased responsiveness due to harmful repeated stimulation. Sensitization is central in pain perception. Both habituation and sensitization can occur in a limited time period, but the augmented or decreased response can become permanent with persistent stimulation. The permanent state of sensitization is assumed to have an impact in patients suffering unexplained, chronic pain, and is termed sensitization due to the lack of periphery input as a cause of pain.

Central sensitization and central sensitization syndromes

In the absence of inflammation or nerve damage, a chronic hypersensitivity to pain is believed to be the cause of different syndromes, depending on the tissue or

organs affected (Aggarwal et al., 2006; Kindler, Bennett, & Jones, 2011; Woolf, 2011). This is presumed to be a central amplification of pain perception, termed central sensitization. Irritable bowel syndrome (IBS), tension headache, temporomandibular disorders, complex regional pain syndrome, periodic limb movement during sleep, fibromyalgia, chronic fatigue syndrome and generalized chronic pain are among the syndromes speculated to share the mechanism of central sensitization (M. B. Yunus, 2007a). Central sensitization is a neuropsychological process assumed to explain both painful and non-painful stimuli in these disorders (Bourke et al., 2015; Kandel et al., 2014; Woolf, 2011; M. Yunus, 2013; M. B. Yunus, 2007a, 2007b, 2008).

Mechanisms of central sensitization

Pain modulation consists of two parallel processes, the facilitating (ascending) and the inhibitory (descending) system. A disturbance in these systems is believed to cause central sensitization, an increased activity in the facilitating system and in decreased activity in the inhibitory system (Meeus & Nijs, 2007). Reduced inhibition and augmented facilitation leads to a slow summation of stimulus, where stimuli with the same intensity become more painful (Bourke et al., 2015). Summation refers to the progressive increase in pain perception as a result of repeated stimulation. This is referred to as wind-up or temporal summation (Meeus & Nijs, 2007). The neural mechanism behind summation is the repeated stimulation of unmyelinated C-fibres in the dorsal horn in the spinal cord, which causes an increase in electrical discharges from second order neurons in the spinal cord.

In a sensitized state, non-painful stimuli may still activate nociceptive cells in the dorsal horn and cause allodynia, a perceived pain without any actual nociception. Allodynia does not entail constant pain. In the state of allodynia, periphery stimulation leads to a perceived pain, whether nociceptive or not (Kandel et al., 2014). The changing of nociceptor activity can also lead to an augmented response to painful stimuli, known as hyperalgesia. Hyperalgesia and allodynia are both common symptoms in chronic pain conditions, such as fibromyalgia.

Risk factors for central sensitization and measurement

There is often not a clear peripheral source to pain in the conditions considered to be caused by central sensitization (M. Yunus, 2013). The absence of painful input

in the periphery has led many physicians to believe the pain in conditions like fibromyalgia to be a manifestation of "something mental" (M. Yunus, 2013).

Previous research suggests a variety of contributing factors to the development and maintenance of central sensitization, such as genetics, sleep problems, infections, physical or psychological trauma, early childhood trauma, psychosocial stress, environmental irritants, disorders in autonomic nervous system, dysregulation of the HPA-axis (hypothalamic pituitary adrenal-axis), and probably also other unknown factors (Aggarwal et al., 2006; Kim & Chang, 2012; M. Yunus, 2013; M. B. Yunus, 2007a, 2008).

Central sensitization represents a possible biomarker for vulnerability to develop a condition without structural pathology, but the development of specific syndromes may be triggered by the individual's environment (Aggarwal et al., 2006; Kindler et al., 2011; Woolf, 2011; M. Yunus, 2013). For central sensitization to be a bio-marker, it necessarily needs to be measured. Currently there are no standardized methods or agreement on how to. However, Quantitative sensory testing (QST) and nociceptive flection reflex (NFR) are two recognized methods for measuring the extent of central sensitization. QST is performed in a pain laboratory and participants and subjected to different types of sensory stimuli in both a measurable and controlled manner (M. B. Yunus, 2007a). NFR is considered an objective measure of central sensitization (M. Yunus, 2013). Under NFR the electromyographic response in the biceps femoris is measured after direct electrical stimulation of the sural nerve (JA Desmeules et al., 2003). NFR are mediated by central neurons and is a test of central sensitization independent of patient response (M. Yunus, 2013).

Central sensitization in fibromyalgia

Studies have demonstrated sensitization of the central nervous system in both fibromyalgia and chronic fatigue syndrome (JA Desmeules et al., 2003; Kindler et al., 2011; Meeus & Nijs, 2007; Zhou, Fillingim, Riley, & Verne, 2010). Findings indicating central sensitization in fibromyalgia include spatial summation, secondary hyperalgesia and failure to activate endogenous inhibitory pain systems (JA Desmeules et al., 2003; Julien, Goffaux, Arsenault, & Marchand, 2005; Meeus & Nijs, 2007).

Julien et al. (2005) compared fibromyalgia patients with chronic lumbar pain patients, in addition to a healthy control group by lowering of the arm in 12 degrees

cold water. The control group and patients with lumbar pain reported a different pain sensation by lowering of the arm compared to lifting the arm out of the water, while the fibromyalgia patients did not report a significant difference between the conditions. This indicates a dysfunctional endogenous inhibitory pain system in fibromyalgia patients.

Findings in fibromyalgia patients show reduced pain threshold (Berglund, Harju, Kosek, & Lindblom, 2002) and an increased sensitivity outside tender points, abnormal wind-up and prolonged pain after discontinued painful input, expansion of receptive fields, sensitization of cognitive and emotional systems, abnormalities in cerebrospinal blood flow (rCBF), hyper activation of spinal cord, impaired perfusion in pain related brain structures, and higher levels of substance P (transmitter substance essential in pain pathways) in cerebrospinal fluid (Berglund et al., 2002; JA Desmeules et al., 2003; Kindler et al., 2011; Meeus & Nijs, 2007; M. Yunus, 2013; M. B. Yunus, 2007a, 2007b, 2008). An elevated level of substance P can lead to a reduced firing threshold for neurons in the spinal cord and an expansion of pain area (Kindler et al., 2011). These findings support a general hypothesis that fibromyalgia reflect a disorder affecting the modulation of pain sensitivity (Meeus & Nijs, 2007).

qEEG and Nevrofeedback

What is qEEG?

Brain imaging techniques are used to inspect brain structure or brain dynamics and function. One way to describe the differences between the different imaging techniques is to look at their relation to time. Both EEG (electro encephalography) and MEG (magneto encephalography) can identify neurophysiological responses that differ in timing, amplitude and spatial orientation. These methods are therefore time sensitive, measuring brain activity down to the millisecond. fMRI (functional magnet resonance imaging) and PET (positron emission tomography) on the other hand, are not as sensitive to time, and can only spot changes occurring over seconds. When responses to stimuli are the focus of an investigation, EEG and MEG are the only methods that can reveal the immediate response. While EEG and MEG measure neurophysiological responses that differ in timing, amplitude and spatial origin, fMRI and PET can be used to localize the dipoles that generate the EEG/MEG data. Another way to localize the neural basis of a signal, is the software LORETA (Evans

& Abarbanel, 1999). The neural basis of a signal in an EEG recording can be identified by LORETA by a triangulation of the signals.

What does EEG measure?

EEG measures electrochemical signalling between groups of neurons in the brain through electrodes placed on the scalp. More specifically, the method reveals pooled electrical activity (Tatum IV, 2014). Cortical pyramidal cells in deep layers of the cortex play a major role in generation of the EEG signal because of their unique orientation with long apical dendrites placed perpendicular to the surface (Kirschstein & Köhling, 2009). The dendrites terminate in specific and non-specific thalamic nuclei and distant cortical areas, where they form a myriad of excitatory and inhibitory afferents. Release of excitatory and inhibitory neurotransmitters (from the apical dendrites) activate specific postsynaptic receptors and generate excitatory and inhibitory postsynaptic potentials (IPSP/EPSP).

EEG records pooled activity made by hundreds of thousands of neurons in synchronous activity. The more synchronous the activity, the higher the amplitude of the wave form. The inhibitory and excitatory postsynaptic potentials, and not action potentials, are the source of the potentials. This is because IPSPs and EPSPs have a longer duration than an action potential and are therefore possible to record from the scalp. That is why postsynaptic potentials are responsible for the waveforms and not action potentials (Kropotov, 2010).

The number of electrodes placed on the scalp to measure electrical activity in the brain can vary. Each electrode is represented in the EEG output as a wave, and each wave reveals the electrical activity in that brain region. During an EEG recording it is possible to see different waveforms, eye blinks and perform a basic analysis of the data, but quantitative analysis is necessary to sum up the data and reveal details not visible to the naked.

qEEG is mathematical transformation of the EEG raw data. The transformation enables an easier interpretation of the data because it is compressed which makes it easier to get an overview. qEEG is a valuable tool because it is non-invasive and cost efficient and provides information about brain function during rest, stimulation and cognitive tasks (de Vries et al., 2013). Fibromyalgia syndrome is not a stable disorder, but a cyclic disorder demanding temporal precision, and qEEG outperforms other imaging techniques in the temporal domain (Jones, Huneke, Lloyd,

Brown, & Watson, 2012).

Brain waves

The brain exhibits cyclical electrical activity that can be measured in Hertz (Hz), which is defined as the number of waves per second (also called frequency). While the brain of a dead person would have an activity of zero Hz, the brain of a living person would range from above zero Hz up to about 30 Hz and higher. The frequency bands are called alpha (8-13 Hz), beta (beta 1: 13-20 Hz, beta 2: 20-30 Hz), theta (4-8 Hz) and delta (0-4 Hz) (Activity above 30 Hz is referred to as the gamma band) (Kropotov, 2010). Alpha rhythm indicates relaxed wakefulness and occurs most often when eyes are closed, beta rhythm indicates mental activity and attention and theta indicates drowsiness, while delta rhythm indicates deep sleep or pathological activity. In addition to measuring brain activity in Hz, one does also describe the amplitude (size of the waves, measured in mV), and latency (the timing of the waves). As the brain waves are of little importance in this project, because this investigation will focus on ERP's, brain waves will only be mentioned briefly.

The alpha rhythm is often the starting point of an EEG analysis because it is usually easily identified in the occipital part of the brain when the eyes are closed, but 25% of young adults do not exhibit this wave. The alpha rhythm is divided into three sub types (Kropotov, 2010). The alpha rhythm appears when the brain is relaxed or at rest, but not sleeping. This kind of alpha is supressed by visual information and is therefore only present when the eyes are closed. This suppression of neural activity is called desynchronization. When the eyes are closed it is referred to as synchronization because many neurons fire simultaneously. The second sub type is the mu rhythm demonstrated in the sensorimotor area, which occurs when the motor area is at rest. The third sub rhythm is the tau rhythm. It appears over the auditory cortex. It can be dampened by auditory stimuli, but the rhythm it is difficult to spot on the raw EEG.

The beta band is often found in frontal and central parts of the brain, but is possible to measure over the entire scalp. The beta frequency is divided in two: rolandic beta and frontal beta. Rolandic beta is localized in the sensorimotor area. And appears during spontaneous activity. Frontal beta is associated with attention, stimuli assessment and decision-making. The presence and location of beta depends upon stimuli, task and diagnosis.

Theta rhythm appears along the central/frontal midline when the brain is working with problem-solving, consolidation or retrieval of memories. The wave is only visible in 10-40% of the adult population. This is could be due to the source of the oscillation is placed too deep in the brain to be measured by electrodes on the scalp.

The delta wave is the slowest wave and characterizes deep sleep. In a wake brain, you would see beta activity and some alpha activity, but as you slip into the first stage of sleep the brain exhibits theta waves. The third and fourth stage of sleep is characterized by delta waves. It is possible to exhibit delta activity when you are not sleeping, but this is a sign of pathology.

Event Related Potentials

In studying how the electrical activity in the brain changes in response to specific stimuli and events, it is assumed that one can attain information about how the brain is functioning. The averaging of time-locked activity related to a specific event makes it possible to discern event related potentials (ERPs). ERPs are characterized as voltage fluctuations on the scalp that represent the change in the neuronal activity as a response to a specific stimulus (Blackwood & Muir, 1990; Landa, Krpoun, Kolarova, & Kasparek, 2014; Sur & Sinha, 2009). By recording ERPs in appropriate conditions and focusing on the electrophysiological signal time-locked to the stimulus event, it is possible to obtain a spatiotemporal picture on the flow of the processing events in the brain before, during, and after the critical stimulus or performance (Key, Dove, & Maguire, 2005; Näätänen, 1992).

ERPs are usually recorded with temporal resolution from multiple locations at the scalp, with a precision of milliseconds. By simultaneously recording from a large number of electrodes attached to the scalp, one can obtain maps of electrical activity at consecutive time points (Näätänen, 1992). To successfully outline an ERP, the amplitude of the component has to be greater than the background noise of the EEG activity. Since ERPs are small (1-30 microvolts), it is necessary to average multiple trials to get a sufficient signal-to-noise ratio. Kiesel recommends at least 70 trials for each condition you want to investigate (Kiesel, Miller, Jolicœur, & Brisson, 2008) in order to get a sufficient signal-to-noise ratio. Even though a high number trials improves the signal-to-noise ratio, it is important to note that too many trials can

make the subject less motivated, produce fatigue or/and drowsiness that again can affect the ERPs negatively (Brunner et al., 2013).

ERPs represent the internal processes related to the task performed and provide important insights into perceptual, cognitive, and motor functions. ERPs constitute a millisecond-by-millisecond record of neural information processing, which can be associated with both sensory and cognitive processes such as encoding, inhibitory responses and the updating of working memory (Sur & Sinha, 2009). ERPs have been useful to clinically assess psychiatric and neurological diseases like schizophrenia, depression and posttraumatic stress disorder (Sur & Sinha, 2009). ERPs provide a safe non-invasive means to study psychophysiological correlates of mental processes and brain functioning in patients with cognitive disorders, since it does not require a behavioural response from the subject (Näätänen, 1992; Sur & Sinha, 2009).

qEEG and the interpretation of ERPs can reveal both physiological and behavioural functioning. Many researchers have tried to associate particular features of ERP waveforms with specific cognitive processes (Otten & Rugg, 2005). The findings from such studies make it possible to use specific ERP features as markers for the engagement of the cognitive processes with which they are correlated. These markers are referred to as "components" and are usually defined with respect to both their functional significance and their underlying neural source(s) (Otten & Rugg, 2005).

The ERPs, or components, are thought to have a different amplitude, latency and topography depending on stimulus modality, but can also be influenced by changes in brain functioning, deviant information processing, or problems related to attention or the encoding of sensory stimuli. Using ERP as an indicator of how (well) the brain is functioning and responding to sensory stimuli is therefore reasonable (Brunner et al., 2015). Functional interpretations of ERP components are usually made from differences in neural activity. These are computed between the conditions that are presumed to isolate the process(es) of interest (Otten & Rugg, 2005).

Measurement and classification

ERP components are measured and classified by assessing the amplitude, latency, polarity and location. ERP waveforms are usually described in terms of positive and negative deflections and the latency of the peak or the sequence in which

the peak occurs. Taking the example of a negative waveform occurring approximately 100ms after stimulus onset would be labelled N100 (referring to the approximate latency of the peak) or N1 (referring to that it is the first negative peak after stimulus onset). A positive waveform occurring around 300ms after stimulus onset would be labelled either P3 or P300. The description of the latency of an ERP is locked to a specific time point. On the other hand, this does not mean that it always appears at this time point; it varies between individuals and conditions. The latency of an ERP varies between individuals and conditions, but the latency is relatively stable within an individual. On these accounts, ERPs are suitable objective measures for comparing individuals or groups of people.

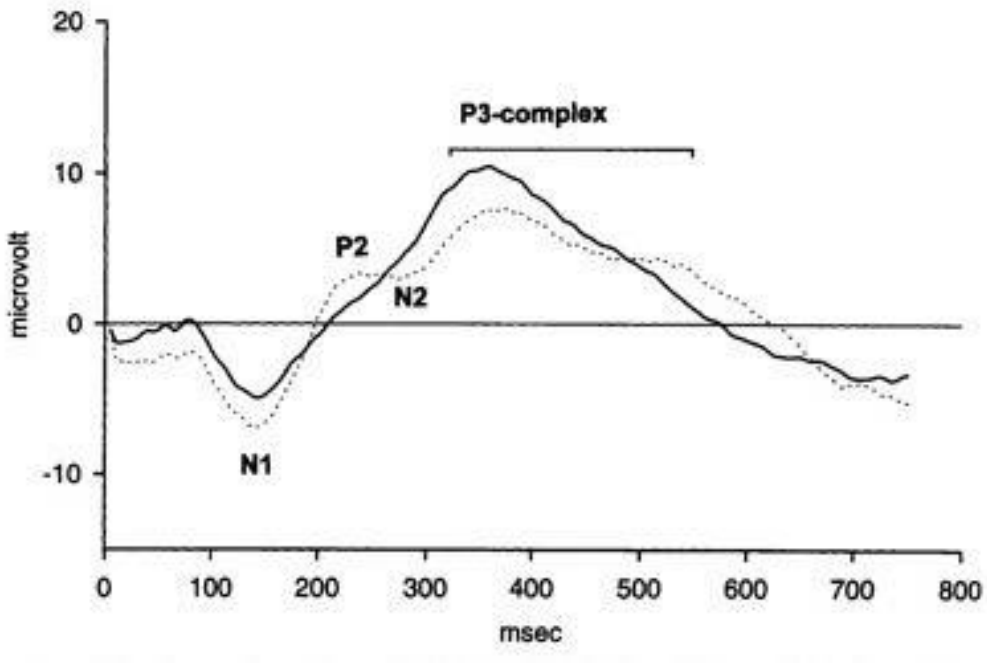

Figure 1: Example of ERPs elicited in two different conditions, illustrated with a solid and a dotted line.

The time window range for a wave varies with stimulus modality, task conditions, subject age etc. (Polich, 2007). This means that the P3/P300 wave does not necessarily occur at exactly 300ms after stimulus onset in every individual or task condition. Amplitude (μV) is defined as the difference between the mean pre-stimulus baseline voltage and the largest positive on-going peak of the ERP waveform within a time window, often considered as a measure of intensity (Kok, 2000). Latency (ms) is defined as the time from stimulus onset to the point of maximum positive amplitude within a time window. The latency of a component can be calculated with one of

several temporal measures of the component: onset, peak latency, rise time, or duration (Otten & Rugg, 2005).

Differences in the time course (latency), amplitude and the distribution of ERPs on the scalp correlates with the type of stimuli presented and it is possible to make assumptions about the underlying cognitive processes (Otten & Rugg, 2005). It is important to note that the onset latency of an ERP does not necessarily reflect the actual time point when the brain responds to the stimuli, but the time point where the cognitive processing associated with the ERP start to differ from baseline (Otten & Rugg, 2005).

ERPs can be divided into two main categories: exogeneous and endogeneous. Exogeneous components are early waves peaking within the first 100-200ms after stimulus onset and are presumed to reflect the sensory perception of the physical stimulus (Landa et al., 2014; Näätänen, 1992; Sur & Sinha, 2009). Endogeneous components occur later and are dependent on the evaluation of a stimulus. Endogeneous components are often referred to as cognitive components (Landa et al., 2014; Näätänen, 1992; Sur & Sinha, 2009).

The scalp distributions of the components tell us the topography of the location the ERP usually occur and at which electrodes the maximum amplitudes typically occur. This can be useful when trying to interpret peaks occurring at the same time in different scalp areas reflecting different cognitive processes, but this does not necessarily reflect the brain regions involved in generating the signal (Key et al., 2005).

Paradigms

ERP components have been investigated in a variety of paradigms, like different versions of the Oddball paradigm, the Stop signal paradigm, the pop-out paradigm, and the Go/NoGo-paradigm. A version of the Go/NoGo-paradigm will be used in this study, and explained below.

Go/NoGo paradigm and VCPT

Go/NoGo and visual continuous performance test (VCPT) are two neuropsychological tests designed to measure complex attentional function such as response inhibition and sustained attention (Jonkman, 2006; Kirmizi-Alsan et al., 2006).

In a typical Go/NoGo task, a series of two different stimuli are presented, usually with 50% probability for Go or NoGo stimuli (Weintraub, 2000). CPT is a repetitive task requiring sustained attention and response preparation followed by a motor performance or motor inhibition. The simple CPT paradigm is built up similarly, but with lower probability of Go stimulus in addition to distractor stimuli corresponding to the NoGo condition. A complex version of the CPT includes primer stimulus, a cue, followed by Go or NoGo stimulus (a target). In this version, the subjects usually are supposed to respond as fast as possible to the Go stimulus, and to withhold the response to the NoGo stimulus.

It is assumed that the presentation of a primer stimulus generates a bias for a coming Go stimulus and a preparation for a fast motor response. Arguably, this makes it more difficult for the subject to withhold a response and is hence a good measure of inhibition. A prepotent response is prepared by a cue, which has to be executed or inhibited depending on the subsequent stimulus. The presence of a large set of distractors in the cued CPT paradigm makes it more complicated and more difficult for an individual/participant to focus their attention on the Go and No/Go stimuli and consequently builds a higher demand of sustained attention compared with the Go/NoGo paradigm (Kirmizi-Alsan et al., 2006).

Depending on the task condition (Go or NoGo), the Go/NoGo task can be used to investigate cognitive control functions, such as selective attention, stimulus or response expectation and preparation, conflict monitoring, and response inhibition (Jonkman, 2006). There are different versions of the Go/NoGo task, but they all consist of a random and a sequential presentation of stimuli that the subject is instructed to respond (Go) or not respond to (NoGo). When the EEG is recorded during the task, ERPs can be computed by averaging EEG in time locked periods for Go and NoGo stimuli. The NoGo stimuli evoke a positive P3 wave (P3 NoGo), which differs both in latency and topography from the P3 wave in the Go condition (Brunner et al., 2013).

According to one theoretical model, the ERPs in Go/NoGo task are associated with several independent operations such as active sensory mismatch, action inhibition and conflict monitoring (Kropotov, Ponomarev, Hollup, & Mueller, 2011). Presumably, the greater the expectancy, the more a response can be planned, and therefore a greater inhibition and/or conflict is produced when an unexpected stimulus occurs (Smith, Smith, Provost, & Heathcote, 2010). If a component reflects response

inhibition in the Go/NoGo task, is should be generally larger for NoGo compared to Go trials, as well as being increased for unexpected relative to expected NoGo trials (Smith et al., 2010).

ERP components

P3 – general

The P3 component is the most studied component of ERPs and appears in any task that involves discrimination between stimuli, such as the Go/NoGo task (Polich, 2007). It is a positive ERP with a latency range between 250-600ms, depending on task conditions, stimulus modality or individual differences (Kok, 1997). It is usually larger at the posterior (parietal) scalp sites and minimal at the frontal electrode.

P3 is produced by a distributed network of brain processes associated with attention and memory operations (Polich, 2007). For a P3 to be elicited, the participant must pay attention and respond (overtly or covertly) to the stimulus (Key et al., 2005). The P3 is influenced by cognitive demands during a dual-task performance and its latency is usually interpreted as the speed of classification resulting from discrimination of one event from another (Sur & Sinha, 2009). P3 peak latency is proportional to stimulus evaluation timing. It is sensitive to task processing demands and varies with individual differences in cognitive capability (Polich, 2007). The shorter the latency, the faster the subject is discriminating and this is associated with superior mental performance.

The amplitude of the P3 is affected by attention and cognitive demands, whereas greater attention capacity produces a larger P3 wave (Sur & Sinha, 2009). P3 develops if the subject is actively engaged in the task of detecting the targets (Landa et al., 2014). Passive stimulus processing usually produces smaller P3 amplitudes than active tasks, due to the stimulus and non-task events engage attentional resources to reduce amplitude (Polich, 2007). P3 amplitude is smaller and peak latency longer for tasks that require greater amounts of attentional resources (Kok, 2000). Since the P3 is greater in individuals with good attention capacity, the P3 will be even smaller for individuals with attention problems.

Since P3 amplitude varies with the amount of attention paid to the stimuli, this component is widely studied in populations with attention deficits (e.g., ADHD) as it is interpreted to reflect information regarding various attentional functions (Key et al., 2005). The sensitivity of the P3 amplitude to the amount of attentional resources

engaged can hence be used as a measure/marker to look at the differences between conditions as well as different populations, patient groups, age groups etc.
Genetic factors strongly contribute to the P3, and P3 amplitude can be interpreted as a possible biomarker of a neurobiological vulnerability underlying disorders as alcohol- and drug dependence, and also antisocial behaviour (Polich, 2007; Sur & Sinha, 2009).

Neural sources of the P3 are not clearly identified, but intracranial recordings indicate that the medial temporal lobe, hippocampal region, parahippocampal gyrus, amygdala, or thalamus to contribute here (Friedman, Cycowicz, & Gaeta, 2001).

P3a and b

The P3 is proposed divided into two subcomponents: the P3a and P3b (Polich, 2007). Polich (2007) claims that P3a and P3b interact, but that they represent different processes in different cortical areas, but the full ontology of the subcomponents are still unknown (Polich, 2007). P3a is a novelty component and the NOGO-p3 most likely is variants of the same ERP (Polich, 2007). P3a has a latency-range around 240-400ms, with a latency peak earlier than regular P3. It originates from stimulus-driven frontal attention mechanisms during task processing. P3b has a longer latency, 300-600ms, and originates from temporal-parietal activity associated with attention and appears related to subsequent memory-processing (Polich, 2007). There seems to be a spatiotemporal overlap between P3a and P3b, where P3b is thought to reflect the true P3 component where two peaks are observable (Hruby & Marsalek, 2002).

P3Go and NoGo

P3Go is elicited in the Go-condition in a Go/NoGo task with a latency of 300-600 ms (Friedman et al., 2001). It has it's maximum amplitude in central and frontal scalp and is associated with executive control functions (Bokura, Yamaguchi, & Kobayashi, 2001). In the post-response phase of the task, P3 may be involved in performance evaluation, error detection and/or preparation for future trials (Roche, Garavan, Foxe, & O'Mara, 2005).

NoGo-p3 is elicited in NoGo-trials with maximum amplitude at Fz and Cz with a latency of 300-500ms, in response to infrequent non-target stimuli. P3b (Go) has more posterior distribution, max peak at Pz and earlier latency (Falkenstein, Hoormann, & Hohnsbein, 1999; Pfefferbaum, Ford, Weller, & Kopell, 1985).

Because the P3NoGo has a later peak latency than the P3Go; they attribute some of the amplitude and topographic differences to coincidental CNV resolution (Simson, Vaughan, & Ritter, 1977).

NoGo stimuli elicited an enhanced P3 component relative to Go stimuli, which is consistent with that P3 modulation is considered as an inhibitory mechanism (Bokura et al., 2001). The probability of an event influences the amplitude of the P3NoGo: events with lower probability elicit a larger P3 component. Bokura et al. (2001) found that P3NoGo was more widely distributed in the anterior brain regions than P3Go, termed "NoGo anteriorization". P3NoGo component seems to be linked to inhibitory neural activity in the frontal lobe (Bekker, Kenemans, & Verbaten, 2004; Bokura et al., 2001).

The P3NoGo as a marker of inhibition is controversial, as it not only appears when an action is supressed, but also in situations where the prepared action must be replaced by an alternative action (Brunner et al., 2013). P3NoGo has been demonstrated to have a higher amplitude in fast vs. slow responders (Brunner et al., 2013). Brunner et al (2015) propose that rather than reflecting inhibition, the P3NoGo wave may reflect a more general control process of replacing a pre-potent response (Brunner et al., 2015). If a component reflects motoric inhibition, then its amplitude should increase as a function of prior levels of preparation. TheP3NoGo has been found to be associated with the CNV amplitude, which is a manifestation of this preparation (Bekker et al., 2004; Smith, Johnstone, & Barry, 2007).

The difficulty in defining the functional correlate of the P3NoGo wave, could partly be explained by its multiple generators; ERP waves are regarded as the sum of multiple sources generated in different locations and associated with different neural processes (Brunner et al., 2013). The inconsistency regarding the functional meaning of the P3NoGo wave in the previous studies might be explained by the fact that the wave can be decomposed into at least two functionally distinct components: P3a and P3b (Kropotov et al., 2011).

CNV

Contingent Negative Variation (CNV) is a slow wave negative potential appearing between a warning/cue and an imperative stimulus during a Go/NoGo paradigm. It is a slow negative deviation of EEG activity on the scalp with a fronto-

central maximum, which occurs in the interval between a cue stimulus (S1) and target stimulus (S2) that is followed by a mental or motor response (Landa et al., 2014).

A typical CNV wave is observed as a gradual increase in negative amplitude after the first stimulus, up until the second task-relevant stimulus is presented where it returns to baseline (Falkenstein, Hoormann, Hohnsbein & Klensorge, 2003; Tecce, 1972). The amplitude of the CNV reflects the cortical activation before stimulus 2 and is also thought–to represent the level of attention to the task, arousal, stress, level of vigilance and energization, expectation and motor control (Bareš, Rektor, Kaňovský, & Streitová, 2003; Brunner et al., 2013).

The CNV is divided into an early and late component. The early CNV is considered an indicator of arousal processes. Late CNV is associated with attention to the experimental task (Sur & Sinha, 2009), expectation or preparation of a motor response (Bekker et al., 2004) and the maintaining of task-set presentations over time (Kray, Eppinger, & Mecklinger, 2005). It has the strongest negativity right before stimulus 2.

The late CNV arises from approximately 1000 ms post-stimulus and increases to the end of the epoch. The late CNV shows a clear separation at most sites between the different cues, with smallest amplitude for the NoGo-cues, larger for the non-specific cues and largest with specific cues (Smith et al., 2007). The largest CNV amplitude is observed when participants expect a Go-stimulus as S2. This is in line with the theory that the amplitude of the CNV represents the amount of attention paid to the task (Brunner et al., 2015; Smith et al., 2007).

A greater CNV activity reflects a stronger response preparation and the amplitude of the late CNV has been shown to increase when participants receive instructions to invest more effort in speeding up responses (Brunner et al., 2013). A decreased amplitude of CNV may indicate deficits in executive functioning and has been reported in alcoholic patients (Sur & Sinha, 2009).

Visual N1

The visual N1 is the first negative peak after stimulus usually occurring around 150-170ms in the visual modality registered in occipital areas. Visual elicited N1 is typically largest in the occipital region or inferior temporal regions (Bokura et al., 2001; Key et al., 2005). The amplitude of the N1 component is typically larger in

stimulus discrimination tasks, such as the Go/NoGo-task (Mangun & Hillyard, 1991; Vogel & Luck, 2000).

Studies have shown that N1 wave reflects a discrimination process that is applied to the attended location and is thus associated with selective attention and inhibition. Vogel & Luck (2000) tested this by examining the N1 component elicited by attended stimuli under conditions that either required or did not require the subject to perform a discrimination. The results showed a larger N1 wave for choice-RT tasks than for simple RT-task. These results are consistent with the hypothesis that the visual N1 component reflects the operation of a discrimination process within the focus of attention (Vogel & Luck, 2000).

Auditory P2

Auditory P2 is usually defined as a positive peak about 150-275ms after stimuli onset in the auditory modality registered in the central area of the brain (Key et al., 2005). P2 is often referred to as a vertex potential due to the highest amplitude over the central region generated by primary and secondary auditory cortices (Key et al., 2005). The P2 is believed to be related to the process of allocation of attention and to initial conscious awareness of stimulus, as well as awareness of stimulus change, and is thought to be involved in short-term memory (Key et al., 2005; Näätänen, 1992).

The amplitude of the P2 peak becomes larger as the stimulus intensity increases (Key et al., 2005). This amplitude is sensitive to the physical parameters of the stimuli, such as pitch (Novak et al., 1992) and loudness (Hegerl & Juckel, 1993; Hillyard & Picton, 1987). Due to this sensitivity, it can be argued that it is relevant to include P2 in the group of components as they reflect the general sensitivity associated with central sensitization.

Neurofeedback

Neurofeedback, discovered in the 1960s, is a training method aiming to optimize brain activity. It is based on operant conditioning, which can increase a preferred behaviour and decrease an undesired behaviour by providing a reward or a punishment (Sherlin et al., 2011). A reward is a desirable or positive event following a specified response, performed to encourage the subject to make the same response again under the same conditions. A reward functions as a reinforcer. It increases the

probability of the response. The relationship between the behaviour and the reinforcement must be evident to the individual, and the time between the positive behaviour and reward must be short enough to make this possible (Sherlin et al., 2011). A neurofeedback session can be seen as a virtual "mirror" for the on-going activity in the cortex, enabling a person to modify them explicitly.

Neurofeedback is easy to administrate, where the only equipment needed is an EEG amplifier connected to a computer providing real-time information about the brain activity in the patient. This is also known as brain-computer interface (BCI) (Ros, J Baars, Lanius, & Vuilleumier, 2014). To measure brain activity, electrodes are attached to the participant's head, with an exact position depending on the type of neurofeedback administered. Depending on the protocol, the patient is instructed to regulate their own brain activity by following instructions on a screen, receiving instant feedback on their task performance.

A neurofeedback session typically lasts for 20-60 minutes, depending on the protocol, treatment and/or study design. The number of sessions required to see an effect, depends on the diagnosis, the protocol and individual parameters, but in some cases, it is possible to see an effect only after 5-10 sessions. However, it is recommended to do 20-30 sessions to make the changes last. In anxiety, 15-20 sessions may be enough, but ADHD/ADD often requires 40-50 sessions (D Corydon Hammond, 2007).

For the neurofeedback to have an effect outside the clinic, there is a need for the process called generalization (Sherlin et al., 2011). To facilitate generalization, transfer trials have been used. Transfer trials are neurofeedback trials were the feedback is withheld until after the trial is finished, and not instantly.

Initially neurofeedback focused on training brainwaves, and was typically used to increase alpha levels to make the patient more relaxed or as an attempt to reduce seizures in patients suffering from epilepsy (D Corydon Hammond, 2007). Neurofeedback has shown a positive effect in patient groups with learning disabilities, depression, headache, ADHD and autism (D Corydon Hammond, 2007; Leins et al., 2007). There have also been pilot studies conducted focusing on neurofeedback on fibromyalgia patients, with a resulting positive training effect (Caro & Winter, 2011; Kayıran, Dursun, Dursun, Ermutlu, & Karamürsel, 2010; Kayiran, Dursun, Ermutlu, Dursun, & Karamürsel, 2007; Kristevski, 2015). This will be elaborated upon further down.

Different types of neurofeedback

Different types of neurofeedback have been developed through the years, where one can distinguish between frequency band training and the training of slow cortical potentials (SCPs). In frequency band training, the patient is rewarded for the decrease and/or increase of specific frequency band in the EEG. One of the most known frequency band training is the theta/beta with the aim of reducing theta (4-8Hz) and increasing beta (13-20Hz) as an attempt to enhance sustained attention.

In SCP training, the increase of excitation in cortical neurons is the mechanism behind the effect. This increase of excitation is a demonstration is what produces the CNV wave. SCP training is based on recording of SCPs at the vertex, where one electrode is placed in the centre of the top of the head and one behind each ear, while the participant focuses on changing a visual display on the computer (Strehl, 2009; Studer et al., 2014).

SCPs are very low positive or negative polarizations of brain activity with a frequency near 0.01Hz, which is the same as 10 seconds (Strehl, Birkle, Wörz, & Kotchoubey, 2014; Studer et al., 2014). SCPs represent the change between the brains hyper excitability and fatigue, where cognitive processing mirrors a negative shift in direct current potentials and positive slow cortical potentials, which occur during the inhibition of cortical networks. The brain tends to be electro-negative and hyper excitable before a migraine attack or during or prior to an epileptic seizure. After the seizure, the scalp is fatigued and electro-positive.

As SCPs regulate excitation thresholds it may be used for self-regulation training in pathological conditions where excitation thresholds are impaired. This makes the balance between electro-positive and electro-negative cortex is stable, resulting in for example fewer migraine attacks or a reduction in epilepsy seizures (Strehl, 2009).

Slow cortical potentials have been tested in a variety of disorders/diagnoses with promising results (D. Corydon Hammond, 2010) and there have also been evaluations of the long-term effect with a positive outcome. One of the most well known studies of the long-term effect of SCP neurofeedback was conducted by Strehl and colleagues (2014). They conducted a follow-up evaluation of SCP neurofeedback training results in patients with intractable epilepsy and still found a significant decrease in seizure frequency 10 years after the SCP intervention (Strehl et al., 2014). They concluded that the patient's ability to self-regulate their SCPs outside the

treatment-setting may be the reason for the resulting reduced seizure frequency (Strehl et al., 2014).

Studer and colleagues (2014) were one of the first to study the specificity of the effects of both frequency-band-training and SCP on attentional processes and motor system excitability. By assessing event related potentials, they found increased amplitude of the CNV component during negativity trials in the SCP training, which imply an allocation of resources during cognitive preparation. Increased CNV amplitudes after SCP training indicates an improved resource allocation connected to attention and preparation (Studer et al., 2014).

A study by Leins et al. (2007) compared neurofeedback-training of Theta-Beta frequencies and training of slow cortical potentials (SCPs) in children with ADHD. The results showed that both the Theta-beta group and SCP group managed to regulate their cortical activity intentionally, and improved in both attention and IQ (Leins et al., 2007). Behavioural and cognitive improvements were also reported. The effects remained stable six months after the intervention for both groups. There were no differences in behavioural outcomes between the groups.

Individualized training and side effects

Neurofeedback should be individualized to each patient to ensure that they get the right training protocol tailored to their specific deviations in the brain (D. Corydon Hammond, 2010). Individualization is usually made by assessing the patient's qEEG, which assists in revealing and understanding possible abnormalities in brain functioning. There is considerable heterogeneity in the EEG patterns associated with diagnostic categories, and some patients may also have more than one diagnosis, i.e. comorbidity, that influences the qEEG pattern. Due to the possibility of subtypes, it may be problematic to give the same kind of neurofeedback to two patients with the same diagnosis. qEEG has revealed two subtypes of ADHD and giving the same neurofeedback training to both could result in one of them becoming even more hyperactive (D. Corydon Hammond, 2010). The abnormalities found, in addition to the patient's self-reporting of symptoms, will help the practitioner to decide which protocol to use.

Neurofeedback is known for its minimal to non-existent side effects. When applied cautiously, reported adverse effects of neurofeedback are very rare (D. Corydon Hammond, 2010; Ros et al., 2014) and most appear limited to mild

headaches, which normally pass in the aftermath of training. It is believed that most side effects of neurofeedback stems from a lack of individualization of training and a lack of objective and comprehensive assessment of brain functioning (D. Corydon Hammond, 2010).

Medications and placebo

qEEG provide a baseline of brain function at the current time, and can be affected by medications (D. Corydon Hammond, 2010). If the plan is to give neurofeedback instead of medication, it is important to take a new EEG without medication before deciding on a protocol.

Placebo is an active factor in almost every type of therapy and there have been discussions about whether neurofeedback can be affected by the placebo effect. Studies have shown that placebo plays a minor role in neurofeedback. One of the first neurofeedback studies was conducted on cats and on the placebo question the answer given was that cats unlikely would form expectancies about being more seizure resistant because of the fact that a researcher attached electrodes on their head (D Corydon Hammond, 2007).

Neurofeedback in fibromyalgia

Neurofeedback in fibromyalgia has given varied results and there is currently no agreement in the field on whether or which type of neurofeedback is sufficient in treating fibromyalgia. Existing literature on neurofeedback in fibromyalgia syndrome suggests lasting beneficial effects, in both pain symptoms as well as improvements in mood, sleep, fatigue, cognitive clouding among others (D. Corydon Hammond, 2010; Kristevski, 2015).

One of the first studies examining the effects of neurofeedback on 30 fibromyalgia patients was an uncontrolled and exploratory investigation conducted by Mueller et al (2001). They used a form of neurofeedback called electroencephalograph-driven stimulation (EDS), which is a conditioning of brain waves (Mueller, Donaldson, Nelson, & Layman, 2001), in contrast to most neurofeedback protocols based on operant conditioning. They found significant improvements on the symptom checklist 90-Revistied (SCL-90-R), VAS symptom scales, a decreased level of alpha, theta and delta frequencies, fewer and smaller distribution of tender points (Mueller et al., 2001).

In a pilot study (Caro & Winter, 2011) it was tested whether SMR neurofeedback was effective on attention problems in fibromyalgia. They also hypothesized that the SMR protocol would improve somatic symptoms, since SMR neurofeedback has shown effects on central nervous system functioning (Caro & Winter, 2011). The results showed that visual, but not auditory, attention improved significantly and the patients additionally showed an improvement in fatigue, pain and tenderness (Caro & Winter, 2011). These improvements are consistent with other findings, such as the earlier study by Kayiran et al (2007) who found improvement in pain, fatigue, depression and anxiety in three fibromyalgia subjects with an EEG-BF SMR (EEG BioFeedback Sensory-motor rhytm) protocol (Kayiran et al., 2007).

In 2010, Kayiran, Dursan, Dursun, Ermutlu, and Karamursel designed a follow-up to the study from 2007. They compared neurofeedback with the treatment with Lexapro in a randomized, blinded, control group study and found that both treatments gave significant improvements in symptoms, with greater benefits in the neurofeedback group. Kayiran et al. hypothesized that neuroplasticity and normalization of central nervous system disinhibition lies behind the efficacy of neurofeedback (Kayıran et al., 2010).

Kravitz, Esty, Katz, and Fawcett (2006) performed a randomized, double-blind, placebo-controlled experiment using low-intensity neurofeedback with 64 fibromyalgia patients. A significant difference between the placebo group and treatment group was demonstrated (Kravitz, Esty, Katz, & Fawcett, 2006).

A recent study by Kristevski (2015) examined the effects of neurofeedback in fibromyalgia syndrome, were all the participants showed improvements in subjective ratings of pain, decreased Fibromyalgia Impact Questionnaire (FIQ) scores, changes on EEG indices and also reported satisfaction with the treatment (Kristevski, 2015).

Pain and qEEG

The brain function of chronic pain sufferers is different from healthy peoples brain activity (Baliki et al., 2008; de Vries et al., 2013). The brain's morphology and function seems to be altered by chronic pain over time (Arendt-Nielsen, Graven-Nielsen, Svensson, & Jensen, 1997).

A PET scan of eight fibromyalgia patients showed reduced resting regional cerebral blood flow (rCBF) in the retrosplenial cortex when acute pain was

induced(Wik et al., 2006). This demonstrates that fibromyalgia patients have a deviant cognitive processing of pain and possibly also increased attention towards subnoxious somatosensory signalling, which indicates the presence of CS (Bellato et al., 2012).

EEG findings indicate that fibromyalgia patients have alpha intrusion during sleep, which is thought to increase tenderness and pain, contributing to inefficient sleep (Moldofsky, 2008). Lentz (1999) demonstrated that the disruption of slow wave sleep several nights in a row increases discomfort, fatigue and decreases the pain threshold(Lentz, Landis, Rothermel, & Shaver, 1999).

Additionally, Fibromyalgia patients have shown a lacking ability to dissociate sensory from affective components in pain-related information (Sitges et al., 2007). This abnormal information processing was slower than in healthy controls. This was discovered during a self-endorsement task and simultaneous EEG recording where the participants evaluated if pain-related words suited their experience of pain.

qEEG in central sensitization?

The nociceptive processing of acute pain is well understood, but it is not understood how this system operates during chronic pain such as rheumatic pain or FMS. There are, however, several indicators of central sensitization being a part of both (Graven-Nielsen & Arendt-Nielsen, 2010; Gwilym et al., 2009; Jones et al., 2012; P. J. Mease, Hanna, Frakes, & Altman, 2011; Schmidt-Wilcke & Clauw, 2011). Arguments for the presence of CS in fibromyalgia are the lack of peripheral damage, abnormalities in the tissue and inflammation (Staud, 2010) and the presence of enhanced temporal summation, dynamic tactile allodynia and secondary hyperalgesia (Jones et al., 2012).

An fMRI study showed increased periaqueductal grey (PAG) activation following stimuli of a painful area in osteoarthritis (OA) patients (Gwilym et al., 2009). They hypothesize that increased activity in the brainstem can be seen as a biomarker of central sensitization. If CS is a part of fibromyalgia and OA and there is evidence of functional alterations in OA patients' brains, there is reason to believe that testing of FMS patients will yield similar results.

Montoya (2006) demonstrated that fibromyalgia patients show a lack of habituation. This was investigated by EEG recording during tactile or auditory

stimulation (Montoya et al., 2006). Somatosensory ERPs were reduced from stimulus 1 to stimulus 2 in healthy controls, but not in fibromyalgia patients, indicating a reduced ability to habituate to repetitive stimuli.

Importance of this study and hypothesis

Widespread chronic pain and other symptoms such as fatigue, cognitive impairments and depressive symptoms have a substantial impact on a patient's social and daily life. The considerable overlap between chronic pain conditions, chronic fatigue syndrome and other syndromes often referred to as unexplained, makes it difficult to separate the illnesses. If findings from this study substantiates that there are differences between the syndromes, we not only strengthen the assumption of the legitimacy of them as separate clinical diagnoses, we strengthen the idea of a possible biomarkers for the diseases.

Aim of the study and hypothesis

Because of the substantial overlap between symptoms and comorbidity between chronic fatigue and chronic pain, this study will investigate whether the groups differ and how they differ from each other. Earlier studies have shown deviances in brain waves and an altered latency and amplitude in some ERP components.

Fibromyalgia is a complex, unexplained chronic pain condition with no functioning treatment. Genetic factors have been identified together with neurophysiological changes and abnormal response to stress, reflecting the existence of a physiological cause. An abnormally functioning default mode network has been found in chronic pain patients, which indicates a reorganization of the brain over time by way of plasticity. The theory of PM as a salience detection system suggests that chronic pain patients have altered attentional mechanisms that causes increased sensation of pain.

There is reason to believe that fibromyalgia patients have deviances in their qEEG patterns and that neurofeedback can be effective in changing or normalizing these deviances as well as relieve symptoms. Neurofeedback has the ability to optimize rhythms in the brain and there is evidence of successful neurofeedback training in fibromyalgia patients in the literature.

Abnormal brain activity can be assigned to a sensitization of the central nervous system. If the central nervous system is sensitized, it is necessarily visible in the brain.

Based on this, the research questions for this project are:

1. Are fibromyalgia patients a distinct patient group compared to patients suffering from chronic pain and chronic fatigue syndrome?
2. Does Slow Cortical Potentials Neurofeedback have an effect on the ERPs of fibromyalgia patients?

Chapter 2: Method

To answer the two hypotheses, the project was divided into two parts. Hypothesis 1 was investigated by analysing and comparing qEEG recordings from three different groups of patients. Previous recordings from ME/CFS patients and chronic unexplained pain patients were compared with EEG recordings from fibromyalgia patients recorded in this project. Hypothesis 2 was investigated by analysing qEEG recordings from fibromyalgia patients that were conducted with a pre-test post-test design. After recruiting and informing the participants, they were asked to fill out the Fibromyalgia Impact Questionnaire (FIQ, 1991) and perform a qEEG recording (pre-test) while performing a visual continuous performance task (VCPT). The participants that wished to proceed continued to the intervention, the neurofeedback training Slow Cortical Potential (SCP), while the participants that did not wish to proceed had completed their contribution to the project at this point. Nine of the participants wished to continue in the intervention group and they completed in total 30 SCP sessions that lasted approximately 30 minutes each. Upon completion of these sessions, the participants were asked to answer the FIQ again and perform the second and last qEEG recording (post-test) while performing the same VCPT. ERPs produced by the VCPT were plotted by hand, where the 20 fibromyalgia patients were compared to ME and chronic pain patients with a multivariate analysis of variance (MANOVA). The ERPs from the participants who chose to proceed with the neurofeedback were also compared with the post-intervention recordings. The neurofeedback software used in this project produces a summary that was monitored after every tenth training, but this summary was not analysed statistically in this project.

Participants/REK/NSD

Participants

This study was conducted by collecting data from patients suffering from fibromyalgia syndrome. The patients were recruited through the fibromyalgia association (Fibromyalgiforeningen), a Norwegian patient group in Trondheim. 20

women between the ages 35-71 agreed to participate in the study. For comparison with other patient groups, data collected in earlier studies were used.

Chronic pain group

The pain group consisted of 43 patients, within the age 28-76, undergoing assessment at the Pain day unit at Hospital Traunstein in Germany. This group consisted of patients suffering from different kinds of pain conditions, including myofascial neck pain, shoulder and back pain, chronic headache, migraine, lumbalgia, fibromyalgia, gluteal pain with ischialgia, polyarthrosis, lumbal ischialgia, gonarthrosis, osteoporosis, atypical face pain, and somatoform pain. There was no information available to this project regarding the recorded patients' diagnosis and if they were on any medication at the time of the recording.

Chronic fatigue group

The chronic fatigue group consisted of 42 patients, within the age 29-66, recruited from the Pain Care Unit at St. Olavs Hospital in Trondheim between the years 2009-2012. The patients were all suffering from chronic fatigue, where fatigue is the core symptom, but due to physical complaints, they were admitted to the Pain Care Unit.

After exclusion of subjects with less than 70 trials in each condition, 26 viable qEEG-recordings were left, as a minimum of 70 trails is recommended to get a sufficient signal-to-noise ratio (Kiesel et al., 2008). There were no records of any of these patients being on medication at the time of the qEEG-recordings.

Measurements/equipment

Data from the participants with fibromyalgia and chronic fatigue was recorded in the same lab using the same software and hardware, however at different points in time by different people. Data from the participants with unexplained chronic pain were recorded in Germany.

The EEGs were recorded using a 19 channel digital amplifier from Mitsar (St.Petersburg, Russia). The electrode caps were made of tin (Sn) (Electrocap International Inc.) filled with conductive gel, and they were placed according to the 10-20 international standard montage with the reference electrode on the ear lobes

and the ground electrode on Fpz (Klem, Lüders, Jasper, & Elger, 1999). The impedance was kept at 10 KOhm and the exclusion threshold at 100 microvolts. High pass filter for slow waves was set to 0.53 Hz and low pass filter for fast waves was set to above 50 Hz. The pre stimulus baseline was 50 ms and the presentation of each picture lasted for 100 ms. Notch filter (45-50 Hz) was in use during the VCPT to reduce electrical noise. The majority of the recordings had a sampling rate of 250 Hz, but a few had a sampling rate of 500 Hz and were compressed to 250 Hz for ERP analysis. Input impedance for the amplifier was 200 MOhm and A/D was 14 bit per second. The data was stored on a computer for off-line analysis, and each recording was visually inspected to ensure quality.

Before the EEG data can be analysed, it is necessary to remove elements that disturb the data, like muscle tension and eye blinks. This is called artefact correction, and is performed with the WinEEG program by performing an independent component analysis (ICA) and by visually inspecting the data and removing disturbances.

The neurofeedback training (slow cortical potential) was performed using BioTrace+ software (V2015B) and the Nexus 10 amplifier from MindMedia. No specific instruction was given, the patients were told to find the most successful mental strategy that worked for them. Participants were given 30 sessions and each session lasted for approximately 20 minutes, depending on how well they did. Their progress was evaluated for each 10^{th} session based on statistics in BioTrace and the patients' subjective reports.

Stimuli and procedure

19-channels EEG was recorded in two resting conditions prior to the task; 180 seconds with eyes open (EO) and 180 seconds with eyes closed (EC). Afterwards, the visual continuous performance task (VCPT), a Go/NoGo-task, was performed in order to assess the participants´ capacity for sustained attention and response control.

In this study the resting condition (EO/EC) was used to make the patient comfortable before the testing condition (VCPT) and to check for anything unusual in the signal or the recording. The participants were seated in a sound isolated room, in a comfortable chair placed 100 cm from a 22" screen, with a resulting visual angle for the images of 5 degrees.

Stimuli was presented by the software tool PsyTask (Mitsar, St. Petersburg,

Russia). This was a visual continuous performance task (VCPT), a visually cued Go/NoGo-task, designed for studying ERPs (Kropotov & Ponomarev, 2009). The VCPT lasted for 20 minutes, with 400 trials altogether. After every 5 minutes the patient was given a short break to promote a continuous good performance and to reduce task-related tiredness, and the patients also had a say in deciding the length of the break.

The 400 trials are divided into four conditions, termed a-a (animal-animal), a-p (animal-plant), p-p (plant-plant), and p-h (plant-human), with 100 trials in each. In the p-h condition, the picture of a human was presented simultaneously with a novel sound at 60dB. Each condition was composed of picture-pairings, with every picture shown for 100 ms, followed by an inter-stimulus interval of 1000 ms and a 3500 ms interval between pairings.

In the a-a and p-p trials, the two pictures presented were identical. In each block, there was an equal probability of each condition being presented. The participants were instructed to press a button as fast as possible with their right index finger to the second image in the a-a conditions (Go-condition), to withhold a response to the second image in the a-p conditions (NoGo-condition), and to ignore the two other conditions, p-p and p-h. /The subjects were instructed to press a button with their right index finger, as fast as possible, whenever the second image fulfilled the a-a condition (Go-condition); to withhold a response whenever the second image fulfilled the a-p condition (NOGO-condition), and to ignore the other two conditions (p-p and p-h). This is illustrated in figure 2.

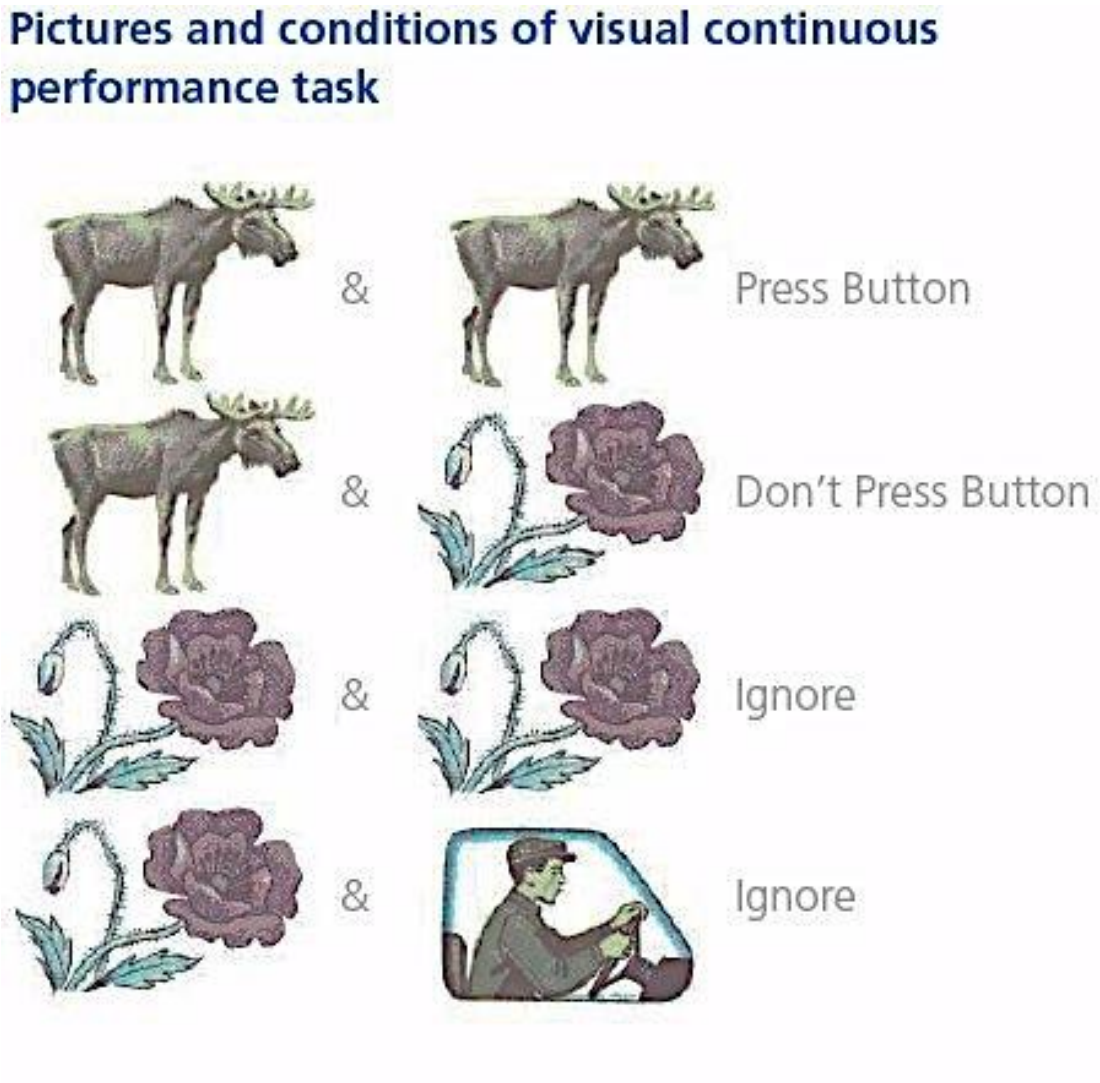

Figure 2: The instruction screen and examples of each condition in the VCPT.

ERP measurement

Fractional area technique was used to measure the latency of the waves on all ERP's, apart from the latency of CNV. A version of fractional area technique called relative criterion, where the onset of the component is defined as the point where the amplitude reaches 50% of its peak amplitude, was used, and the offset is defined as the point where the amplitude decreases to 50% of its peak amplitude. The latency is then set to the median between the onset and the offset. For CNV, peak latency was used. The amplitudes of the components were measured by identifying the largest amplitude within a pre-defined timeframe, based on literature. N1 has a timeframe of 150-170 ms, P2: 150-275 ms, P3GO: 300-600 ms, P3NOGO: 250-600 ms, and CNV appears 100 ms before S2, around 1000ms.

Human brain index reference database (HBI)

The individual ERPs were visually inspected and compared to a reference database (HBI med AG, Switzerland). The comparison concentrated on significant deviances regarding the condition (a-a, a-p, p-p or p-h), and where on the scalp these deviances occurred /were localized. The comparisons were performed in WinEEGs internal statistics engine, and the result of each patient was compared to the mean result of an appropriate age-matched control from the HBI. The HBI database is a clinical tool used in differential diagnostics, and is thus not suitable for group comparisons. The comparisons are single point-estimates, without any information on standard deviations. Therefore, HBI was used only to look at possible tendencies in this study.

FIQ

The Fibromyalgia Impact Questionnaire (1991, see appendix 2) was included as a subjective supplement to the ERP measurements. The participants filled out the questionnaire at the same time as their pre- and post-test EEGs, and chose to either fill it out in the lab or at home. FIQs were also filled out by seven of the twelve participants who did not take part in the neurofeedback training.

FIQ scoring- Norwegian vs. English version

The questionnaire was scored according to the rules (Bennett, 2005), but with deviations as the Norwegian questionnaire differs from the English version. Question one consists of ten sub-questions concerning the ability to perform large muscle tasks, answered on a four point Likert type scale (0-3). The score is averaged according to how many questions the patient has answered (it is possible to delete questions from the questionnaire if the task is irrelevant), giving a total raw score between 0 and 3. Question two asks the patient to identify the number of days they felt good the last week, and it is scored inversely ranging from 0 to 7. Question three, "How many days last week did you miss work because of fibromyalgia?", was changed in the form used in this project to: "To what extent were you on sick leave due to fibromyalgia the last week? (Question not answered by homemakers, unemployed or retired persons)" (in Norwegian: "I hvor stor grad var du sykemeldt p.g.a. fibromyalgi den siste uken? (Besvares ikke hvis du er hjemmeværende, arbeidsledig eller alderspensjonist)"). In addition, the possible answers were changed from 0-7 days to

0%, 25%, 75% or 100%, changing the score from 0-7 to 0-4. Question four to ten ask the patient to rate ability to work, level of pain, tiredness, fatigue, stiffness, anxiety and depression on a visual analogue scale (VAS) from 0-10 (cm). The English and the Norwegian versions are identical for these seven questions. After calculating raw scores, question 1-3 are normalized to range between 0 and 10. Question three and four both concern work and are left unanswered if the participant is unemployed, reducing the total possible score from 100 to 80.

Statistical analysis

Behaviour

A two-way paired samples t-test was conducted to investigate whether there was a significant change in reaction time between pre-test and post-test. Prior to analysis, the data was checked for assumptions.

FIQ scores

To test if the FIQ scores changed significantly between pre-test and post-test, a two way paired samples t-test was performed. Prior to analysis, the data was checked for assumptions.

T-test for pre-test vs. post-test scores.

This was tested with a two-way paired samples t-test using the pre-test and post-test qEEG recordings from the nine participants in the intervention group. Before running the dependent t-test, the data was checked for assumptions. T-tests were calculated for each ERP separately to identify if and on which ERP the neurofeedback training had an effect.

MANOVA

To examine whether there were any significant differences between the groups on a linear combination of the variables, a MANOVA was run. The independent variables were the different participant groups: Pain, CFS and fibromyalgia, and the dependent variables were: P3GOamplitude, P3GO latency, P3NOGO amplitude, P3NOGO latency, CNV amplitude, CNV latency, N1 amplitude, N1 latency, P2 amplitude and P2 latency. A Bonferroni correction was applied to ensure that the statistical threshold was maintained when multiple analyses were performed. Effect sizes were measured with partial Eta squared (η^2) and the size of the effect was considered by the following criteria: $\eta^2 = 0.2$, medium is $\eta^2 = 0.6$, and large is $\eta^2 = 0.8$.

Chapter 3: Results

Behaviour

Testing of the underlying assumptions in the statistical analysis yielded no violations. On average, the participants in the intervention group showed a significantly reduced reaction time after neurofeedback intervention (M=310.78, SE=21.598), compared to before the intervention (M=358.78, SE=26.512). t(8)=2.437, p<.05, r=.426 (see table 1). The participants in the EEG group had an average score of 377.64.

Table 1: Paired sample t-test of reaction time

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 pretest - posttest	48.000	59.091	19.697	2.579	93.421	2.437	8	.041

FIQ

Assumption testing yielded no violations. Out of the nine participants in the intervention group, one was excluded from the pre-test group and one from the post-test group (not the same person) because the questionnaires were not fully completed. On average, participants showed a non-significant score reduction from pre-test (M=46.71, SE=2.06) to post-test (M=40.95, SE=1.99), t(7)=1.956, p=.09 (see table 2). In the EEG group, seven out of 12 participants completed the questionnaire with an average of 48.6.

Table 1: Paired samples t-test of FIQ scores

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1 FIQ pretest - FIQ posttest	5.75875	8.32867	2.94463	-1.20419	12.72169	1.956	7	.091

ERPs

HBI

Since the HBI only gives information about one individual at a time and only bases its comparison on a group mean, this analysis did not produce any meaningful statistics for this project. Every individual was inspected in relation to the database, but there was no visible common pattern. Statistics from HBI is therefore not presented.

T-test - Neurofeedback

Visual inspection of histograms during assumption checking showed small deviations from a normal distribution, and the boxplots revealed several possible outliers. To identify if these visual possible outliers were in fact outliers, the scores for skewness and kurtosis were transformed into z-scores and inspected. In addition, the normality test Shapiro-Wilk was performed. In this sample, the z-scores for skewness and kurtosis showed no significant outliers and Shapiro-Wilk had no significant values, indicating no violation of the normality assumption. In total, the assumption testing resulted in no violations.

The t-tests gave the following results:

- On average, participants showed a significantly greater (away from zero) CNV amplitude after neurofeedback intervention (M=-8,88, SE=1,49), compared to before the intervention (M=-5,06, SE=1,12). t(8)=3,005, p<.05, r=.73
- On average, participants showed a significantly greater P3GO amplitude after neurofeedback intervention (M=25,78, SE=2,55), compared to before the intervention (M=13,65, SE=3,08). t(8)=-3,551, p<.05, r=.78
- On average, participants showed a significantly greater P3NOGO amplitude after neurofeedback intervention (M=29,0, SE=2,69), compared to before the intervention (M=17,21, SE=3,7). t(8)=-4,757, p<.05, r=.86

Table 2: Paired sample t-tests comparing pre-test and post-test ERPs

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	CNV_A_PRE - CNV_A_POST	3.81667	3.81007	1.27002	.88799	6.74534	3.005	8	.017
Pair 2	CNV_L_PRE - CNV_L_POST	5.111	70.534	23.511	-49.106	59.329	.217	8	.833
Pair 3	N1_A_PRE - N1_A_POST	-.24444	2.47905	.82635	-2.15001	1.66112	-.296	8	.775
Pair 4	N1_L_PRE - N1_L_POST	4.667	14.318	4.773	-6.339	15.672	.978	8	.357
Pair 5	P3GO_A_PRE - P3GO_A_POST	-12.13778	10.25366	3.41789	-20.01944	-4.25612	-3.551	8	.007
Pair 6	P3GO_L_PRE - P3GO_L_POST	10.222	27.775	9.258	-11.127	31.572	1.104	8	.302
Pair 7	P3NOGO_A_PRE - P3NOGO_A_POST	-11.80111	7.44166	2.48055	-17.52128	-6.08095	-4.757	8	.001
Pair 8	P3NOGO_L_PRE - P3NOGO_L_POST	10.889	22.608	7.536	-6.489	28.267	1.445	8	.186
Pair 9	P2_A_PRE - P2_A_POST	-1.19778	3.36336	1.12112	-3.78309	1.38753	-1.068	8	.317
Pair 10	P2_L_PRE - P2_L_POST	-9.778	65.226	21.742	-59.915	40.359	-.450	8	.665

Effect sizes for the significant t-tests was calculated by hand. The effect sizes for the amplitudes of CNV (r=.73), P3GO (r=.78) and P3NOGO (r=.86) all showed large effect.

MANOVA – group differences

The initial data set consisted of 96 patients, 20 in the FM group, 43 in the pain group and 36 in the CFS group. We started with preliminary assumption testing for a MANOVA-analysis for the whole dataset, testing for normality, linearity, univariate and multivariate outliers, homogeneity of variance- covariance matrices, and multicollinearity. Two univariate outliers and one violation of the assumption of multicollinearity were found. The 2 outliers were removed, and as an attempt to correct for multicollinearity, cases in the two largest groups were randomly deleted to make the group sizes equal. We ended up with a total of N=58, divided into N=19 in

the FM group, N=19 in Pain group and N=20 in CFS group. The following results are based on these numbers.

Table 4: Descriptive statistics. Mean and standard deviations for each component in each group.

Component	Group	Mean	St.Deviation
CNV amplitude	FM	-6,36	3,11
	Pain	-7,33	2,22
	CFS	-8,03	3,05
CNV latency	FM	992,63	48,47
	Pain	967,79	51,58
	CFS	992,80	54,78
N1 amplitude	FM	-8,78	5,31
	Pain	-6,77	4,16
	CFS	-7,17	4,76
N1 latency	FM	138,53	18,17
	Pain	154,11	19,27
	CFS	143,80	22,51
P3Go Amplitude	FM	18,52	9,10
	Pain	21,31	8,61
	CFS	24,28	8,86
P3Go latency	FM	349,79	44,15
	Pain	349,79	51,96
	CFS	345,30	35,55
P3NoGo amplitude	FM	23,32	12,76
	Pain	24,91	8,14
	CFS	26,27	10,60
P3NoGo latency	FM	397,05	29,56
	Pain	410,32	37,05
	CFS	394,60	20,87
P2 amplitude	FM	4,28	2,62
	Pain	12,12	6,94
	CFS	16,87	9,03
P2 latency	FM	188,53	53,33
	Pain	208,66	21,10
	CFS	229,10	29,22

The preliminary assumption testing was then repeated with N=58, with no serious outliers detected. P-P-plots indicated that all variables were somewhat normally distributed, but with slight skewness. A significant Shaphiro-Wilk/Kolmogorov Smirnov test confirmed this. However, because of no detected outliers and a small difference between mean and trimmed mean (5% of the most extreme values removed), the dataset was considered to be normally distributed.

All variables were analysed for multicollinearity. A bias corrected, accelerated correlational analysis showed significant correlations between several of the components, to varying degrees, but none of them strong enough to violate the assumption of multicollinearity.

Table 5: Levenes Test of Equality of Variances

	F	Df1	Df2	Sig.
CNV Amplitude	2.103	2	55	.132
CNV Latency	.205	2	55	.815
N1 Amplitude	2.975	2	55	.059
N1 Latency	.929	2	55	.401
P3Go Amplitude	.377	2	55	.688
P3Go Latency	.868	2	55	.426
P3NoGo Amplitude	2.642	2	55	.080
P3NoGo Latency	1.523	2	55	.227
P2 Amplitude	8.209	2	55	.001
P2 Latency	4.577	2	55	.013

Levenes test for equality of variances showed varying results for the 10 variables. The variances for all variables, except P2_A and P2_L, were equal for all

groups (at the .05 level), as seen in table 4.

Due to the significant Levenes test for P2 amplitude and P2 latency, a follow-up with Welch F-test were conducted. The equality of means showed significant results ($p < .05$), and it was therefore appropriate to continue with the analysis.

Box´s Test of equality of covariance matrices was non-significant at the .001 alpha level, and the covariance matrices of the three groups are assumed to be the same (homogeneity of covariance).

The MANOVA was significant for all test statistics. Looking at Pillai´s Trace, there was a statistically significant difference between fibromyalgia group, chronic fatigue group and chronic pain group in the combined dependent variables V = .748, $F(20, 94) = 2.81$, p = .000, Partial $n^2 = .374$.

A univariate analysis of variance (ANOVA) was conducted to determine how the dependent variables differ. The test of between-subjects effects-table revealed non-significant effects on 8 of the 10 variables. Group membership thus seems to have a statistically significant effect on P2 amplitude (F (2.55) = 16.996; p = .000, Partial $n^2 = .382$) and P2 latency (F (2, 55) = 5.849, p = .005, Partial $n^2 = .175$). After correction of the alpha level for the multiple ANOVAS run, the acceptable significance was set to $p > .005$. This did not make any difference for the numbers of significant variables; P2 amplitude and P2 latency still came out significant.

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first function explained 74,7% of the variance, canonical $R^2 = .71$, whereas the second function explained only 25,3% of the variance, canonical $R^2 = .50$. In combination, these discriminant functions significantly differentiated the patient groups, $\Lambda = 0.377$, $\chi 2(20) = 49.32$, $p = .000$, but removing the first function indicated that the second function did not significantly differentiate the groups, $\Lambda = 0.749$, $\chi 2(9) = 14.61$, $p = .102$. Two underlying dimensions in combination can thus explain the group differences found in the MANOVA.

Table 6: Standardized Canonical Discriminant Function Coefficients.

Component	*Function 1*	*Function 2*
CNV_A	-,611	,489
CNV_L	,214	-,573
N1_A	-,065	,509
N1_L	-,024	,793
P3GO_A	,388	,216
P3GO_L	,048	,012
P3NOGO_A	-1,023	,659
P3NOGO_L	-,008	,621
P2_A	,818	-,001
P2_L	,499	-,346

Standardized discriminant function coefficients (Table 5) and the structure coefficients (Table 6) were examined to determine which of the variables contributed to the differences between the three groups. The correlations (Table 6) between outcomes and the discriminant functions revealed that P2 amplitude loaded higher on the first function (r = .786) than on the second (r = .149). As did the P2 latency (r = .464 on the first and r = -.028 on the second), P3Go amplitude (r = .275 on the first and r = -.023 on the second), CNV amplitude (r = -.251 on the first and r = -.027 on the second) and P3NoGo amplitude (r = .117 on the first and r = .003 on the second).

N1 latency loaded heavier on the second function (r = .530) than on the first (r = .116), as did the P3NoGo latency (r = .407 on the second and r = -.031 on the first), CNV latency (r = -.401 on the second and r = -.002 on the first), N1 amplitude (r = .204 on the second and r = .145 on the first) and P3Go latency (r = .044 on the second and r = -.043 on the first). We can also see that the first function affects P2 amplitude (r = .786) and P3Go amplitude (r = .275) in a similar way, but the second function affects P2 amplitude (r = .149) and P3Go amplitude (-.023) in a different way.

Table 7: Structure matrix: Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions.

Components	*Function 1*	*Function 2*
P2_A	,786	,149
P2_L	,464	-,028
P3GO_A	,275	-,023
CNV_A	-,251	-,027
P3NOGO_A	,117	,003
N1_L	,116	,530
P3NOGO_L	-,031	,407
CNV_L	-,002	-,401
N1_A	,145	,204
P3GO_L	-,043	,044

To determine which groups the functions discriminate between, we had a look at the Function of group centroids (Table 7), which shows the average function score for each group. Function 1 discriminates fibromyalgia and chronic pain group from chronic fatigue group. Function 2 discriminates chronic pain group from fibromyalgia and chronic fatigue. Function 1 discriminates the groups stronger than the 2nd function, since the values are further away from zero.

Table 8: Functions at Group Centroids. The mean for each group along the two functions in a multivariate space. The further away from 0, the more discriminative the respective function is.

Group	Function 1	Function 2
Fibromyalgia	-1,222	-,383
Chronic Pain	,022	,808
Chronic Fatigue Syndrome	1,140	-,404

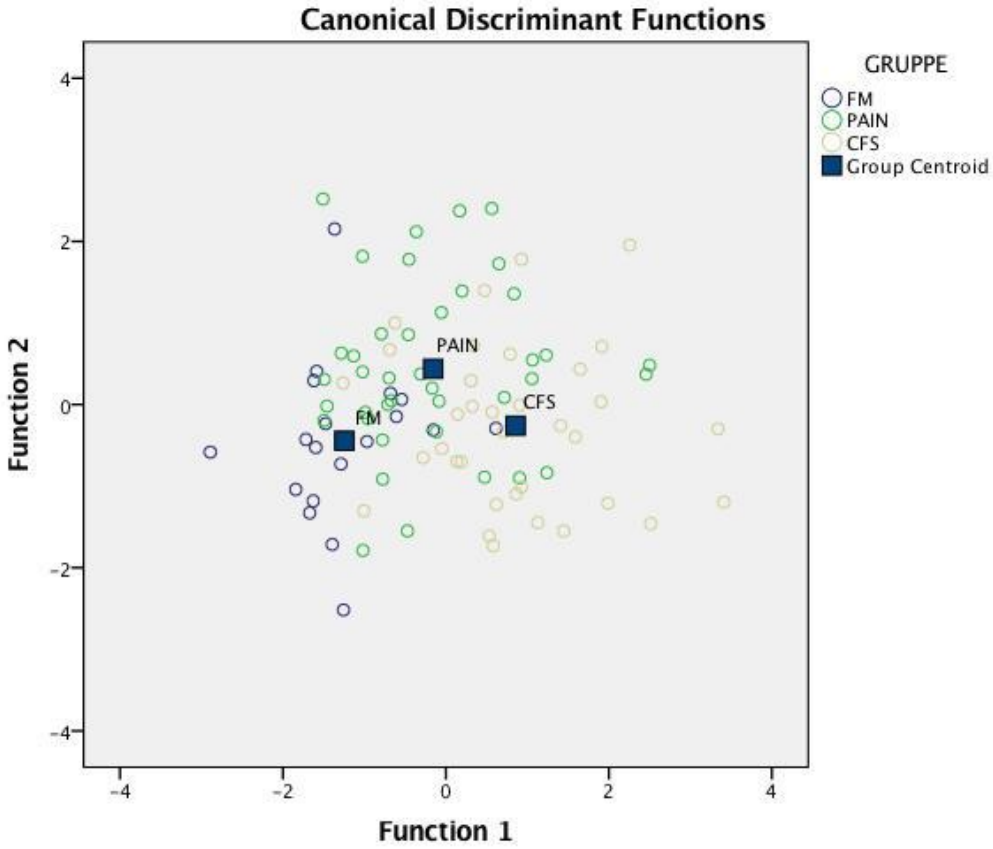

Figure 3: Canonical Discriminant Functions. The multivariate space where the mean of each group is marked with a dark box. Each circle is a single value (participant), and their placement is computed along both functions.

The discriminant function plot (Figure 3) shows the multivariate space, where the mean of each group are marked with a dark box. According to this, we can see that function one discriminates stronger than function two, but the functions only discriminates the groups significantly in combination (when both functions are considered). Function 1 discriminates the fibromyalgia and chronic pain group from chronic fatigue, and function 2 discriminates the chronic pain group from chronic fatigue and fibromyalgia.

Classification statistics is based on how close an individual is to each group centroid in the multivariate space. An individual is classified into the group that it is closest to. Classification statistics indicated that 69% of original group cases were correctly classified by the 10 variables, 73,7% of the subjects in the FM-group were correctly classified, while 68,5% and 65% of the subjects were correctly classified into the Pain- and CFS-groups, respectively.

Chapter 4 – Discussion

Main findings

Aim of the study

This project had two research questions. The main purpose was to investigate whether SCP Neurofeedback manages to improve brain patterns in fibromyalgia patients and relieve symptoms. The second purpose was to investigate whether the brain patterns of fibromyalgia patients differ from the qEEG patterns of generalized chronic pain patients and chronic fatigue patients in a multivariate space.

Behavioural data

The participants in the intervention group showed a significant reduction in reaction time on the VCPT, from 358,78 to 310,78 ms, indicating faster information processing after neurofeedback training. The participants in the EEG group had a longer reaction time. This may indicate that the participants in the intervention group were less severely cognitively afflicted by the disease compared to the EEG-group.

FIQ

In this project, the questionnaire was intended as a subjective supplement to the objective ERP measures to identify whether the neurofeedback training had a clinical effect. The 1991 version was used because it is the only one validated in Norwegian. Because our project was a part of another fibromyalgia project, we were imposed to use it. The eight participants in the intervention group showed an average decrease in the FIQ score of 5,21 points (from 46,16 to 40,95 points), but this was not a significant reduction. The EEG-group had a slightly higher average score than the intervention group (48,6) indicating a somewhat lower level of functioning, larger overall impact and worse symptoms than the women in the intervention group. However, the difference between the two groups is too small to be conclusive (48,6 - 46,16=2,44).

The FIQ results indicate that neurofeedback intervention had a small effect on physical functioning, overall impact and symptoms, but not a significant effect. However, the participants in the intervention group scored lower on both FIQ and the VCPT reaction time compared to the participants in the EEG group. Additionally,

they showed a significant reduction in reaction time after the neurofeedback intervention, which indicates that the FIQ does not capture the improvement in the VCPT.

T-test

The significance level is two-tailed, as we had no prediction as to which direction the results might go. The t-tests resulted in three significant values. The amplitude of CNV(sig= .017), the amplitude of P3Go (sig= .007) and the amplitude of P3NoGo (sig= .001). The significant values tell us with high degree of certainty that neurofeedback training had an effect on the amplitudes of CNV, P3Go and P3NoGo. The three significant t-tests all showed large effect sizes, which means that they all represent substantial findings.

Group differences – MANOVA

The significant MANOVA indicates that the groups differ along a combination of variables in a multivariate space. The test of between subject's effects indicates that it is the P2 component (both amplitude and latency) that separates fibromyalgia, chronic pain and chronic fatigue patients. Because the multiple ANOVAs studies each variable separately, and not taking into account the combination of variables that we were interested in, they were not emphasized. To study the combination of variables, the MANOVA and a subsequent discrimination analysis has been used, instead of looking at post hoc tests. Effect sizes for the MANOVA was .374, which is considered a small to medium effect.

The discriminant analysis revealed two functions that separate the groups significantly, in combination. One function discriminates between the pain conditions and the chronic fatigue patients, while the second function separates chronic fatigue and fibromyalgia patients from chronic pain patients. Interpretation of this will be elaborated later in the discussion.

Interpretation of main findings

VCPT, FIQ and t-test

The nine participants completing 30 sessions of neurofeedback showed a significantly reduced reaction time on the post-test VCPT. This significant reduction in reaction time indicates that neurofeedback training had a positive effect on the participants' attention. Small improvements in reaction time on a VCPT are not uncommon, as a learning effect can occur, but a significant improvement is larger than an anticipated learning effect. The questionnaire was executed in the lab or at home the same day as the VCPT, however it did not yield any significant results. A possible explanation for this is that the 1991 version of the FIQ does not capture domains like cognition, attention and memory and instead focuses on physical function and emotional wellbeing. When comparing the event related potentials from the VCPT, three ERP's came out significant. The amplitudes of CNV, P3Go and P3NoGo showed significant increase after SCP training compared to before. In addition, they all had good effect sizes, emphasizing that they were all substantial findings.

Small improvements in ERP's can occur, but an individual's ERPs are normally quite stable. The significant alterations on the three amplitudes may be due to SCP training or other treatments (as this was not an isolated project). There is reason to believe that SCP neurofeedback training is the cause of improvement, due to the significant alterations for the participants as a group. The question that remains to be answered is the practical meaning of these altered amplitudes.

The CNV amplitude tells us something about the level of attention the individual invests in a task. Increased amplitude after the intervention indicates that the level of attention has increased. The increased amplitude of the CNV may also reflect increased level of arousal, stress and vigilance. As the functional meaning of an increased CNV amplitude is thus ambiguous, it is difficult to conclude.

P3, on the other hand, is easier to interpret. In general, the P3 component reflects discrimination between stimuli and is associated with attention and memory

processes. A reduction in P3 latency signifies a faster cognitive processing of information. This was not the case in this study, as the latency remained unchanged. Prior research has concluded that attentive problems give smaller P3 amplitude, and that greater attention produces larger amplitude. P3Go amplitude in particular, is associated with executive control function. An increase in this amplitude may signify an increased executive control. P3NoGo is associated with inhibition and control processes. An increase in P3NoGo amplitude is positive, as fast responders have higher amplitudes than slow responders. This finding is in accordance with the reduced reaction time on the VCPT. The participants also reported the experience of a better attention span and memory, which is in line with an increase of P3Go and P3NoGo amplitude.

Research has concluded that fibromyalgia patients have substantial cognitive and memory difficulties. Legarin et al.'s (2011) theory about the pain matrix (PM) redefines it as a salience detection system. The theory suggests that chronic pain patients have altered attentional mechanisms and that this affects the way pain is processed. The amplification of pain perception is, in this theory, explained by the chronic pain patient's over-responsiveness to their surroundings and possible threats. Kutcyi & Davis (2014) explain the alterations in the attention network in a different way. In their theory on the dynamic pain connectome, they claim that networks relevant for spontaneous fluctuation of attention are disturbed in chronic pain patients. They claim that this difference in connectivity is the cause of difference in pain perception and amount of attention given to pain. Eccleston & Crombez (1999) believe pain captures attention because the organism needs to be open to information from their surroundings due to the superior goal of self-protection. According to capacity models of attention, the amount of attention an individual has is not infinite, but restricted. When you have exceeded your maximum capacity, your thoughts and behaviour become flawed. According to this theory, if pain works like a constant interruption and takes up part of your capacity of attention over time, there is less capacity of attention left to use on other things. The lack of continuous attention due to interruption and use of attentive capacity on pain result in disrupted thought and behaviour. When the maximum capacity of your attentive system is reached, the consequence might be that there is no capacity left to filtrate information from the surroundings, resulting in wrongful, augmented pain processing. These theories may to some extent explain how chronic pain patients' attentional systems are disrupted

and how attention can affect pain processing. The findings in this project indicate that these attentive problems are possible to improve with SCP training.

The intention behind the use of the 1991 FIQ was to identify a potential decrease in symptoms due to SCP training. The non-significant results of the FIQ tell us that the participants did not experience significant symptom relief as a result of SCP training. The significant decrease in reaction time on the VCPT and increased amplitudes of CNV, P3GO and P3NOGO indicate the opposite. In the revised version of FIQ, memory, and subsequently attention, is included, but the version we used focuses on emotional wellbeing and physical level of functioning. This could explain why the questionnaire yielded no significant results even though ERP amplitudes and reaction time improved. A possible interpretation of the results is that attention is improved, but the FIQ does not measure it.

MANOVA

Looking at the significant MANOVA alone, it tells us that the groups are different from each other in a combination of the variables in a multivariate space. This can be interpreted as the patient groups being independent syndromes and thus gives added weight to an assumption of possible bio-markers for each diagnosis. Looking at the discriminant analysis, however, it is revealed that the syndromes may also have some things in common, which is in line with the previous literature about extensive overlap of symptoms and comorbidity.

The point of interest is that the discriminant analysis proposes two underlying functions that separate the groups, in combination, but in different ways. The first function separates the groups along one dimension; it separates the chronic pain group and fibromyalgia patients from those suffering from chronic fatigue. The second function separates fibromyalgia patients and chronic fatigue patients from those with chronic pain. This implies that function 1 covers something that fibromyalgia and chronic pain have in common, and that function 2 covers something that fibromyalgia and chronic fatigue patients have in common. As we are investigating diagnoses with a substantial overlap of symptoms, it is reasonable to believe that the functions separating the groups represent symptoms. The main symptom of both chronic pain and fibromyalgia is pain. Since function 1 separates those patients from the chronic fatigue patients, who do not have pain as the core symptom, it is plausible that function 1 represent the symptom of pain. When it comes to function 2, it represents

something that fibromyalgia patients and chronic fatigue patients have in common, that separates them from the chronic pain group. From what we know of the symptoms of fibromyalgia, chronic pain and chronic fatigue, it looks like function 2 may represent either the fatigue or the cognitive complaints/deficits that many patients report.

The result of the discriminant analysis can also be interpreted in a way that supports the assumption of a common underlying mechanism. This common mechanism is hypothesized to be central sensitization of the nervous system. This sensitization is believed to be visible in the brain and therefore in the qEEG and ERP components.

Looking at the variables contributing the most to each function, this gives us some potential answers. The variables contributing to function 1 (suggested to represent pain) are mostly amplitudes of the components, except the P2 where the latency also loads heavily on the first function. As mentioned in the theory section, amplitude can be interpreted as the intensity of a stimulus. The discriminant analysis does not say whether the amplitudes are high or low, but it tells us that the amplitude of the components is important for separating fibromyalgia and chronic pain from chronic fatigue. Looking at the descriptive statistics, this reveals that the group having the overall highest amplitude is the chronic fatigue group. Since we do not have a control group and HBI did not give any meaningful statistics, it is impossible to know whether the groups had significant higher or lower amplitudes than normal. If low amplitude reflects a more intensive experience of pain, this may be the key to why amplitude is important for separating patient groups with pain from a patient group where pain is not the core symptom. Low amplitudes can be related to an abnormally functioning attention system. In turn this may affect the default mode network connected to the pain matrix and hence the subjective experience of pain.

The variables loading the most on function 1 are the P2 amplitude and latency. P2 is elicited in the P-H condition, after the second picture, where there is a sound. In addition to be related to attention, the P2 component is thought to be sensitive to physical parameters of a stimulus and that the amplitude is greater with a higher stimulus intensity (Hegerl & Juckel, 1993; Hillyard & Picton, 1987; Key et al., 2005; Novak, Ritter, & Vaughan, 1992; Näätänen, 1992). The descriptive statistics reveals that chronic fatigue patients also have the highest P2 amplitudes, which points to chronic fatigue patients processing sound more intensively.

When it comes to function 2, the main contributors are variables representing the latency of the ERPs in addition to the amplitude of N1. This function represents what fibromyalgia and CFS patients have in common, suggested to be fatigue or cognitive deficits. Cognitive deficits and attention problems can be related to latency, as latency represents the time of encoding. This could be compatible with a prolonged latency and may reflect prolonged processing due to problems with focus and attention. However, the descriptive statistics reveals no pattern when it comes to the latency of the groups and thus making it difficult to support this interpretation.

If this interpretation of function 1 and 2 is correct, it entails that out of the three patient groups the chronic fatigue patients is the group experiencing least pain, and the chronic pain patients is the group experiencing least attentive/cognitive difficulties. This can also possibly be ascribed to an underlying sensitization, manifested in the syndromes in different ways, and thus resulting in different aetiologies.

qEEG and neurofeedback as diagnostic tools.

Great heterogeneity in the fibromyalgia patient group in general, in addition to the sustainable overlap with other diseases is well-documented. This makes it important to have diagnosis criteria that capture more than just the core symptoms. While theories and research stay current and progress, the means of diagnosis are arguably out dated.

qEEG and neurofeedback may be good tools for diagnosing and treating fibromyalgia patients due to the possibility of individual treatment. In this project, all participants received identical neurofeedback training, but there is also possible to tailor a neurofeedback protocol to the needs of the individual. qEEG make it possible to assess the patients' deviances in brain functioning are with a vCPT. This is not possible with other imaging techniques as qEEG is superior in the temporal domain. When the deviances are identified, a tailored neurofeedback protocol can be made.

Even if one might see some deviances on the qEEG of fibromyalgia patients, it is still difficult to say whether the deviances are the result of a sensitization processes in the central nervous system or if these deviances represent a genetic vulnerability. We know that qEEG patterns and the form of ERP waves can be hereditary, and we also know that there is a bigger chance of being diagnosed with

fibromyalgia if it is already in the family. Whether it is the vulnerability or the sickness itself that is the genetic factor, is difficult to say and warrants further investigation. It would then be interesting to look at the qEEG patterns of family members, or even monozygotic twins, where one of them has the diagnosis, and the other one has not. This would indicate whether there are, and what kind of, similarities or differences there are in the qEEG.

Regardless of the concept, there is a question whether to treat the overlapping disorders as a group or separately. One syndrome will manifest differently in different individuals. However, patients suffering from one "unexplained" disorder/syndrome are likely to have symptoms belonging to other similar syndromes. Our results have clearly presented some shared features between chronic pain patients and fibromyalgia patients and other shared features between the fibromyalgia and CFS patients, represented by 2 factors. This shows that despite the shared features, the disorders are possible to separate, if not completely. With both substantial overlap and shared features across the groups, the only treatment recommended is an individually tailored one that does not emphasize the diagnosis, but the individual.

Why bio-markers?

Even if researchers manage to find bio-markers for fibromyalgia, or other unexplained syndromes, the subjective well-being of the individual is the most important. It does not matter if a bio-marker says that you have fibromyalgia if you do not have the symptoms. Together with finding bio-markers, there comes a responsibility. Researchers have to ask themselves why we need it, and how it will help the patient. Together with earlier findings and reports from the patients participating in this study, we presume that a bio-marker will make it easier to diagnose and categorize patients (especially when in doubt of which of the unexplained disease the patient is suffering from). A bio-marker will be an objective and visible "proof" of an illness that is otherwise not taken seriously. Having an "invisible" illness is not easy for the sufferer. Many patients in our study reported they felt the desire to be taken seriously. As such, making the illness "visible" and discernible may help the patient feel they are being taken seriously.

The Biopsychosocial model of sickness emphasizes that diseases have a biological contribution, as well as psychological and social. This project did not focus on social factors, or their contribution to fibromyalgia. However, many of the patients

reported traumatic life events, but we did not keep a record of this since this was beyond the scope of the project. It would be interesting in future projects to put such variables in system. It could be investigated further how many of the patients have experienced traumatic life events and whether it could be a trigger for an underlying vulnerability.

Another social aspect is that more women than men are diagnosed with fibromyalgia. Based on this study, it is not possible to explain why, since only women participated in our study. It is unclear whether this is due to statistical chance, if only women are active in the Fibromyalgia association or if men in general are not interested in studies. We know that men also have the diagnosis, but there are significantly fewer of them. This could also be down to social factors such as that men may go to see their doctors less frequently, talk about symptoms in another way or that doctors may interpret men differently than women. However, there may also be biological explanations grounded in genetic differences between the sexes. Men have shown to have a significantly higher pain threshold than women, and thus score lower on the tender points test. As fibromyalgia may manifest slightly differently in men than in women, today's criteria may not be as useful in diagnosing fibromyalgia in men, as it is in women. This would be a good argument for revising the diagnostic criteria and the implementation of more objective measures. The indentification of bio-markers might give some answers.

Limitations & implications

Participants and control group

The first and biggest limitation of this study is the lack of a control group. With a control group, it would be possible to compare the patient groups with age-matched healthy controls to look for potential bio-markers. There were several reasons for not having a control group and they were carefully considered. First, having a control group would have required a substantial amount of time to gather participants. This was unfortunately not possible due to time constraints of the master thesis only covering 2 semesters. It would also require an approval from REK, which would prolong the waiting period before the data collection could start. The approval of this study, took about 4 months. To ensure a good age-match, the necessary

corresponding data would have needed to be obtained after knowing the age of the fibromyalgia patients. This means that the data collection period would have lasted for over 6 months, unfortunately with our time constraints this was not feasible or achievable without postponement. It was discussed whether to use already collected data from other studies to make a control group. We based our decision on that if we were to use a control group if would be best to collect it ourselves to make sure the investigation was ethical and methodically similar to ours to reduce methodical limitations.

The only control group, or comparison with a healthy population, we have in this project is the HBI. This gives us some indications of deviances, but there are several reasons for dismissing this database. Firstly, the database is Russian. Even if Russia is not far from Norway, we cannot be sure that the Russian population is similar to the Norwegian population. Furthermore, since the participants are performing a vCPT, this would mean taking more variables into account. Secondly, the data was collected by unknown third part and leaving many questions unanswered in addition to very little information on testing situations and the corresponding cofounding variables. Thirdly, there does not exist a record of the standard deviations in the HBI. Only a mean is provided for the whole group and with no single values. Due to this, it is not possible to use SPSS to make comparisons and we had to use the winEEG for this purpose.

Variables

Another limitation is the lack of control of possible confounding variables in the vCPT. There are many variables that can influence the VCPT-results: the participants' age, experience with computers, left-handed vs. right-handedness, sight/vision, other diagnoses (like migraine), time of the day and medication. Most important is the way the instructions are given before the vCPT. The protocol chosen is determined by which components and cognitive processes one is interested in, but for the right component to appear in every setting/patient it is important that the exact same instructions are given to every participant. The vCTP in this study is a reaction time task, where patients are instructed to respond as fast as they can. If some of the patients in the other groups did not get this instruction clearly, this may have an impact on several of the components. This is crucial for the CNV, P3Go and P3Nogo,

which are seen as the components of preparation, execution, processing and inhibition of actions.

The number of components is also a possible limitation. We have 5 components with both amplitude and latency: resulting in 10 dependent variables. Even though we had 10 variables and had to do a bonferroni-correction, this correction did not influence the number of significant components. However, many of the ANOVAS after the MANOVA did not come out as significant, and it is not easy to know if this had something to do with the high number of variables, the components chosen for investigation, the number of participants or other cofounding variables. We chose 5 components with both latency and amplitude, because there is no consensus in earlier research on which and how the ERP components differ in our populations. We consider our project a pilot project because of the small number of participants and little earlier research to lean on.

We cannot be certain that neurofeedback is responsible for the changes in the individuals. This could maybe have been solved with a placebo or control group given another treatment. Since neurofeedback consist of 30 sessions, it would be unethical to give that many sessions as placebo. The use of both ERPs and the FIQ contribute in measuring the clinical outcome and we consider it a strength of the study that we have used both subjective (FIQ) and objective (ERP) measures to assess the amount of improvement. However, it is a challenge that the questionnaire fails to measure cognitive abilities like attention and memory.

Representativeness

20 participants did the initial qEEG, and 10 participants proceeded with neurofeedback training. It was voluntary to proceed with neurofeedback training, and was not asked any questions if the participant did not want to proceed after the initial qEEG. Some of those who only did the qEEG told us that they could not commit to do as many as 30 sessions during 3 months because they never knew if they had the energy level to keep an appointment, others said they did not have time or wanted to prioritize other things. The fact that we could not guarantee an effect of the neurofeedback, made some of the patients sceptical to invest such an amount of time on it. On the basis of the answers from the patients and also what we saw on the qEEG results, one can assume that the patients proceeding and completing 30 neurofeedback sessions were those least affected by the disease and also those most

motivated to try something that might not work. One can only speculate how the results of the Neurofeedback would have been for the most severely afflicted. In addition, we know that there are individuals suffering from fibromyalgia that did not even get the chance to participate in this study. It is difficult to facilitate the treatment in a way so that those most severely afflicted can participate. Perhaps this could have been possible with more flexible time schedules and a longer period of data collection.

Participants were recruited via the Fibromyalgia association, and it is not possible to know if those who are active there are representative of fibromyalgia patients in general. Some people with fibromyalgia may be so severely afflicted that they do not have the energy to engage in that kind of associations at all or they may not be active in associations simply because they are not interested.

FIQ

The biggest challenge concerning the questionnaire is partly due to the fact that the form is outdated. It has been revised tree times since 1991 and both the questions and the scoring method has changed. Most importantly, the scoring of question three and four has been changed. They are both related to work. If you are not able to work because of fibromyalgia, you cannot answer these two questions, reducing the scale from a total of 100 possible points to 80. This was corrected in the 1997 version of the questionnaire (Williams & Arnold, 2011). Question 3 now includes house work making it possible for everyone to answer (Bennett, 2005). Among the 17 participants who completed the questionnaire, five were employed. It would have been possible to alter the scoring method to compensate for the loss of points due to lack of ability to work, but that would entail not scoring the questionnaire according to the rules.

In addition, FIQ might not be the best measure in this particular case, where it seems like pain and physical functioning remain unaltered, and mental fitness increases. Even though FIQ is a well-known and validated form, it has not been emphasized in this study because it is outdated and focuses on physical and emotional fitness. The form itself is not hard to answer, but several participants did not complete it. A possible reason for this can be the environment the questionnaire was answered in. the participants chose if they wanted to fill out the form at home or in the lab. Several of the participants were too reduced after the qEEG to answer it in the lab and

chose to do it at home where they could answer it without time pressure. When answering the form in the lab, they had the opportunity to ask us about things that were unclear. On the other hand, answering a personal questionnaire in a room with strangers may activate social bias. In this context, social bias may cause the participants to exaggerate their answers in order to prove that they are ill. Answering the form at home can give the participants time to think and give better answers than they would have in the lab. To give conclusive answers, all the forms in both groups should have been completed and they should have been answered under the same conditions. In addition, the number of participants is too small to be conclusive in this case. Further research is needed, preferably using a validated version of a Norwegian FIQR on a larger group of patients.

Design and statistics

When it comes to the design and statistics, there is room for improvement. The Neurofeedback project has a pre-test post-test design and to test whether the treatment had an effect, multiple t-tests were performed. Multiple t-tests is not ideal in any research project and should be avoided due to increased chance of committing a type 1 error, but there were factors that made the t-test necessary. The ideal for a pre-test post-test design on one group is to do a RANOVA – repeated measures ANOVA. However, this requires that the groups are measured 3 times; one pre-test, one halfway and one post-test. We needed to have as many as 30 sessions with neurofeedback and many of the patients dropped out during the period of neurofeedback. To have a qEEG measure half way would have required more time and effort from the patients and could mean that more of them would have quit or not participated at all. Since concern for the patients should be the most important consideration, we decided not to go for repeated measures. The fact that many of the patients reported mild fatigue and headache after the qEEG, made us feel we had made the most ethically correct decision.

As we performed several t-tests, the chance of detecting a false positive, also called type 1 error, increases. This means that the null hypothesis is rejected when it is actually true. The practical implication of an increased chance of committing a type 1 error in this project is that the tree t-test that came out significant might not be. On the other hand, the three values were highly significant, strengthening the assumption of them as true findings.

Reliability and validity

The limitations mentioned above may have had an impact on the study's validity and reliability. Validity concerns an instruments ability to measure what it is supposed to measure. Reliability is the instruments ability to produce similar scores at different points in time. Concerning hypothesis 1 and 2, the validity is strengthened due to the use of objective measures (ERPs) as opposed to subjective. Variables affecting the validity of ERP measures are EEG noise/artefacts not adequately removed. Artefact correction is done by hand and the different patient groups have been artefact corrected by different people.

Prior research has concluded that the FIQ shows high test-retest reliability, but in this project the validity of the questionnaire was poor due to the lacking ability to capture improvement in attention.

The analysis of reaction time in the VCPT is both valid and reliable, but the interpretation of reaction time improvement as increased attention because of SCP training might not be. The reason is that this was not an isolated project, and other factors than SCP training might have improved the score.

Future research / implications of the study

If we were to replicate the study, there are some things we would have done differently or included in the project. Ideally, our study should have included a control group, more participants, maybe two different neurofeedback protocols or even customized neurofeedback protocols based on the qEEG recording, a qEEG halfway to see improvement and make other and better statistics possible. In addition to more powerful statistics and a more representative sample, more participants would also make it possible to control for possible confounding variables and thus heightening the reliability of the study. Cofounding variables in this study could have been concomitant syndromes, medication use and other treatments.

Future research should also look deeper into components associated with fibromyalgia and sensitization to see if and which ones can be possible bio-markers for the disease. A wider recruitment would be beneficial, not only through the fibromyalgia association, to reach out to those who are better and worse than those

active in this association. An updated version of FIQ with focus on cognition and memory would also be preferable.

It is also important for future research to elaborate the findings from the MANOVA and discriminant analysis. Including more syndromes in the research could enable this, but most importantly; having bigger sample sizes and trying to control for the elements mentioned above. Even if the overlap between the disorders is large, it is not enough to demonstrate a bio-marker in one of them to draw conclusions about all of them. It has not been proven that there are similar pain mechanisms in the disorders. It is important that future studies look deeper into the mechanisms and use the same tests for a better basis for comparison (Meeus, Nijs, Huybrechts, & Truijen, 2010).

Both psychological and physical variables in each patient should be considered in an attempt to investigate the degree of affliction, since the same disorder can manifest differently in different individuals and also be experienced differently. Focus on sickness behaviour, other somatic symptoms and negative life events can shed light on associated factors and also lead to the discovery of individuals at risk for developing either fibromyalgia or related syndromes (Aggarwal et al., 2006). Further research on associated factors is needed to identify risk factors, which would also enable prevention or early intervention.

Chapter 5 - Conclusion

The significant MANOVA indicates a difference in ERPs between the patients suffering from fibromyalgia, chronic pain and chronic fatigue, indicating that they are three distinct diagnoses. This is confirmed by the combination of two factors distinguishing the groups. However, they are not mutually exclusive, as they are bound together by a substantial overlap in symptoms. The two factors not only separate the groups, but may also represent features the diagnoses have in common. Those features are interpreted to be the symptoms pain and fatigue. Our results strengthen the assumption of them as separate clinical diagnoses as well as the existence of possible individual biomarkers. On the other hand, the two factors binding them together do not point in the direction of central sensitization, but may reveal differences in manifestation of central sensitization.

The significant improvement in reaction time on the VCPT and the three significant increases in ERP amplitudes, demonstrate that neurofeedback training have an effect on fibromyalgia patients. We have suggested that this effect reflects an improvement in attention due to SCP training. In addition, the FIQ scores showed a moderate improvement after neurofeedback training, indicating a slightly better level of physical functioning, overall impact and symptom severity, but the change was too small to conclude.

The limitations in this study have been discussed thoroughly. Further research should be conducted to verify our findings using a larger sample of patients in addition to a proper age-matched control group.

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List of tables and figures

Appendix 1

Informed consent

Informert samtykke i forbindelse med "qEEG og Nevrofeedback på Fibromyalgipasienter"

Bakgrunn for prosjektet
Vi, Kari Bøhle og Anne Bøe, er masterstudenter i psykologi ved NTNU og skal i forbindelse med vår masteroppgave drive et prosjekt i samarbeid med førteamenuensis Stig Hollup og psykiater Egil Fors.

Prosjektet går ut på å undersøke hjerneaktivitet hos fibromyalgipasienter, samt å utprøve en treningsmetode på samme gruppe. Forhåpentligvis kan vi bidra med ny kunnskap om fibromyalgi og kanskje også et bedre alternativ til dagens behandling.

For å måle hjerneaktiviteten, vil vi bruke en målemetode kalt Kvantitativ ElektroEncefaloGrafi (qEEG). Denne måler hjernebølger i ulike områder av hjernen og man har mulighet til å se om noen områder skiller seg ut med høy eller lav aktivitet. Videre vil vi bruke en treningsmetode kalt nevrofeedback. Det er en treningsmetode som krever minimalt med fysisk innsats; man skal sitte foran en dataskjerm med elektroder på hodet i ca 30 minutter. Denne treningsmetoden er uten ubehag og bivirkninger.

Hva studien innebærer
Ved deltakelse i studien vil vi først gjennomføres en samtale med deg samt en qEEG-måling i et rom ved NTNU Dragvoll, som er spesielt egnet for dette. Denne målingen, inkludert samtale før og etter, vil vare i ca 1 time. EEG-målingen foregår ved at du får en hette med elektroder på hodet som er koblet til en datamaskin, som måler hjerneaktivitet. For å opprette bedre kontakt mellom elektroder og hjernen vil vi bruke en saltholdig gele. Selve EEG-målingen innebærer et opptak på 3 minutter med åpne øyne, 3 minutter med lukkede øyne, samt et 20 minutters opptak med en øvelse hvor man trykker på en knapp når bilder dukker opp på en dataskjerm. EEG-målingen vil bli gjort totalt 2 ganger, en gang i starten av prosjektet og en gang ved slutten. Dette for å måle hvorvidt treningsmetoden vi tester har hatt effekt.

Selve treningsmetoden er det vi kaller nevrofeedback. Her vil du få 3 elektroder festet til hodet (en enklere versjon av hetta ved EEG) og bli plassert foran en dataskjerm i ca 30 minutter. Man skal etter instruksene gitt konsentrere seg om bildet på skjermen som er tilbakemeldingen på din egen hjerneaktivitet (feedback). Dette er også helt uten ubehag og risiko. Denne treningsmetoden går ut på at hjernen skal trene seg selv opp til ønsket hjerneaktivitet ut fra resultatene vi fikk på EEG. For at treningen skal kunne ha effekt må vi utføre repeterte treninger, i dette prosjektet vil det være 30 stk per deltaker. Det er ingen begrensning på hvor ofte man kan utføre treninger og hvor raskt vi blir ferdige med alle behandlingene kommer an på den individuelle tidsplan vi legger opp. Men vi ser for oss 2-3 økter i uka over en periode på 10-15 uker. Etter 30 treninger, vil vi utføre en ny EEG-måling samt ha en samtale med deg. Dette gjør vi for å kunne se om treningen har hatt en effekt.

Oppbevaring og bruk av dine opplysninger
EEG-opptakene og opplysningene om deg skal kun brukes slik som beskrevet i hensikten med prosjektet. Alle opplysninger og qEEG-opptak vil bli behandlet uten navn og fødselsnummer eller andre detaljer som gjør det gjenkjennelig. Vi vil gi dine opplysninger en ID i en navneliste, som vil være oppbevart innelåst ved NTNU. Denne listen vil kun prosjektleder ha tilgang til.

Vi ønsker også å kunne oppbevare de anonymiserte dataene i en database for å i fremtiden kunne benyttes i videre studier. Dersom du ikke ønsker at dine data blir lagret (anonymt) i databasen etter endt prosjekt, kan du reservere deg mot slik bruk.

Dersom du selv ønsker å se resultatene fra opptakene, kan du ta kontakt med prosjektansvarlig.

Frivillig deltakelse
Det er frivillig å delta i prosjektet. Dersom du ikke ønsker å delta, trenger du ikke å melde ifra. Det er kun de som signerer og leverer samtykkeskjema som vi tar videre kontakt med. Dersom du signerer samtykket til å delta i studien, kan du likevel trekke dette når som helst, uten å måtte oppgi noen grunn.

Dersom du ønsker å delta, signerer du samtykkeerklæringen på neste side. Selv om du nå sier ja til å delta, kan du likevel trekke dette samtykket når som helst.

Samtykke til deltakelse i fibromyalgi-prosjekt

Jeg samtykker til å delta i denne studien

……
(Signert av prosjekt-deltaker, dato)

Jeg gir min tillatelse til at mine anonyme qEEG-opptak kan benyttes i videre studier ved qEEG-lab/inngå i en qEEG-database i EEG-lab JA ☐ NEI ☐

Appendix 2

FIQ

Pasientnr: | | | | | | |

Fibromyalgi spørreskjema - FIQ

1. Klarte du i løpet av den siste uken, **i den grad du ønsket det,** å: (kryss under det svaret som passer, velg uaktuelt for oppgaver du ikke pleier å gjøre, eller som du ble forhindret fra å gjøre av andre årsaker enn fibromyalgi)

	Alltid	Oftest	Iblant	Aldri	Uaktuelt
a) Handle?	☐ 0	☐ 1	☐ 2	☐ 3	☐
b) Vaske tøy i maskin?	☐ 0	☐ 1	☐ 2	☐ 3	☐
c) Lage mat?	☐ 0	☐ 1	☐ 2	☐ 3	☐
d) Vaske opp tallerkener og gryter for hånd?	☐ 0	☐ 1	☐ 2	☐ 3	☐
e) Støvsuge en rye?	☐ 0	☐ 1	☐ 2	☐ 3	☐
f) Re senger?	☐ 0	☐ 1	☐ 2	☐ 3	☐
g) Gå lengere enn 1 km?	☐ 0	☐ 1	☐ 2	☐ 3	☐
h) Besøke venner eller slektninger?	☐ 0	☐ 1	☐ 2	☐ 3	☐
i) Drive med hagearbeid?	☐ 0	☐ 1	☐ 2	☐ 3	☐
j) Kjøre bil?	☐ 0	☐ 1	☐ 2	☐ 3	☐

2. I hvor mange av de siste 7 dagene hadde du det bra? (Kryss av for tallet som passer)

   ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

3. I hvor stor grad var du sykemeldt p.g.a. fibromyalgi den siste uken? (Besvares ikke hvis du er hjemmeværende, arbeidsledig eller alderspensjonist)

   ☐ 0% ☐ 25% ☐ 50% ☐ 75% ☐ 100% (Kryss av for tallet som passer)

   ☐ Sykemelding ☐ Attføring ☐ Uføretrygd (Kyss av)

Snu arket!

Draft

Pasientnr: | | | | | | |

De følgende spørsmålene besvares ved at du setter en liten loddrett strek på det punket på linjen som best beskriver hvordan du har hatt det den siste uken. Hvis du ikke har vært på jobb siste uke, hopp over 4. og gå direkte til spørsmål 5.

4. Spørsmål 4 besvares bare hvis du har vært på jobb siste uken. I hvor stor grad har smerter, eller andre fibromyalgisymptomer, påvirket hvordan du utførte jobben din?

Intet problem med å utføre jobben	Store problemer med å utføre jobben

5. Hvor sterk har smerten din vært den siste uken?

Ingen smerte	Meget sterk smerte

6. Har du vært trett den siste uken?

Ingen tretthet	Meget trett

7. Hvordan har du følt deg når du står opp om morgenen den siste uken?

Våknet frisk og uthvilt	Våknet meget trett

8. Hvor kraftig har stivheten din vært den siste uken?

Ingen stivhet	Meget stiv

9. Har du følt deg anspent, nervøs eller engstelig den siste uken?

Ikke anspent	Meget anspent

10. Har du følt deg deprimert eller nedfor i løpet av den siste uken?

Ikke nedstemt	Meget nedstemt

Draft