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QEEG and Infra-Low Frequency Neurofeedback Training in Fibromyalgia: A Pilot Study

Master's thesis in Psychology
Supervisor: Stig Arvid Hollup
May 2019

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Preface and Acknowledgment

Chronic pain is a growing health problem which severely influences the quality of life of those affected. A patient once told me that "chronic pain is not something you die from, but something you die with". Even though you can't see chronic pain physically, such as a broken leg, it does not mean that the pain experienced is not real and severe for the person affected. Additionally, chronic pain is often accompanied by other symptoms, such as cognitive difficulties, fatigue, and a variety of psychosocial problems. Chronic pain patients often struggle with being taken seriously, especially those with a fibromyalgia diagnosis, a complex disease with no distinct spatial localization of the experienced pain.

Therefore, the motivation behind writing this thesis lay in opposing the current understanding of fibromyalgia as a low-status diagnosis, as well as improving the currently available diagnostic tools and treatment options for this disease. Through investigation of potential neurobiological markers for fibromyalgia and exploring the effects of infra-low frequency neurofeedback as an intervention for all symptoms implicated in the disease, we believe that this thesis is a contribution to a much-needed improvement of diagnosis and treatment for fibromyalgia.

The amount of work and technicalities involved in this project have been overwhelming to say at least. There are several people involved in the project that I would like to thank. First and foremost, I would like to thank all the inspiring patients that participated in this study and shared their stories and experiences with us. We are sincerely grateful for your time and effort. I want to give a huge thank you to my supervisor Stig Arvid Hollup for excellent guidance, support, conversations, and for allowing me to explore my two scientific passions; the neuroscience field, and chronic pain. I would also like to thank Line Luckman, my lab-partner in this project, for great teamwork and help with data collection. Additionally, I would like to thank Frederick Anyan for taking his time to discuss statistical and methodological choices with me.

Sammendrag

Bakgrunn: Fibromyalgi (FM) er en kompleks kronisk smertesykdom karakterisert av diffus smerte, fatigue (utmattelse), og fibrotåke (kognitive vanskeligheter) som i betydelig grad påvirker pasientenes livskvalitet. Årsaken til og effekten av fibromyalgi er uklar og gjør det utfordrende for legepersonell å gi en korrekt diagnose. I tillegg finnes det ingen behandling for fibromyalgi som fokuserer på sykdommen som en helhet. Forskning indikerer at sentrale sensitiviserings mekanismer er en del av symptombildet, i tillegg til abnormal smerteprosessering i hjernens «dynamic pain connectome» (DPC).

Dette pilotstudie hadde to formål; *(a)* å sammenligne FM pasienters hjerneaktivitet med friske kontroller for å se om hjerneområdene som viser avvik er tilknyttet DPC, og videre vurdere om disse kortikale regionene kan bidra til å avdekke nevrobiologiske markører for fibromyalgi; *(b)* å undersøke effekten av infra-low frekvens nevrofeedback-trening (ILF NFT) på FM symptomer for å evaluere ILF NFT som en potensiell intervensjon for fibromyalgi.

Metode: Pasientene gjennomførte 10-15 treninger med ILF NFT, i tillegg til pre- og post-test undersøkelser (EEG-opptak og utfylling av spørreskjemaer relatert til grad av symptomer og livskvalitet).

Resultater: Wilcoxon Signed-Rank Tester indikerte signifikant symptom-reduksjon og normalisering av hjerneaktivitet blant pasientene etter ILF NFT. Posisjoneringsanalyse indikerte at alle pasientene viste avvik i et eller flere av hjerneområdene inkludert i DPC. Begrensninger ved studien og tolkninger av resultatene er diskutert.

Nøkkelord: Infra-low frekvens nevrofeedback, dynamic pain connectome, sentral sensitivisering, hjernefrekvens-aktivitet, fibromyalgi

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1. Introduction

Fibromyalgia (FM) disease is a chronic pain disorder associated with several painful symptoms affecting daily life. In Norway, the estimated prevalence ranges from 2-8 % and occurs most often among women. Moreover, fibromyalgia represents the biggest group of women applying for disability benefits (Mork & Nilsen, 2012; Mork, Vasseljen, & Nilsen, 2010; Wigers, 2002). The cause of this disease is unclear due to the lack of evidence for distinct spatial localization of the experienced pain, in addition to, the source of the other symptoms accompanied by the pain, such as fibrofog and fatigue (den Boer et al., 2019). Accordingly, treatment options for FM are limited, and the disease is challenging to diagnose correctly. Several studies indicate that FM patients show deviant brain activity in cortical areas located to the brains´ pain networks (Fallon, Chiu, Nurmikko, & Stancak, 2018; Lim, Kim, Kim, & Chung, 2016). These networks consist of the default mode network (DMN), the salience network (SN), and the antinociceptive system (AS). Together, they constitute the dynamic pain connectome (DPC). The functional connections between these networks modulate the experienced chronic pain and are affected by infra-low frequencies (Kucyi & Davis, 2015; Ploner, Sorg, & Gross, 2017). Quantitative electroencephalography (QEEG) provides a non-invasive method for measuring brain activity, and source analysis estimated by standardized low-resolution brain electromagnetic tomography (sLORETA) makes it possible to position estimate the activity recorded. Neurofeedback is a tool providing real-time, instantaneous feedback about an individual´s brainwave activity which makes it possible to retrain brain frequency bands to an optimal state (Niv, 2013). By using neurofeedback to uptrain infra-low frequencies in FM patients, it is possible to normalize deviant brain activity and strengthen the functional connectivity between pain inhibiting networks in the DPC.

This pilot study aims to investigate FM patients´ QEEG data and the effect of infra-low frequency neurofeedback (ILF NFT) on FM symptoms. The thesis has two parts. Firstly, a preliminary analysis that compares FM patients´ QEEG data with age-matched controls in the HBI (Human Brain Institute) normative database to investigate and position estimate the brain activity of FM patients. Secondly, pre-test post-test analyses of QEEG data and symptom score measures to examine the effect of ILF NFT on FM symptoms.

1.2 The Chronic Pain Brain

The International Association for the Study of Pain (IASP) define pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The IASP has defined chronic or persistent pain as pain without any apparent biological value that has persisted beyond average tissue healing time. Chronic pain is usually pain that persists for more than six months (International Association for the Study of Pain, 1986). Acute pain has a biological value because it serves primarily as a protective function, evolutionary essential for survival. In contrast, chronic pain is experienced as long-lasting, unpleasant sensations without any biological value. Consequently, chronic pain has the potential to lead to a cycle of distress and disability, affecting the patient's quality of life, often with poor general physical health, unemployment, social alienation and interpersonal stress as associated factors (Blackburn, 2018).

Latham and Davis estimated that chronic pain affects approximately 30 % of the population globally (Latham & Davis, 1994). Unfortunately, these chronic pain patients are often diagnosed inaccurately with a host of co-morbid conditions including depression, fatigue, and weight loss. The typical chronic pain patient will on average experience 4-5 referrals before reaching a satisfactory diagnosis. Additionally, chronic pain patients usually report pain in the absence of tissue damage or any likely pathophysiological cause, which causes many clinicians to tie the pain to psychological reasons, and not to a painful stimulus (Saab, 2014). Recent studies investigating chronic pain have focused on brain networks to explain chronic pain diseases such as fibromyalgia. Brain research may shed light on how to differentiate between chronic pain diseases and how to treat chronic pain properly.

1.2.1 The dynamic pain connectome. In the brain, pain and attention are dynamically connected. Since pain evolutionary signifies an immediate threat to survival, it has a unique attention-demanding quality. Attention-demanding tasks, stimuli, and thoughts can change the quality and salience of pain, in addition to, the neural processing of nociceptive input. Consequently, attention toward pain naturally waxes and wanes as "perceptual decoupling". The brains´ integration process has to be very flexible to adjust pain to the momentary attentional and behavioural demands. It requires dynamic changes of neuronal integration at timescales which can only be provided by changes in functional connections, not by changes in structural connections. This type of functional network reorganization has been described as the "dynamic pain connectome" which represents the integration of all features of pain, including cognitive, affective, and sensorimotor aspects (Kucyi & Davis, 2015; Ploner et al.,

2017). Three key brain networks and their dynamic interaction with each other make up the dynamic pain connectome (see Table 1). An underlying assumption is that these interconnected systems affect each other's activity, reflected as synchronous modulation in the BOLD fMRI signal (Borsook, Edwards, Elman, Becerra, & Levine, 2013).

Table 1

Cortical areas implicated in the DPC with corresponding Brodmann areas

Default mode network	Brodmann area
Ventral medial prefrontal cortex (vMPFC)	24, 10, 32
Posterior cingulate/retrosplenial cortex (PCC/Rsp)	29/30, 23/31
Inferior parietal lobule (IPL)	39, 40
Lateral temporal cortex (LTC)	21
Dorsal medial prefrontal cortex (dMPFC)	24, 32, 10, 9
Hippocampal formation	28(EC), 27, 36, 37, 30(PH)
Anterior cingulate cortex (ACC)	24, 32, 33
Salience network	
Dorsal anterior cingulate cortex (dACC)	24, 32, 33
Anterior right insula (aRI)	13
Inferior frontal gyri (IFG)	45, 46, 44, 47
Temporal parietal junction (TPJ)	39
Dorsolateral prefrontal cortex (dlPFC)	46
Mid-cingulate cortex (MCC)	24, 23, 32

Note. EC = enthorinal cortex; PH = parahippocampal cortex.

1.2.1.1 Default mode network. The default mode network (DMN) is a brain system much like the visual system or sensory-motor system. It contains a set of interactive brain networks functionally connected and distinct from other brain systems. The cortical regions implicated in the DMN are coactivated during passive tasks, show intrinsic functional correlations with each other, and communicate via direct and indirect anatomic projections. The system is most active during passive settings and tasks that direct attention away from external stimuli (Buckner, Andrews-Hanna, & Schacter, 2008). Hence, the DMN represent the brain´s resting state and is related to chronic pain as chronic pain processing is characterized by intrinsic brain activity even in the absence of explicit brain input or output.

Thus, alterations in a patient's brain at "resting state" can result in a different DMN organization. Also, potential changes in the DMN activity could be related to symptoms commonly exhibited by chronic pain patients, such as sleep-disturbances and depression (Baliki, Geha, Apkarian, & Chialvo, 2008; Kucyi & Davis, 2015).

1.2.1.2 Salience network. Activity in the cortical areas implicated in the salience network is known to track the degree to which external stimuli are salient and thereby intrinsically capture attention (Downar, Mikulis, & Davis, 2003; Kucyi & Davis, 2015). Downar and colleagues (2003) showed that some regions in the salience network (TPJ and ACC) display a transient response to changes in a non-painful stimulus, but a sustained response during a painful stimulus (Downar et al., 2003), which implicates the network´s role in pain. Moreover, research has shown that salience-related responses to sustained painful stimuli differ in chronic pain patients, compared to healthy controls. In healthy controls, sustained painful stimulation becomes less painful over time, but this effect is absent among chronic pain patients (Borsook et al., 2013). Functional connectivity between the SN and DMN is thought to be essential for cognitive control and focused attention. SN activity is enhanced by external stimuli that are behaviourally salient, whereas the DMN display enhanced activity when subjects have an internal focus of attention (Jilka et al., 2014). Therefore, focused attention on pain may enhance SN activity, while focused attention away from pain may enhance DMN activity, pointing to these two opposing forces as core candidates for pain modulation.

1.2.1.3 Antinociceptive system. The third system involved in the dynamic pain connectome is the descending modulatory (antinociceptive) system (AS) which includes a region in the periaqueductal grey (PAG) of the brainstem. This system is associated with pain modulation. Research indicates that functional connectivity between PAG and DMN increases when attention fluctuates away from pain, which suggests that dynamic communication between DMN and AS has a central role in pain modulation. Sustained attention on pain may represent inflexible, recurrent feedback loops of spontaneous communication between the DMN and AS. Over time, these dynamic connection patterns may entrain network-level structural and functional abnormalities in the pain connectome, leading to the development of chronic pain (Kucyi & Davis, 2015). In line with this hypothesis, Tracey and colleagues (2002) found a significant increase in PAG activation when subjects were distracted away from pain, supporting the notion that increased activity

within the PAG has a “top-down” influence on pain perception. Furthermore, the PAG contains significant quantities of endogenous opioid peptides. Therefore, it is possible that increased PAG activity caused by distraction away from pain, allows PAG to release endogenous opioids that exert their antinociceptive effect on pain pathways (Tracey et al., 2002).

1.2.2 Dynamic pain connectome activity in chronic pain patients. In addition to the brain´s regular resting activity, the brain of chronic pain patients is continuously processing spontaneous background pain. While investigating the BOLD fMRI signal in chronic pain patients, Baliki and colleagues (2011) found that patients under resting-state exhibited a shift towards higher frequencies in oscillatory activity. These enhanced BOLD oscillations (0.10-0.25 Hz) was primarily related to the mPFC and brain regions within the DMN. Functionally, the shift in oscillations was associated with reorganized connectivity between the mPFC, insula, cingulate cortex, and secondary somatosensory regions, which are all involved in pain processing. Indicating that the presence of pain may interfere with the transmission of information, by altering how pain-relevant regional frequencies co-oscillate (Baliki, Baria, & Apkarian, 2011).

Several other studies investigating the brain activity of FM patients have found increased connectivity between regions within the DPC that correlate with reports of increased chronic pain (González-Roldán, Cifre, Sitges, & Montoya, 2016; Napadow et al., 2010). To further explore these findings, Napadow and colleagues (2012) used acupuncture as a treatment for fibromyalgia and investigated its efficacy in treating symptoms. Following treatment, the patients experienced significantly less pain. Furthermore, the diminished pain correlated positively with reduced intrinsic connectivity between the DMN and insula, a core region involved in the integration of information regarding the significance of a stimulus into the decision of pain (Wiech et al., 2010). These results provide further support for intrinsic brain connectivity as a potential cause for the subjective experience of chronic pain (Napadow, Kim, Clauw, & Harris, 2012).

Additionally, Flodin and colleagues (2014) conducted a whole-brain analysis of FM patients, revealing diminished resting-state connectivity between pain-related areas and primary sensory cortices. This reduced resting-state connectivity could reflect a “pain state of mind”, where brain areas implicated in the processing of pain are operating under fewer constraints by other inhibiting brain networks. Furthermore, this disturbed thalamocortical

connectivity in chronic pain patients could reflect an obstructing gate-keeping function of the thalamus, leading to enhanced pain perception (Flodin et al., 2014).

1.3 Fibromyalgia

Fibromyalgia (FM) is a complex multisystem disorder characterized by several clinical features, three of the most severe ones are wide-spread pain, fatigue and "fibrofog" (cognitive difficulties) (Galea, Fernández-Aceñero, & de la Fuente, 2017; Glass, 2008). FM patients experience so-called "tender points" on the body, where even light pressure can cause pain. These pressure points include upper chest, hips, and knees (Galea et al., 2017). One of the most distinctive symptoms of FM is fibrofog, characterized by a significant decrease in memory, attention problems, and a feeling of mental slowness (Glass, 2008). These memory and attentional difficulties may be caused by attentional distraction towards pain (Leavitt & Katz, 2006).

1.3.1 Diagnostic criteria. In 1990, the American College of Rheumatology (ACR) established diagnostic criteria for fibromyalgia. The criteria required tender points in at least 11 of 18 specified sites, the presence of widespread pain on both sides of the body, and chronic pain persisting for at least 3 months.

Although the ACR classification from 2009 increased the recognition for fibromyalgia, the classification criteria raised a series of objections. It became clear that few physicians knew how to examine for tender points. Consequently, the tender point count was rarely performed in primary care where most fibromyalgia diagnoses occurred. Secondly, the criteria did not include some increasingly known fibromyalgia features such as fatigue, cognitive symptoms, and the extent of somatic symptoms. Furthermore, the ACR classification criteria set such a high bar for diagnosis that there were little room for variations in symptoms. Patients who improved did not fit the criteria which made it hard to assess and treat them (Wolfe et al., 2010). Based on these issues, the ACR classification criteria was later revised in 2010.

According to the American College of Rheumatology (ACR) fibromyalgia classification criteria from 2010, the following 3 conditions have to be fulfilled to get diagnosed with fibromyalgia: *(a)* Widespread pain index (WPI) ≤ 7 and symptom severity (SS) scale score >5, or WPI 3-6 and SS score ≥ 9; *(b)* Symptoms have been present at a similar level for at least 3 months; and *(c)* The patient does not have a disorder that would otherwise explain the pain. Because diffuse pain can occur in a variety of other medical conditions, they

should be considered before making a fibromyalgia diagnosis. These related conditions may include diabetes, metastatic cancer, rheumatoid arthritis, Lyme disease, and HIV/AIDS, among others (Marcus, 2009). This revised diagnostic criterion is not meant to replace the ACR classification criteria from 1990 but was designed as a supplement which recognizes the importance of cognitive problems and somatic symptoms not included in the previous ACR classification criteria. Also, it is meant to be used as a supplement for clinical diagnosis in primary care, which ordinarily does not involve a tender point count (Wolfe et al., 2010).

1.3.2 Treatment. Symptom reduction from medications is often modest at best and should be combined with other non-medication treatments (Marcus & Deodhar, 2011). Nevertheless, there are some effective medications for reducing fibromyalgia symptoms. These include SNRI antidepressants duloxetine and milnacipran, and neuromodulating antiepileptics, with analgesic properties. A meta-analysis of antidepressant therapy for FM patients showed that short-term usage of antidepressants could improve pain, depression, fatigue, and sleep disturbances symptoms (Häuser, Bernardy, Üçeyler, & Sommer, 2009). Research has also shown that FM patients treated with milnacipran experience a reduction in pain sensitivity, in addition to, a parallel activity increase in brain regions implicated in the descending pain inhibitory pathways. Indicating that the lower pain threshold for the nociceptive system seen in the patients is due to decreased activity of the descending inhibitory pathways (Mainguy, 2009).

Non-pharmacological treatments for FM include exercise, neurofeedback, and transcranial direct-current stimulation (tDCS). Studies have shown that FM patients who consistently exercise, report fewer symptoms, enhanced physical function, and improved quality of life (Fink & Lewis, 2017; Marcus, 2009). Type of exercises should be individualized to meet the needs and tolerance of the individual patients, and there should be a gradual onset and increase (Fink & Lewis, 2017). In addition to exercise, numerous studies have also demonstrated that neurotherapy leads to symptom reduction among FM patients (Caro & Winter, 2011; Castillo-Saavedra et al., 2016; Fagerlund, Hansen, & Aslaksen, 2015; Kayıran, Dursun, Dursun, Ermutlu, & Karamürsel, 2010).

1.3.3 Theories about cause and impact. The lack of evidence for both peripheral sensitization and distinct spatial localization of the pain experienced by FM patients makes it difficult to explain the cause of this disease. Nevertheless, research suggests a variety of causes based on clinical findings, such as neurophysiological changes, abnormal stress

response, altered central neural processing in nociceptive pathways, and reduced inhibitory control in the central nervous system (Sluka & Clauw, 2016). There seems to be an emerging consensus that the mechanisms implicated in central sensitization can explain these clinical findings (den Boer et al., 2019).

1.3.3.1 Central sensitization. Central sensitization can be defined as increased responsiveness of nociceptive neurons in the central nervous system compared to their normal or sub-threshold afferent input, that elicits pain hypersensitivity (den Boer et al., 2019; Woolf, 2011). Pain perception or "nociception" is a complex sensory process influenced by emotion, context and prior experience. Mainly two types of pain receptors are activated by nociceptive input; *(a)* low-threshold nociceptors connected to fast conducting A-delta pain fibers, and (*b)* high-threshold nociceptors connected to slow (unmyelinated) C fibers. These fibers innervate the dorsal horn of the spinal cord and synapse with spinal cord neurons. Different neurotransmitters (i.e., glutamate and substance P) can modulate the postsynaptic responses with further transmission to the thalamus and cortical sites via the ascending pathways (Kandel, 2013; Meeus & Nijs, 2007). There are several neurobiological theories for the cause of central sensitization. These neurobiological mechanisms revolve around plasticity both in the central nervous system and the brain, caused by prolonged pain. Some of these mechanisms are; hyperalgesia, allodynia, enhanced facilitation of NMDA receptors, temporal summation, and expansion of the receptive fields.

Temporal summation refers to a central spine mechanism in which repetitive noxious stimulation results in a slow temporal summation experienced as increased pain. The dull second pain transmitted by C fibers is most strongly related to chronic pain diseases, such as fibromyalgia. During the neuronal transmission through C-fibres, NMDA-receptors of second-order neurons in the dorsal horn of the spinal cord become activated and induces calcium-entry into the dorsal horn neurons, causing nitric oxide (NO) synthesis. NO can enhance the release of substance P from presynaptic neurons, and in turn, contribute to the development of hyperalgesia, experienced as an increase in responsiveness and prolonged effects of noxious stimuli. Substance P is an essential nociceptive neurotransmitter because the neurotransmitter can extend for long distances in the spinal cord and sensitize dorsal horn neurons from a distance. Enhancement of substance P release can additionally cause expansion of receptive fields, called secondary hyperalgesia, and activate other neurons by non-nociceptive afferent impulses causing a painful perception of non-painful stimuli, called allodynia (den Boer et al., 2019; Meeus & Nijs, 2007; Woolf, 2011).

Studies have demonstrated that FM patients experience increased efficacy of temporal summation and prolonged after-sensations when noxious thermal stimulation is applied, suggesting that the efficacy of central processing is increased (Price et al., 2002; Staud, Vierck, Cannon, Mauderli, & Price, 2001). Further evidence indicates that FM patients experience stronger pain and larger referred areas after painful stimuli, compared to healthy subjects (Sörensen, Graven-Nielsen, Henriksson, Bengtsson, & Arendt-Nielsen, 1998).

Dysregulation of neuroimmune activation in FM patients is also a potential mechanism contributing to the central sensitization. An inflammatory profile has been described for FM patients, showing evidence of elevated levels of fractalkine and interleukin-8 (IL-8) in cerebrospinal fluid (CSF) (Bäckryd, Tanum, Lind, Larsson, & Gordh, 2017). Both of these proteins participate in neuronal-glial communication. Glial activation can be studied using radioligands that bind to the 18-kDa translocator protein (TSPO). TSPO is a protein localized primarily in the outer mitochondrial membrane. This protein is involved in translocation of cholesterol from the outer to the inner mitochondrial membrane, a vital step in the synthesis of steroids and neuro-steroids (Rupprecht et al., 2010).

TSPO activation is low in healthy tissue but is upregulated in microglia and astrocytes under inflammatory conditions such as chronic low back pain (cLBP) (Albrecht et al., 2018). Albrecht and colleagues (2019) recently found evidence for this upregulation in FM patients. Their study revealed increased glial activation in several brain regions included in the dynamic pain connectome. Among the regions demonstrating neuroimmune activation was the precuneus, a core region of the default mode network. Compared to the earlier findings in cLBP patients, FM patients showed a more spatially extended cortical activation pattern which might reflect the more widespread pain and cognitive issues experiences by FM patients. Additionally, the elevated TSPO in the cingulate cortex correlated with elevated levels of fatigue among the FM patients. This TSPO activation was also found in chronic fatigue patients, which might suggest that glial activation in this region could be a potential mechanism underlying pathological fatigue across different chronic conditions (Albrecht et al., 2019). The results of these studies support the notion that FM is a disease characterized by hypersensitivity of pain, caused by central sensitization.

1.4 EEG

An approach to the study of mental processes is the recording of electroencephalography (EEG). The EEG measures the brains´ electrical activity with a non-invasive approach using electrodes attached to the scalp. The EEG has a high temporal

resolution. However, it has low spatial resolution due to it being recorded at the scalp. Popular functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have some advantages over EEG; better spatial resolution and an ability to detect cellular activity in structures that do not contribute to scalp EEG, such as the cerebellum and subcortical structures. Nevertheless, EEG can detect changes in brain activity a thousand times faster than other techniques. Moreover, EEG technology has advantages such as portability, inexpensiveness, and a 75-year history of investigation (Fröhlich, 2016; Kaiser, 2007).

QEEG (quantitative electroencephalography) is a quantification of the raw EEG-recording. Quantitative analysis of EEG data allows for more objectivity and specificity focused on the activity time-locked to the events under investigation (Handy, 2005). Statistical analysis can be performed to generate the patient´s mean spectral map of frequencies, amplitude, and their relative power (Legarda, McMahon, Othmer, & Othmer, 2011). Also, the performance protocols used in the EEG recording provide us with information about the patient´s event-related potentials (ERPs), which are significant voltage fluctuations resulting from evoked neural activity initiated by an internal or external stimulus (Kropotov, 2009; Teplan, 2002).

1.4.1 Neurophysiological basis of EEG. The EEG signal (electrical potential) is a graphic representation of the difference in voltage between distinct cerebral locations plotted over time. The electrical potential is mainly generated by the collective electrical behaviour of hundreds of thousands of small dipoles corresponding to pyramidal cells and interneurons. Both inhibitory postsynaptic potentials (IPSPs) and excitatory postsynaptic potentials (EPSPs) contribute to the activity recorded as EEG, by creating the local currents which induce the electrical dipoles (Kropotov, 2009). For an EPSP or an IPSP to occur, there must be a transmembrane current (flow of ions across the membrane) which changes the transmembrane potential in a given neuron and thereby give rise to electrical mean fields. The local mean field recorded at any given site reflects the sum of overlapping field-generated current sources (current from the intracellular space to the extracellular space) and sinks (current from the extracellular space to the intracellular space) distributed adjacent multiple cells. The duration of postsynaptic potentials is ten times longer than the duration of a single spike caused by action potential generation. As a result, the effects of postsynaptic potentials can propagate much further in the extracellular space, and they have a much higher chance to occur in a temporally overlapping manner, in contrast to brief action potentials. Furthermore, EPSPs and

IPSPs are displayed by many more neurons than spikes, because only a small number of neurons reaches the threshold for triggering an action potential at any instant in time (Buzsáki, 2006; Kropotov, 2009; Olejniczak, 2006).

1.5 Event-Related Potentials

Event-related brain potentials (ERPs) are small changes in the brains´ electrical activity, recorded from the scalp and caused by some external or internal event. These EEG changes are time-locked to sensory, motor or cognitive events. ERPs are usually recorded with a temporal resolution in the order of a few milliseconds from multiple scalp locations, due to the rapid changes and spatially extended fields. Scientists often use ERPs as a tool to understand their manifestations in behaviour and how subjective experience can arise from brain activity.

1.5.1 Measurement and classification. Researches often describe and examine ERPs as distinct entities, but it is more accurate to describe a given component as belonging to a group of components with similar polarities and temporal characteristics (Woodman, 2010). Polarity, timing, scalp distribution, and sensitivity to task manipulations define distinct groups of components. In general, the letter "P" in abbreviations indicate positive waves, and the letter "N" indicates negative waves, according to their polarity. The number behind the abbreviations indicates the latency (milliseconds) or the ordinal position of the component in the waveform. For example, the N1/N100 component refers to a component with a negative peak polarity appearing approximately 100 milliseconds after stimulus onset. When using ERP components to examine changes in association with disorders, patients´ ERPs are compared with controls to investigate potential differences in amplitude and peak latency. 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 defined time window, often considered as a measure of intensity. Whereas latency (milliseconds) is defined as the time from stimulus onset to the point of maximum positive or negative amplitude within a defined time window (Handy, 2005; Landa, Krpoun, Kolarova, & Kasparek, 2014; Niedermeyer & Lopes da Silva, 2005).

1.5.2 The VCPT and Go/NoGo paradigm. ERP components have been tested in various performance tests to investigate different types of information processing. Some examples are the Oddball paradigm, Posner´s task, the Stop signal paradigm, and the

Go/NoGo protocol. A version of the Go/NoGo protocol was used in this study. The Go/NoGo visual continuous performance task (VCPT) is a neurophysiological test designed to measure complex attentional functions such as sustained attention and inhibitory control, thought to be mediated by the prefrontal cortex. In Go/NoGo tasks, subjects are presented with a categorical task and instructed to make a response to only one of the choices (go trials) and not the other (no-go trials). In a standard Go/NoGo task the proportion of go-stimuli and no-go stimuli is most often 50:50 (Kirmizi-Alsan et al., 2006; Ratcliff, Huang-Pollock, & McKoon, 2018). The number of trials needed to obtain an acceptable signal-to-noise ratio depends on the size of the signal you are attempting to record, and the noise level of the data. A rule of thumb is that you have to have at least 60 trials per condition to look at components such as the P3 wave, N2 wave, and P1 wave (Handy, 2005).

The VCPT has a large set of varying distractor stimuli which makes it complicated for the subject to focus his/her attention on the stimuli, thereby building high demand for sustained attention. In the VCPT task, the frequency in which a subject can successfully detect a target over time, reflect that person´s ability to maintain a state of readiness to respond (sustained attention). A high level of focused attention is needed because the performance depends on both the correct representation of the primer stimulus and the maintenance of this information during the delay period before the presentation of either go or no-go stimuli (Kirmizi-Alsan et al., 2006; Ratcliff et al., 2018). The VCPT Go/NoGo tasks have been widely used to study, amongst others, inhibitory control in a range of clinical disorders, such as ADHD, depression, and PTSD. The time range in which an individual makes a go response to a no-go stimulus represents an index of that person´s inhibitory control. Considering the great attention-demanding quality of pain possibly disturbing the brains´ inhibitory control, the VCPT protocol is a well-suited task for investigating the brain of chronic pain patients (Kropotov, 2009; Kucyi & Davis, 2015).

1.5.3 N1, CNV, and P3 NoGo (early and late). N100 (typically peaking at 100-150 ms post-stimulus) is related to early perceptual processes, such as feature integration and encoding. It responds more to the physical properties of a stimulus (location and intensity) than task demands (Sumich, Castro, & Kumari, 2014). The N100 is generated by cortical sources primarily from sensory cortices, in addition to, frontal regions such as the dorsal anterior cingulate cortex (dACC) (Premkumar et al., 2014), and is thought to be influenced by spatial attention (Luck, 2005). It seems like N1 amplitude increases with the intensity of a

stimulus. Hence, enhanced N1 amplitudes may reflect perceptual overload (Hillyard, Vogel, & Luck, 1998).

The contingent negative variation (CNV), a slow negative potential appearing between a cue stimulus and a target stimulus, is a promising ERP component for studying proactive executive processes. The amplitude of this wave may reflect a combination of the task setting process and the level of energy invested in maintaining focus and reactivating this task-set over time (Brunner et al., 2015; Luck, 2005). As the first stimulus (S1) usually serves as a preparatory signal for the second stimulus (S2), which requires a motor response (such as pushing a button), it is likely that the CNV represents neuronal activity necessary for sensorimotor integration and is related to planning or execution of externally voluntary movement. Within the total CNV, to subcomponents can be distinguished. Early CNV is evoked by S1 and is related to sensory processes associated with processing and evaluation of the first warning stimulus. Late CNV precedes S2 and is related to both motor and cognitive preparation, in addition to the anticipation of relevant information included in the second stimulus. Due to the frontocentral scalp distribution of the CNV and the fact that the CNV occurs in situations involving behaviour typically ascribed to the frontal lobes, the frontal cortex is considered as the prime candidate for generation of the CNV component (Chao, Meyerhoff, Cardenas, Rothlind, & Weiner, 2003; Kowalski et al., 2018).

We know a great deal about the effects of various manipulations on the P3 amplitude and latency. Nevertheless, there is no clear consensus about what neural or cognitive processes the P3 wave reflects. P3 amplitude is larger when subjects devote more effort to a task, leading to the possibility that P3 amplitude is as a measure of resource allocation. Also, P3 amplitude is smaller when the subject is uncertain of whether a given stimulus is a target or a non-target. In contrast, P3 latency is not sensitive to the amount of time required to select and execute a response once a stimulus has been categorized (Luck, 2005). There are several distinct ERP components in the time range of the P3 wave. The NoGo stimuli in a VCPT task 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). Two components within the P3 NoGo wave can be distinguished, P3 NoGo early and P3 NoGo late. These components have different topographies and latencies. Besides, they are thought to reflect different cognitive processes. Brunner and colleagues (2015) showed that P3 NoGo early had a peak latency of 330 ms with a central distribution, and P3 NoGo late had a peak latency of about 380 ms with a more fronto-central distribution. It seems like energization correlates with the amplitude of P3 NoGo early, while monitoring is associated with the amplitude of P3 NoGo late (Brunner

et al., 2015; Kropotov, 2016). The late positive fronto-centrally distributed P3 component elicited in the NoGo-condition is a candidate for investigating reactive executive processes. This component represents the engagement of many different and intrinsically related cognitive processes. It is unlikely that the P3 NoGo wave is an inhibitory operation because of its late appearance. Nevertheless, it may be regarded as a conscious decision to withhold a response (Brunner et al., 2015).

1.5.4 ERP deviations in fibromyalgia patients. P3 latency is a measure of information processing speed and variations in P3 amplitude is thought to express the degree to which incoming information is processed and stored in the working memory (Polich, 1998). A decreased P3 amplitude is therefore believed to reflect poor performance of working memory functions. Considering these characteristics, the P3 component might be a valid measure of the cognitive difficulties (fibrofog symptoms) seen in FM patients. Several studies have found that FM patients display reduced P3 amplitudes, compared to healthy controls (Alanoğlu et al., 2005; Ozgocmen et al., 2003; Yoldas et al., 2003). Additionally, Yoldas and colleagues (2003) found that P3 amplitude correlated with reported pain-levels. Alanoglu and colleagues (2005) also found that FM patients had prolonged P3 latencies, which may reflect a decrease in information processing speed within this patient group.

Because N1 is related to early sensory processing, its amplitude might reflect the ability to filter out irrelevant perceptual stimuli. The N1 component is enhanced to attended-located stimuli, which seems to be a general characteristic of the spatial focusing of attention across a variety of task situations (Hillyard & Anllo-Vento, 1998). Consequently, enhanced amplitude could reflect hypersensitivity to incoming stimuli. FM patients generally experience hypersensitivity to perceptual stimuli because of the central sensitization mechanisms implicated in the disease. Therefore, FM patients might show enhanced N1 amplitudes, compared to healthy controls. Choi and colleagues (2016) found that FM patients exhibited enhanced N1 amplitudes following auditory stimuli repetition, which might reflect the inability to filter out irrelevant sensory stimuli (Choi, Lim, Kim, & Chung, 2016).

Several studies have shown enhanced CNV amplitudes among migraine and headache patients (Böcker, Timsit-Berthier, Schoenen, & Brunia, 1990; Kropp & Gerber, 1993; Siniatchkin, Gerber, Kropp, & Vein, 1998). Studies have also found enhanced amplitudes of the CNV component during induced pain (Stude et al., 2003), and during the anticipation of induced pain (Babiloni et al., 2005), compared to non-pain conditions. The enhanced amplitude might reflect overactivation of cortical areas responsible for pain perception.

Babiloni and colleagues (2005) found that CNV amplitudes became enhanced during the expectation of painful stimuli and that this activation was located to somatosensory cortices and insula. Therefore, enhanced CNV amplitudes among chronic pain patients might reflect distorted sensorimotor processes in the cortical regions involved in pain processing.

1.6 Brain Oscillations

The brain exhibits rhythmic activity patterns at different spatial and temporal scales, referred to as oscillations. In essence, oscillations reflect an alternating pattern of depolarization and hyperpolarization that enables or disables effective translation of incoming synaptic input into postsynaptic action potential firing (Fröhlich, 2016). Oscillations at different frequencies participate in different "biological hardware". Initially, the different oscillations were defined based on their time of discovery, using Greek letters such as alpha, beta, delta, and theta.

1.6.1 Generation of thalamocortical brain oscillations.

Neuronal oscillations may arise due to different mechanisms, such as alternating excitation-inhibition of neurons, pacemaker cells, resonance, or subthreshold membrane oscillations (Pevzner, Izadi, Lee, Shahlaie, & Gurkoff, 2016). A general function of all thalamocortical oscillations is their role as a gatekeeper, controlling whether and when information about the outside world, detected by peripheral sensors, can pass through the thalamus and be distributed for further information processing in cortical networks. Three types of neurons are detected in the thalamic relay nuclei (TRN): *(a)* the thalamocortical (TC) neurons whose axons project to the cortex; *(b)* the reticular nucleus (RE) neurons that contribute to the inhibitory feedback control of TC neurons, and *(c)* local intrinsic neurons. The RE neurons are located in the ventral part of thalamus and are interconnected with TC neurons through a feedback loop. The reticular nucleus consists of inhibitory GABAergic neurons, making the feedback loop between TC neurons and RE neurons inhibitory. TC neurons can work in one of two ways; *(a)* as relay cells which depolarise and produces single spikes in response to input stimuli, or *(b)* as oscillatory cells producing bursts of high-frequency spikes repeated in a rhythmic fashion. It is the resting membrane potential of the neuron that determines which mode the TC neuron is active in (da Silva, 1991; Kropotov, 2009; Steriade, Gloor, Llinás, Lopes Da Silva, & Mesulam, 1990).

For example, spindles arise due to RE neurons hyperpolarizing thalamocortical neurons with a rhythmic burst of inhibitory synaptic potentials (IPSPs). The hyperpolarization

leads to the activation of low-threshold Ca^{2+} channels. The following Ca^{2+} inward current induces depolarization of the TC neuron, followed by an action potential. Subsequently, TC neurons generate a burst of excitatory synaptic potentials (EPSPs), which activates the RE neurons as well as corticothalamic neurons and, and give rise to a spindle. Further, the EPSP input onto RE neurons activates low-threshold Ca^{2+} channels, which sends prolonged IPSPs back to TC neurons through feedback connections, allowing the oscillatory cycle to start again. The time to go through one oscillatory cycle prescribes the observed frequency. In the case of spindles, 7-14 Hz (Kropotov, 2009; Pevzner et al., 2016).

1.6.2 Theta, alpha, and beta frequency bands. The theta band has a frequency of 4-8 Hz. Theta cycles may be considered as an information quantum because they allow for the exchange of information among linked members in a phase-locked manner. This cyclic mode of operation temporarily segregates and link neuronal assemblies to perform various cognitive operations. Hence, theta oscillations can be understood a process bringing together the activity of sensory- and memory-activated neurons in time, consequently affecting behavioural output and plasticity (Buzsáki, 2002). Based on wavelet transformation of neuronal responses in different tasks, the HBI normative database has shown that there may be at least two separate theta rhythms in humans. The frontal midline theta rhythm increases with task load, has a higher amplitude to meaningful stimuli and habituates if the same stimulus is presented several times. Additionally, this rhythm is associated with the hippocampal theta rhythms, caused by cooperative behaviour of a large number of hippocampal pyramidal cells firing in synchrony to produce theta oscillations. Therefore, frontal midline theta oscillations may reflect the "on-line" state of the hippocampus (Buzsáki, 2002). Another type of theta rhythm, the parietal alpha-theta rhythm emerges only in task conditions. This rhythm seems to appear in even shorter bursts than the frontal midline theta rhythm. It has a lower amplitude, does not depend on the behavioural meaning of the stimulus, and does not habituate with repetition of trials (Kropotov, 2009).

Alpha rhythms have frequencies covering the range from 8-13 Hz. There are at least three distinct types of alpha rhythmicity appearing during relaxed wakefulness; *(a)* the posterior (α) rhythm recorded at occipital or occipital-parietal areas; *(b)* the sensory-motor mu rhythm (μ) recorded over the sensory-motor strip, and *(c)* the tau (τ) rhythm recorded at mid-temporal areas using magneto-encephalogram (MEG). Although these alpha rhythms are generated in cortical areas, their oscillations are driven by rhythmic bursts of firing (high-threshold bursting) from thalamocortical neurons. The frequency of alpha rhythms decreases

with declining depolarization in these thalamic nuclei. The mu rhythm has its cortical source in the primary somatic sensory cortex and correlates with high-threshold bursting in the posterior nucleus of the thalamus. The occipital rhythm has its cortical source in the primary visual cortex. This area of occipital cortex receives projections from the lateral geniculate nucleus (LGN), which is the first-order relay nucleus in the visual system. The most likely cortical generator of the parietal alpha rhythms is assumed to be the posterior cinguli cortex. This area seems to receive projections from the pulvinar nucleus of the thalamus, which is the second-order relay nucleus in the visual system (Buzsáki, 2006; Fröhlich, 2016).

The beta frequency band involves frequencies between 13 Hz to approximately 30 Hz, located to frontal and central areas of the cortex. The beta frequency band is usually divided into low beta (13-20 Hz) and high beta (21-30 Hz). The most striking feature of the beta rhythm is its sensitivity to GABA agonists which supports the involvement of inhibitory interneurons in the generation of beta rhythms. GABA agonists, such as barbiturates, increase the power of beta frequencies, suggesting an active role of inhibitory connections in the generation of those rhythms. Additionally, the beta frequency band is implicated in movement, attention, and stabilizing ongoing motor activity (Buzsáki, 2006). At least two distinct beta rhythms can be separated; beta rhythms located over the sensory-motor strip (Rolandic beta rhythms), and beta rhythms located in the more frontal areas of the cortex (frontal beta rhythms). The Rolandic beta rhythms are observed as spontaneous EEG activity over the sensorimotor cortex, during resting state conditions, and can be modulated by motor and cognitive tasks. The frontal beta rhythms exhibit short bursts of small amplitudes and emerge in cognitive tasks related to stimulus assessment and decision making (Fröhlich, 2016; Kropotov, 2009).

1.6.3 Infra-low frequencies and its implications for chronic pain. Infra-low frequencies provide a functional framework that connects slow wave propagations to oscillations at higher frequencies, in addition to, flexible cerebral information flow. An increasing number of EEG and resting state fMRI studies indicate that spontaneous low-frequency fluctuations in cerebral activity represent an essential component of brain functioning, being known to correlate with faster neuronal ensemble oscillations, regulate behavioural performance and influence seizure susceptibility.

Thalamic preparations, in vitro, have discovered that periodic ATP release associated with astrocytic calcium oscillations hyperpolarizes thalamocortical neurons and drives the generation of infra-low membrane potential oscillations in thalamocortical neurons. These

fluctuations are directly associated with an amplitude modulation of thalamic alpha oscillations, which suggests that infra-low oscillations causally drive the amplitude modulation of fast oscillations (Lőrincz, Geall, Bao, Crunelli, & Hughes, 2009).

Additionally, these infra-low fluctuations (ILFs) identify functional anatomical networks, termed resting state networks (RSN). Findings show changes of connectivity not only within but also across cortical regions implicated in these networks, among chronic pain patients. These intrinsic brain networks relate to slowly propagating waves of neural activity at a timescale of about 1 s for the whole cortex, which provides subthreshold depolarization to individual neurons, indicating modulation of cortical excitability (Legarda et al., 2011). Changes of infra-low fluctuations in chronic pain patients might, therefore, indicate an impairment of these slowly propagating waves. These abnormal infra-low waves, particularly in the salience and DMN networks, may interfere with faster oscillations and the flexible routing of information flow in the brain, which could explain the cognitive and affective deficits, experienced by chronic pain patients (Ploner et al., 2017).

1.6.4 Brain frequency band abnormalities in fibromyalgia patients. Several studies investigating the QEEG data of FM patients have found deviances in several frequency bands. Gonzalez-Roldan and colleagues (2016) found that FM patients displayed reduced delta activity in the right insula and temporal cortices, in addition to, enhanced beta activity in right frontal, midcingulate, and motor areas, in comparison with pain-free controls (González-Roldán et al., 2016). Enhanced beta activity was also found in a study by Hargrove and colleagues (2010). They found that FM patients exhibited elevated relative power in beta frequency bands at frontal and central measurement sites, in resting state conditions (Hargrove et al., 2010).

Moreover, several studies have found that FM patients display increased theta frontal amplitude, localized to sensory-motor areas, anterior cingulate, medial prefrontal, and dorsolateral prefrontal cortices (Donaldson, Mueller, Donaldson, & Sella, 2003; Fallon et al., 2018; Lim et al., 2016). Thalamocortical dysrhythmia (TCD) could be a source of this enhanced theta frontal activity. TCD is a resonant interaction between thalamic and cortical activity elicited by low-threshold calcium spike bursts in the thalamus and is characterized by increased spectral power at low frequencies (Fallon et al., 2018; Sarnthein, Stern, Aufenberg, Rousson, & Jeanmonod, 2005; Stern, Jeanmonod, & Sarnthein, 2006).

Fallon and colleagues (2018) found that the pattern of enhanced theta frontal activity was associated with increased fatigue scores in FM patients, which might suggest a

relationship between theta frontal activity and fatigue. Furthermore, Donaldson and colleagues (2003) found a negative relationship between alpha activity and theta activity. In their study, FM patients reporting the least amount of psychological stress and experienced pain displayed enhanced alpha amplitudes and reduced theta amplitudes. In contrast, FM patients that reported the most considerable amount of psychological stress and experienced pain displayed enhanced theta amplitudes and reduced alpha amplitudes, compared to normative values. These findings suggest that FM patients display deviant activity in beta, alpha, and theta frequency in cortical areas related to pain and attentional processing.

1.7 Neurofeedback Training

In the late 1970s, potential clinical usefulness for the retraining of brain frequency band patterns was established. This brain frequency band training is called EEG neurofeedback. Neurofeedback refers to a broad category of therapies, and different target frequencies have been found to produce different outcomes. For example, SMR neurofeedback training appears to strengthen the thalamic inhibitory function and has been applied to ADHD as well as to seizure disorders. In contrast, alpha/theta frequencies are targeted for upregulation in disorders of hyperarousal, such as PTSD (Hammond, 2011; Niv, 2013). Neurofeedback may be producing effects by enhancing synaptic strength through repeated firing. Research indicates that long-term practice of meditation strengthens DMN connectivity and reduce various symptoms, much like neurofeedback appears to do. Based on this finding, some neurofeedback practitioners suggest that neurofeedback regulates DMN activity, leading to improvement of the brain´s self-regulation capabilities (Niv, 2013).

In practice, clinical neurofeedback is operant conditioning of the EEG. It works by placing one or more electrodes on the scalp, and one or more electrodes as reference points, usually on the earlobes. Then, equipment is connected to the electrodes which provide real-time, instantaneous feedback about the individual´s brain wave activity (see Figure 1) (Kropotov, 2009; Legarda et al., 2011; Teplan, 2002). Neurofeedback is a frequency-based approach because it depends principally on the patient´s response to information derived from a small portion of the brain´s frequency spectrum, allowing practitioners to target different parts of the EEG spectrum for particular goals of treatment (Othmer & Othmer, 2017).

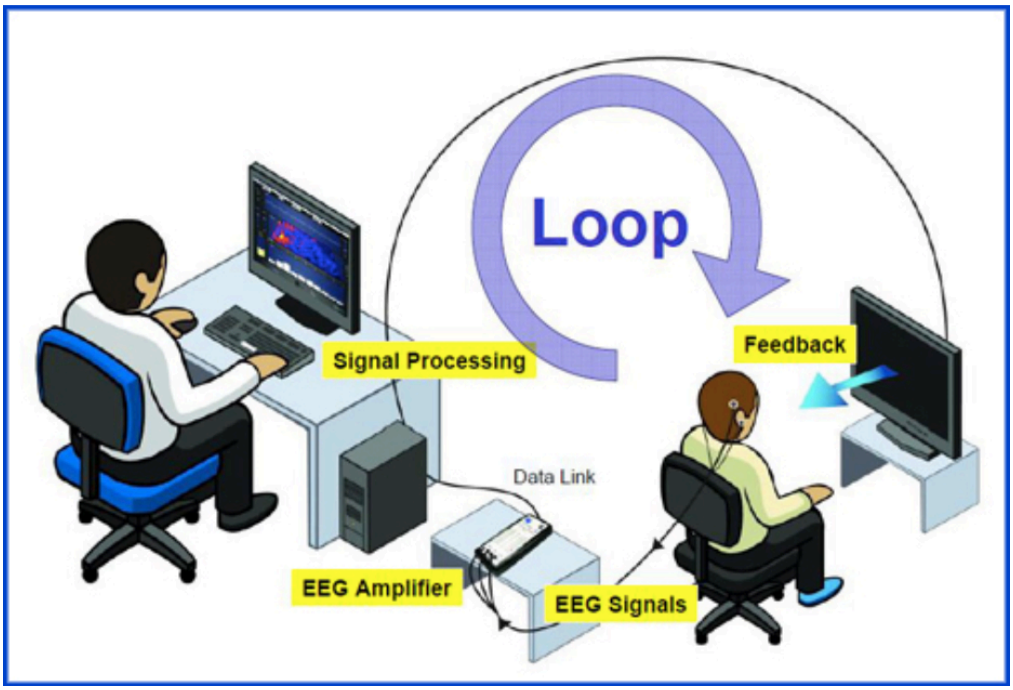

Figure 1. Neurofeedback training procedure. Downloaded 08.02.2019 from https://brainhealthnorthwest.com/neurofeedback/.

1.7.1 Infra-low frequency neurofeedback training as an intervention for fibromyalgia. The entry into infra-low frequency neurofeedback training (ILF NFT) was first undertaken in 2006 when the use of new software permitted the extension of the frequency range to 0.1 Hz, and by 2015 the frequency range was extended even further down to 0.05 Hz. The goal of ILF NFT is to find and enhance the patient´s Optimum Response Frequency (ORF). This process involves moving incrementally to the frequency at which the patient feels maximally calm and alert during the session. The objective is to maximize the positive attributes and minimize the severity of symptoms, by concentrating on a single frequency (the ORF) (Othmer & Othmer, 2017; Othmer, Othmer, Kaiser, & Putman, 2013).

The step into the infra-low frequency region requires a new approach to neurofeedback training. The frequency is too low to permit threshold-based amplitude training within the standard operant conditioning model. Therefore, the patient simply has to watch the unfolding low-frequency signal which reflects the ebb and flow of cortical activation in subtle fluctuations. This process is directly related to skill learning. The brain sees the consequences of its actions, and on that basis refines its response going forward. The skill learned is self-regulation, and the data provided is directly related to the process of self-regulation (Othmer & Othmer, 2016; Othmer & Othmer, 2017). The functional connectivity

within resting state networks governs the quality of this regulation, especially the default mode network. Thus, neurofeedback primarily targets the DMN (Othmer & Othmer, 2017).

The dynamic pain connectome networks oscillate at the infra-low cortical potential frequencies around 0.05 Hz. Neurofeedback that targets these lower frequencies may directly affect the resting state networks implicated in chronic pain (Niv, 2013). If the functional connectivity of resting state networks is being altered, it is to be expected that all functions being sub-served by these networks will also be potentially affected. Therefore, ILF NFT targeting the dynamic pain connectome networks may produce widespread symptom reduction among chronic pain patients (Niv, 2013; Othmer et al., 2013).

1.8 Importance of This Study

The impact of fibromyalgia disease severely affects patients´ psychological and physical health. Fibromyalgia is a complex multi-system disease that includes symptoms overlapping with other similar rheumatic diseases, such as irritable bowel syndrome, chronic fatigue, and arthritis (Glass, 2008; Mueller, Donaldson, Nelson, & Layman, 2001). This overlap in symptoms causes difficulties with providing a correct diagnosis and treatment. Position estimation analysis of the cortical regions displaying brain activity deviances compared to normal, will indicate which cortical regions that can contribute to uncovering potential neurobiological markers for fibromyalgia. Hopefully making it easier for physicians to diagnose fibromyalgia correctly. Today's available treatment for fibromyalgia focuses on the symptoms separately with the use of pain medication, diets, and different training programs. To my knowledge, there are currently no treatment options that take into account all symptoms as a whole when treating the disease (Fink & Lewis, 2017; Marcus, 2009). The results of this study should show symptom reduction after training with infra-low frequency neurofeedback, which might advance the legitimacy of neurofeedback as a treatment intervention, consequently making it possible to implement neurofeedback as a treatment option for fibromyalgia.

1.9 Aim of the Study and Hypotheses

The present study has two parts. The main objective for the first part of this study is to position estimate FM patients´ brain activity deviances to further investigate if the cortical regions implicated in the DPC could contribute to uncovering neurobiological markers for FM. Based on earlier research, three brain networks included in dynamic pain connectome (DMN, SN and AS) and their associated cortical areas are involved in the processing of chronic pain. Therefore, cortical areas implicated in these networks, especially those included in the SN and DMN, could be used as core regions for uncovering neurobiological markers for FM (Baliki et al., 2008; Cifre et al., 2012; Kucyi & Davis, 2015).

The main objective for the second part of this study is to explore the effects of infra-low neurofeedback training (ILF NFT) on FM symptoms. This part is investigated by examining the patients´ power spectra and ERP analysis, and then comparing the brain activity pre-treatment with post-treatment. Based on earlier research, there is reason to believe that FM patients display deviances in their QEEG patterns, and that ILF NFT can be effective in normalizing these deviances, in addition to, symptom reduction (Burgmer et al., 2009; Donaldson et al., 2003; Kayıran et al., 2010). This objective is based on the fact that neurofeedback can optimize brain rhythms implicated in the brain´s resting state networks, specifically the DMN which is associated with the brains self-regulating activity, driven by infra-low fluctuations (Niv, 2013; Othmer et al., 2013).

The investigation of this pilot study is based on three hypotheses:

1. If fibromyalgia is caused by disrupted communication between brain networks implicated in pain processing, ERP analysis, and power spectra analysis will reveal significant deviances within the patient group, compared to the normative database.
2. If fibromyalgia patients display deviances in brain regions implicated in the dynamic pain connectome, this will be measurable by using a source analysis program (sLORETA) to find Brodmann areas corresponding with regions in the dynamic pain connectome.
3. If ILF NFT is capable of improving fibromyalgia symptoms, this effect should be measurable with QEEG data (power spectra analysis and ERP analysis). Patients that receive active ILF NFT should show fewer deviances in their QEEG data post-treatment, compared to pre-treatment. Moreover, the normalization of QEEG data should correlate with a symptom reduction in symptom scores data.

2. Method

2.1 Subjects

This study was conducted by collecting data from patients diagnosed with fibromyalgia (FM) disease. The patients were recruited through the Fibromyalgia Association (Fibromyalgiforeningen) in Sør-Trøndelag and self-help Facebook forums concerning fibromyalgia and rheumatism. Information regarding the study and informed consent schema (see Appendix I) were sent per e-mail to patients who were interested in participating in the study.

To my knowledge, there are no published studies on infra-low frequency neurofeedback as an intervention for FM patients. Therefore, the sample size was based on one previous study investigating the effect of ILF NFT on food addiction (N =12) (Leong et al., 2018). As well as two studies investigating similar types of neurofeedback on FM patients (Caro & Winter, 2011) and ADHD patients (Heinrich, Gevensleben, Freisleder, Moll, & Rothenberger, 2004). These studies found significant interactions between neurofeedback training and symptom reduction (p <.05), with sample sizes of 13 and 15, respectively. To achieve sufficient power to observe potential treatment effects, the sample size was set to be approximately as large as these studies, in addition to, general recommendations for pilot study designs (Hertzog, 2008; Julious, 2005).

15 women and 1 man agreed to participate in the study. Given the small sample size of a pilot study design, only females were included for further analysis, being that fibromyalgia is more prevalent among women compared to men in the general population (Fagerlund, Bystad, & Aslaksen, 2013; Fagerlund et al., 2015; Marcus, 2009; Sawaddiruk, Paiboonworachat, Chattipakorn, & Chattipakorn, 2017). One patient dropped out before the training started, and one patient was excluded due to too few training sessions. 13 women between the ages of 34-63 were included in further analysis (M= 48.08, SD= 9.28). All patients had previously been diagnosed with FM by their physician, and all patients fulfilled the American College of Rheumatology (ACR) Diagnostic Criteria for fibromyalgia (Wolfe et al., 2010). Some patients had other rheumatic related diagnoses such as migraine, fatigue, and muscle pain. Hence, some of the patients were under treatment with other types of medications at the time of the neurofeedback training. Unfortunately, this is an incomplete list, as we do not have the complete documents for all patients regarding diagnoses and medications. However, none of the patients reported any use of medication known to affect the EEG recording or neurofeedback training.

The patients completed one EEG recording and five symptom score measures investigating the severity of FM symptoms, pre- and post-treatment. In addition to, 10-15 training sessions with infra-low frequency neurofeedback. The project was approved by the Norwegian Regional Ethics Committee (REK). All participants gave their informed consent for using the data material presented in this study.

2.2 Apparatus

2.2.1 EEG. The EEG was recorded using a 19-channel digital amplifier from Mitsar (St. Petersburg, Russia). The electrode caps utilized tin (Sn) electrodes and were made by Electro-Cap (Electrocap International Inc.). All electrodes were placed according to the 10-20 international standard montage system, with reference electrodes on the ear lobes and the ground electrode on Fpz (Klem, Lüders, Jasper, & Elger, 1999a). Using conductive gel, the impedance was kept below 10 kOhm. The exclusion threshold for the EEG was set 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 30 Hz. Notch filter (45-55 Hz) was used during trials to reduce the impact of electrical noise. The QEEG data was stored on a computer for off-line analysis, and each recording was visually inspected to check for artefacts. The record´s sampling rate was 500 Hz. Input impedance for the amplifiers was 200 MOhm, and A/D was of 14-bit precision.

2.2.2 ILF NFT. The infra-low frequency neurofeedback training (ILF NFT) was performed using Cygnet software and NeuroAmp II amplifier from BeeMedic. Each session lasted for approximately 20-25 minutes, and participants were given 10-15 sessions, depending on their progress. Due to the lack of standardized protocols, the number of sessions completed was based on the patients´ progression. No more than 15 sessions were given due to time constraints. Participants´ progress was carefully monitored each session based on the patients´ subjective reports.

2.2.3 FIQ. The Fibromyalgia Impact Questionnaire (FIQ) measures diverse aspects of life quality among fibromyalgia patients, such as pain level and the ability to complete daily tasks. The participants filled out the questionnaire on the same day as their pre- and post-treatment EEGs. They chose to either fill it out in the lab or at home. The participants filled out a Norwegian version of the questionnaire, translated by a translator (see Appendix J).

The questionnaire was scored according to guidelines of the English version (Bennett, 2005; Burckhardt, Clark, & Bennett, 1991). The FIQ score ranges from 0-100. Higher scores

indicate a more significant impact of fibromyalgia symptoms on the patient´s quality of life. The FIQ is composed of 10 items. The first item contains 11 questions related to physical functioning, and each item is rated on a 4-point Likert type scale. Scores on each item can range from 0 (always) to 3 (never). Because some of the patients may not do some of the tasks listed, they had the option of deleting items from scoring. Thereby, the scores for the items that the patients rated were summed and divided by the number of items rated, to obtain a correct summed score for item 1-11. Item 2 asks the patient to mark the number of days (0-7) they felt well. This item is scored inversely so that a higher number indicates impairment. Item 3 asks the patient to mark the number of days (0-7) they are unable to work (including housework) because of the fibromyalgia diagnosis. Items 4-10 asks the patient to rate the ability to work, pain, fatigue, morning tiredness, stiffness, anxiety, and depression on a visual analogue scale (VAS) marked in 10 increments. Scores range from 0-10. If the patient marked the space between two vertical lines on any item, that item-score included 0.5.

2.2.4 ACR. The American College of Rheumatology (ACR) preliminary diagnostic criteria for fibromyalgia is a questionnaire used in primary care as a tool to assist physicians in the diagnosis of fibromyalgia. The participants filled out the questionnaire on the same day as their pre- and post-treatment EEGs and chose to either fill it out in the lab or at home. The participants filled out a Norwegian version of the questionnaire, translated by a translator (see Appendix K).

The questionnaire consists of two parts: *(a)* a widespread pain index (WPI); and *(b)* a symptom severity (SS) scale for levels of symptom severity. The patient fulfils the diagnostic criteria for fibromyalgia if the following 3 conditions are met: *(a)* WPI ≥ 7 and SS scale score ≥ 5, or WPI 3-6 and SS scale score ≥ 9; *(b)* symptoms have been present at a similar level for at least 3 months; and *(c)* the patient does not have a disorder that could otherwise explain the pain.

The questionnaire was scored according to guidelines (Wolfe et al., 2010). The widespread pain index score ranges from 0-19. The patient is asked to note the number of areas on the body in which her/him had pain over the last week. Each area identified on the list counts as 1. The symptom severity scale score includes two sections. The first section includes 3 items, and each item is rated on a 4-point Likert type scale. The patient is asked to indicate the level of severity over the past week in three symptom categories (fatigue, waking unrefreshed, and cognitive symptoms), ranging from 0 (no problem) to 3 (severe). The second section is a symptom list for other somatic symptoms and examines the quantity of other

somatic symptoms experienced over the past week. The list contains 33 somatic symptoms, such as depression, insomnia, dizziness, muscle pain, and hair loss. The patient is asked to indicate how many of these symptoms him/her has experienced over the last week. Based on the quantity of the symptoms, the researcher indicates the score that matches the quantity of the somatic symptoms experienced. The score ranges from 0 (no symptoms) to 3 (a great deal of symptoms). The total symptom severity scale ranges from 0-12.

2.2.5 VAS. The Visual Analogue Scale (VAS) is a psychometric response scale used as a measurement instrument for subjective characteristics that cannot be directly measured, such as pain (Price, McGrath, Rafii, & Buckingham, 1983). The patients were given 3 different VAS in Norwegian (fibrofog, fatigue, and pain). The VAS for pain consists of a 100 mm line with the expressions “no pain” and “worst possible pain”. The VAS for fatigue consists of a 100 mm line with the expressions “no fatigue” and “worst possible fatigue”. The VAS for fibrofog consists of a 100 mm line with the expressions “no fibrofog” and “worst possible fibrofog” (see Appendix L). The patient is asked to indicate the severity for each of the three symptoms. All VAS schemas were completed on the same day as their pre- and post-treatment EEG and the patients chose to either fill it out in the lab or at home.

2.3 Procedure

2.3.1 VCPT and EEG recording. 19-channels EEG was recorded in two resting conditions prior to the VCPT; 180 seconds with eyes opened (EO) and 180 seconds with eyes closed (EC). Afterward, the visual continuous performance task (VCPT), a Go/NoGo-task, was performed to assess the participants’ capacity for sustained attention and response control (Mestanikova et al., 2015). In addition to analysis, the resting conditions (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 for the VCPT task was presented by the software tool PsyTask (Mitsar, St. Petersburg, Russia). 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 performance and to reduce task-related tiredness. The patients also had a say in deciding the length of these breaks. The 400 trials were 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 condition. In the p-h condition, the picture of a human was presented simultaneously with a novel sound at 60 dB SPL. Each condition was composed of a picture pairing, with every picture shown for 100 ms, followed by an inter-stimulus interval of 1000 ms and. The inter-trial interval was 3500 ms 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 procedure is illustrated in Figure 2.

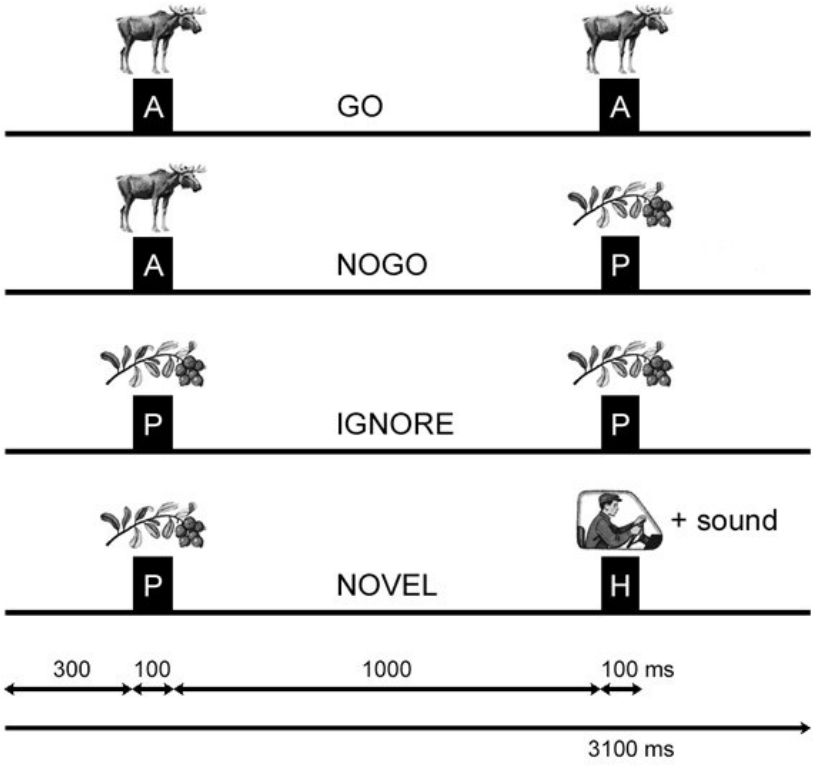

Figure 2. Schematic presentation of the VCPT Go/NoGo task. A, P and H abbreviations refer to the stimulus-pictures of animals, plants, and humans, respectively. “Go trials” required the subject to press a button as fast as possible, and “NoGo trials” required the subject to suppress the prepared response. “Ignore”, and “Novel” trials required no response.

2.3.2 ILF NFT. Electrodes were placed on T3 and T4 (left and right mid-temporal area) according to the international 10-20 system (Klem, Lüders, Jasper, & Elger, 1999b) and reference electrodes were placed on Cz and forehead. T3 and T4 were chosen as placement

based on earlier NFT research recommending T3 and T4 as a standard approach when dealing with emotional and painful symptoms (Othmer, 2005; Sime, 2004). Next, the Cygnet software was connected to the electrodes through the NeuroAmp amplifier, providing real-time, instantaneous feedback about the patient's brain wave activity. The hardware converted the EEG signal recorded at the scalp to digital signals suitable for the software. The patients individually decided which animation they wanted to use in each session. The animations reflected the amplitude of the ILF. The training was conducted in selected infra-low frequencies at approximately 0.05 Hz, depending on the patients´ ORF.

2.4 QEEG Analysis

2.4.1 Artefact correction. Before analysing the EEG data, it was necessary to remove artefacts that disturbed the data, such as muscle tension and eye blinks. The artefact correction was performed with the WinEEG program by implementing an independent component analysis (ICA) on the raw EEG fragments, as well as visually inspecting the data and removing disturbances. The rejection threshold of artefacts for slow waves (0-1 Hz) and fast waves (above 30 Hz) was set at 50 microvolts. The ICA presents a set of templates, some of which corresponds with artefacts. Eyeblink artefacts were removed by zeroing the activation curves of individual independent components corresponding to eye blinks, by subtracting the artefact templates from the raw EEG data. EEG epochs with an excessive absolute amplitude of filtered EEG or excessive faster/slower frequency activity were marked and excluded from further analysis.

2.4.2 ERP measurement and analysis. A relative criterion version of the fractional area technique was used to measure the latency of all ERP components used in the study (Brunner et al., 2013). In this approach, the onset of the component is defined as the point where the amplitude reaches 50 % of its peak-to-peak amplitude (before the peak), and the offset is defined as the point where the amplitude decreases to the same level of onset (after the peak). Next, the latency is set to the median between 50 % onset and offset according to the max amplitude of the waveform. The latencies were calculated manually. The amplitudes of the components were measured by identifying maximum amplitude within a pre-defined timeframe, based on literature. N1 had a timeframe of approximately 100-130 ms, P3 NoGo early; 230-410 ms, P3 NoGo late; 270-480 ms (Polich & Criado, 2006), and CNV appeared 100 ms before S2, around 1000 ms (Brunner et al., 2015; Gomez, Marco, & Grau, 2003). The

CNV component was not possible to calculate using the relative criterion. Thereby, this component was computed using peak latency and peak amplitude.

The individual ERP´s was visually inspected and compared to the mean amplitude and latency of appropriate age-matched controls in the normative database. The comparison concentrated on significant deviances in three of the conditions (a-a, a-p, and p-p) in VCPT, and where on the scalp these deviances occurred. The ERP analysis was performed with WinEEGs internal statistics engine.

2.4.3 Power spectra analysis. Grand average power spectra analysis was performed to examine brain frequency band activity within the patient group, in addition to, individual power spectra analysis to compensate for group variance. As a main rule, the frequency band peak with the largest significant amplitude was selected for further analysis. If there was any doubt to whether EEG artefacts caused the deviant brain activity, raw EEG was visually inspected. Relative power (%) (i.e., the percentage of frequency distribution) and significance level were noted for further analysis. Relative power values were preferred over absolute power values as this eliminates many potential errors due to skull thickness and impedance. Furthermore, relative power has a lower group variability and a stronger test-retest variability than absolute power (Benninger, Matthis, & Scheffner, 1984; John et al., 1983; Moretti et al., 2004; Salinsky, Oken, & Morehead, 1991).

Based on existing literature, frontal (F3, F4, Fz), central (C3, C4), and temporal (T3, T4) theta (4-8 Hz), alpha (8-13 Hz) and beta (13-30 Hz) frequency bands were examined for further analysis (Donaldson et al., 2003; González-Roldán et al., 2016; Hargrove et al., 2010). Additionally, all spectra power analyses were examined with independent component analysis and then exported to sLORETA to position-estimate the QEEG activity found in the EO, EC and VCPT conditions.

2.4.4 Source analysis. sLORETA was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity, to further examine whether the patient group displayed deviations in Brodmann areas implicated in the dynamic pain connectome. The spatial resolution of QEEG is about 5 cm^2. Five hits covering about the same range in sLORETA were, therefore, reported to conduct a detailed investigating of which Brodmann areas displayed deviant brain activity.

2.5 Statistical Analysis

Statistical analysis was performed in the Mitsar WinEEG 2.129.100 software and the SPSS 25.0 software package. Mitsar WinEEG 2.129.100 was used to estimate the statistical significance of the deviances in EEG parameters, found by comparing the power spectra's, ERPs and ICA files with the normative database. Statistical significance was accepted at the level of $p < .05$. For correlation analysis, Spearman´s rho (r_s) was used as effect size and calculated for all significant relevant correlations. For Wilcoxon Signed-Rank Tests, Pearson´s r was used as effect size and calculated for all significant Wilcoxon Signed-Rank Tests. The effect size is an objective and standardized measure of the magnitude of the observed effect. It measures the strength of the relationships between two variables and indicates the size of any observed effects. According to Cohen, $r / r_s = .10$ is a small effect, $r / r_s = .30$ is a moderate effect, and $r / r_s = .50$ is a large effect (Field, 2018). Relevant descriptive statistics for all variables pre-treatment and post-treatment is presented in Appendix C.

2.5.1 The assumption of normality and the use of non-parametric statistical tests.

All variables were checked for the assumption of normality. Shapiro-Wilk tests, skewness values, and kurtosis values were calculated for all variables, pre-treatment and post-treatment (see Appendices A and B). Also, histograms for all variables were inspected visually. Some of the variables fulfilled the assumption of normality. Nevertheless, the sample size ($N = 13$) is small, and even though some of the distribution of scores on individual variables are normal, it doesn´t mean that the sampling distribution from which the parameter is estimated, and the computed significance test are derived, is also normally distributed. Ranking the data by using non-parametric tests can be less powerful than parametric tests, but this statement is only valid if the assumption of normality is met (Field, 2013). When the sampling distribution is normal, the Type 1 error rate (generally set at 5 %) of tests based on a normal distribution is 5 % so that we can calculate statistical power. However, when the sampling distribution is not normal, the Type 1 error rate of tests based on a non-normal distribution will not be 5 % because it depends on the shape of the distribution. Therefore, non-parametric tests are only less powerful than parametric tests when the sampling distribution is normal (Field, 2018; Howell, 2007). In this case, we have a small sample size in which the sampling distribution is assumed to be non-normal. Accordingly, non-parametric test statistics are used for analysis.

2.5.2 QEEG and source analysis. Power spectra analysis and ERP analysis was performed in the Mitsar WinEEG 2.129.100 and was used to estimate statistical significance

for QEEG deviations. To examine the patients' brain activity compared to the HBI normative database, a grand average displaying significant deviances for all patients pre-treatment are presented for ERP components and power spectra. Additionally, a table for the patients' individual significant deviances pre-treatment compared to the normative database, are presented for ERP components and power spectra to examine tendencies among the patients and to compensate for group variance.

To examine tendencies within the patient group from pre-treatment to post-treatment, a table and bar-chart displaying the percentages of patients showing deviances in power spectra pre-treatment versus post-treatment is presented for all frequency bands and corresponding cortical areas. Also, individual deviances in amplitude for all ERP components are presented as bar-charts, pre-treatment versus post-treatment.

To position estimate the cortical source of the deviant brain activity, ICA for all patients individually were exported to sLORETA. A table is presented with the percentage of patients displaying deviances in Brodmann areas involved in the dynamic pain connectome.

2.5.3 Wilcoxon Signed-Rank Tests. To examine potential treatment effects, Wilcoxon Signed-Rank Tests was calculated pre-treatment versus post-treatment for all 24 variables individually; *(a)* latency and amplitude for all independent ERP components (N1, CNV, P3 NoGo early and P3 NoGo late); *(b)* theta, beta, and alpha frequency bands at temporal (T3, T4), central (C3, C4), and frontal (F3, Fz, F4) sites; *(c)* reaction time and reaction time variability; and *(d)* FIQ, ACR, VAS fatigue, VAS fibrofog, and VAS pain.

2.5.4 Correlation analysis. Non-parametric Kendall´s tau (τ) and Spearman´s rho (r_s) correlation analysis was separately performed on all variables pre-treatment to investigate potential relationships between the measures used in the study. Both values are reported. Kendall´s tau has generally been given preference over Spearman´s rho because it´s a better estimate of the corresponding population parameter, and its standard error is known, making it a more robust and efficient measure (Croux & Dehon, 2010; Howell, 2007). Furthermore, Kendall´s tau generally calculates a more accurate significance level when dealing with small sample sizes (Field, 2018).

Nevertheless, Kendall´s tau is not numerically similar to the either Pearson´s r or Spearman´s rho and does not tell us about the proportion of variance shared by two variables, or the ranks of those two variables. Consequently, Spearman´s rho is also reported as it gives us the proportion of variance in the rank that two variables share, which is usually a good

approximation of R^2 and thereby provide us with an effect size for significant correlations (Field, 2018). Significant correlations between measures are presented with associated effect sizes. A correlations analysis table for all measures pre-treatment is presented in Appendix E.

3. Results

3.1 Preliminary Analysis

3.1.1 Grand average of power spectra analysis. There were no significant deviances in the EO condition. Comparison with the normative database in the EC condition revealed significant deviances in theta and beta frequency bands at temporal (T5, T6) and central (C3, C4, Cz) sites, respectively (see Figure 3). Comparison with the normative database in the VCPT condition revealed significant deviances in the theta frequency band at both frontal (F7) and temporal (T6) sites (see Figure 4).

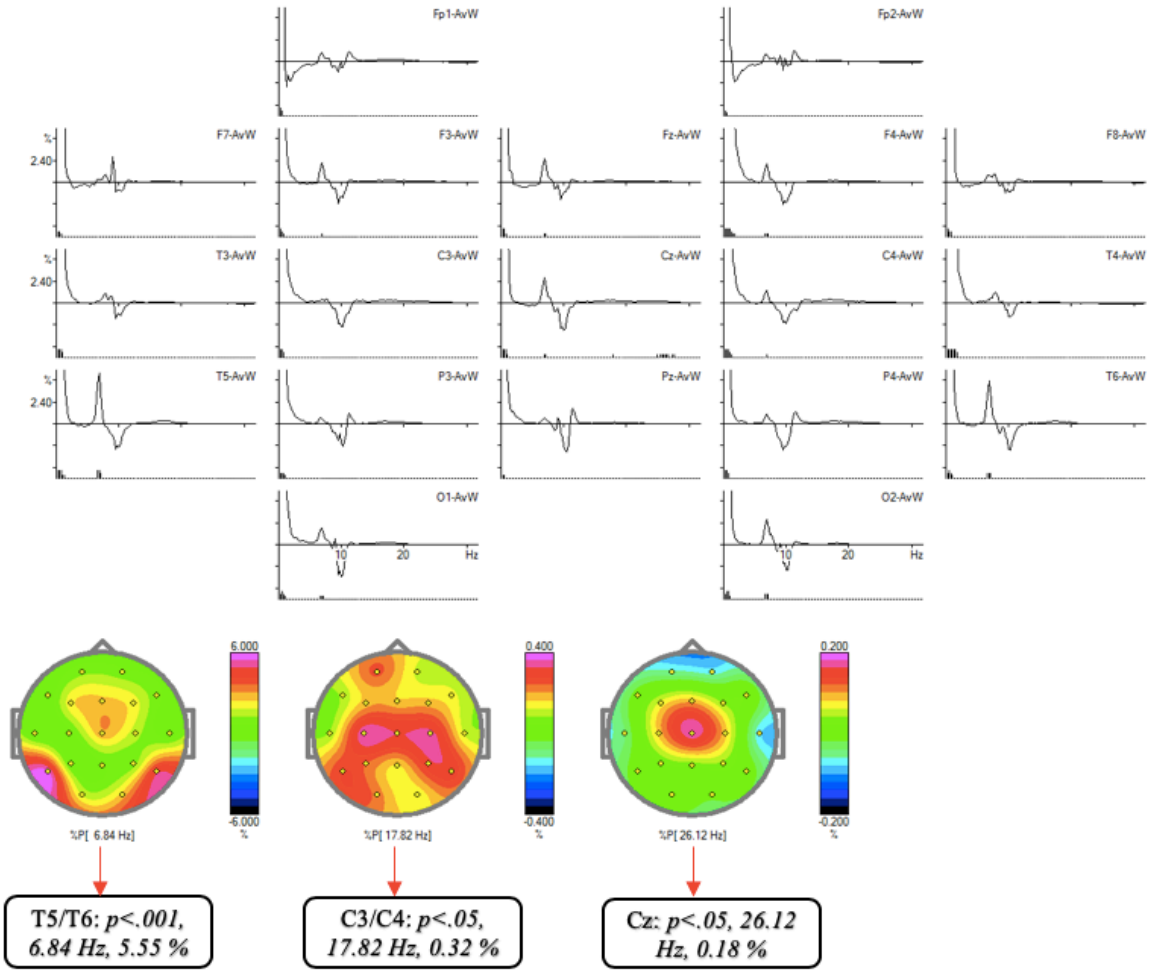

Figure 3. Patients´ grand average spectra of significant deviances compared to the normative database, displaying relative power (%), significance value, cortical area and frequency in the EC condition, pre-treatment.

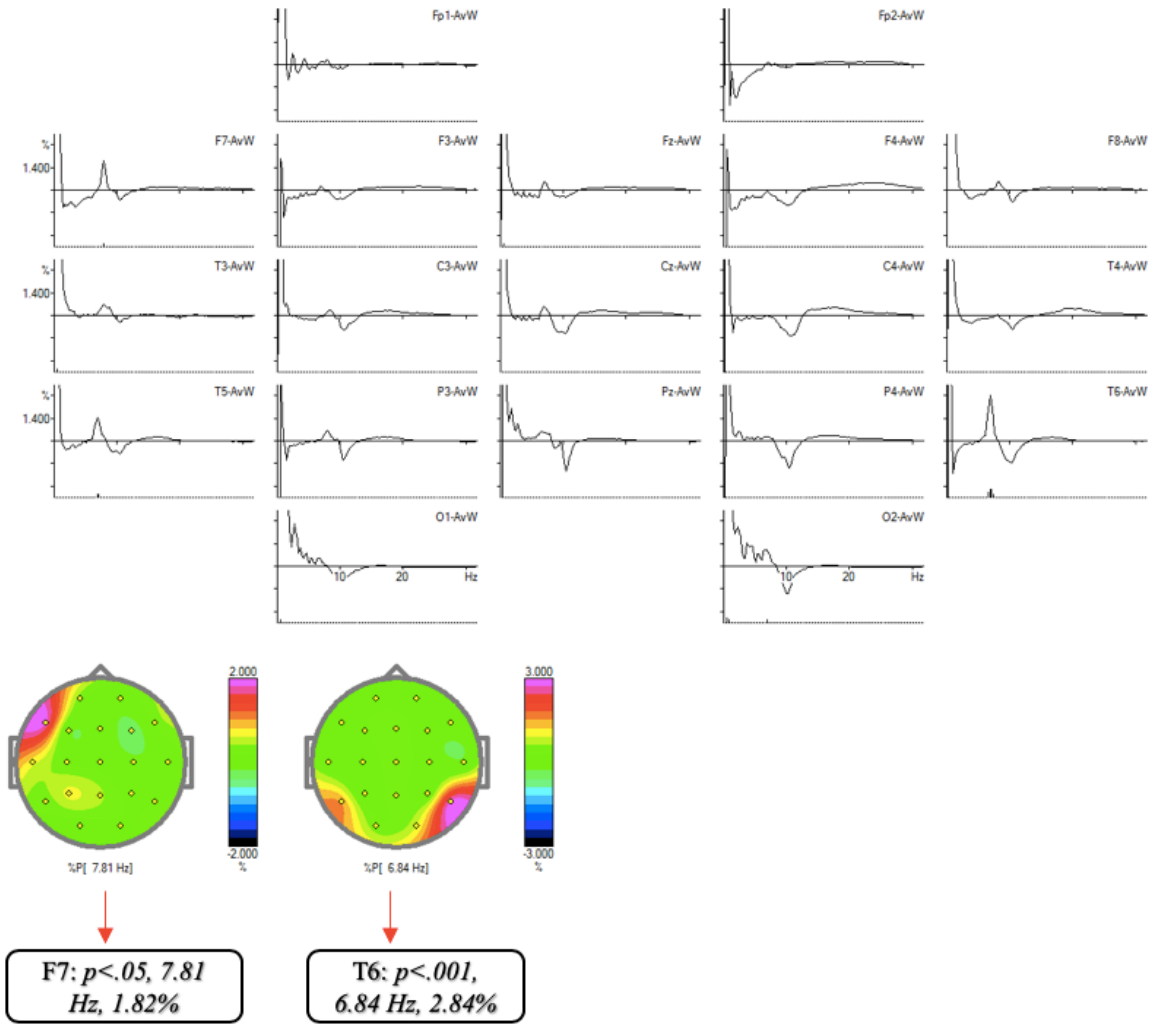

Figure 4. Patients´ grand average spectra of significant deviances compared to the normative database, displaying relative power (%), significance value, cortical area and frequency in the VCPT condition, pre-treatment.

3.1.2 Power spectra analysis of individual patients. Patients´ individual power spectra compared to the normative database revealed several significant deviances. An overview of the significant deviances in power spectra between each patient compared with age-matched controls from the normative database for all three conditions, pre-treatment, are presented in Tables 2, 3, and 4. Some of the position estimates (BA) for significant deviances could not be located by sLORETA.

As seen in the tables, deviances in power spectra were rather constant both in the resting conditions and the active condition. For the eyes opened condition, 30.77 % of patients showed deviances in the theta frequency band, 30.77 % showed deviances in the alpha frequency band, and 84.62 % of the patients showed deviances in the beta frequency

band. For the eyes closed condition, 23.08 % showed deviances in the theta-frequency band, 38.46 % showed deviances in the alpha frequency band, and 84.62 % of the patients showed deviances in the beta frequency band. For the VCPT condition, 23.08 % showed deviances in the theta frequency band, 23.08 % showed deviances in the alpha frequency band, and 76.92 % of the patients showed deviances in the beta frequency band.

All conditions together, 45.15 % of the patients showed significant deviances in the theta frequency band, 53.85 % showed significant deviances in the alpha frequency band, and all patients showed significant deviances in the beta frequency band (100 %). For the theta frequency band, none of the patients showed significant deviances at central sites, 23.08 % showed significant deviances at temporal sites, and 30.77 % of the patients showed significant deviances at frontal sites. For the alpha frequency band, 15.38 % of the patients showed significant deviances at central sites, 30.77 % of the patients showed significant deviances at temporal sites, and 15.38 % showed significant deviances at frontal sites. For the beta frequency band, 84.62 % of the patients showed significant deviances at central sites, 53.85 % showed significant deviances at temporal sites, and 76.92 % showed significant deviances at frontal sites.

The deviances were located by sLORETA to areas of the brain associated with various types of information processing; somatosensory processing (BA 1, 2, 3, 5, 7, 30, 31, 40), motor functioning and planning (BA 6, 4, 13, 32), integration and governing of executive functions (BA 9, 10, 46, 11, 47), visual processing (BA 17, 18, 19), among others (Bernal & Perdomo, 2008). A more detailed description of the source analysis is presented in section 3.1.5.

Table 2

Overview of individual significant deviances from the normative database in relative spectra and the location of those deviances for the EO condition, pre-treatment (N =13)

Frequency band	Cortical area	Fib001	Fib002	Fib003	Fib005	Fib006	Fib008	Fib009	Fib0010	Fib0011	Fib012	Fib0013	Fib0015	Fib0016
Theta	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	4.09*** BA 19-7-39	-	-	-	3.54* Missing	-	-	-	-	-	-	-	-
	Frontal	6.31*** Missing	-	1.37* BA 10-11-47	-	-	-	-	-	-	-	-	-	1.33* Missing
Alpha	Central	-	-	-	10.70* BA 9-45-46	-	-	-	-	-	-	-	-	-
	Temporal	-	-	-	-	-	-	-	4.55** Missing	-	2.57* BA 10-11-32	-	9.16** BA 21-22-39	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	Central	0.97** BA 1-4-2	1.57*** BA 42-40-22	0.71* BA 40-2-5	1.03** BA 22-42-21	0.53* BA 6-4-5	1.12** BA 6-4-3	-	-	-	-	1.08*** Missing	-	-
	Temporal	-	-	-	2.15*** BA 39-19-22	-	1.08** BA 37-19-21	-	-	-	-	1.55*** BA 19-18-17	-	-
	Frontal	-	1.02*** BA 8-6-9	-	-	-	0.51* Missing	-	1.19** BA 11-10-32	0.85** BA 10-9-32	0.97* BA 10-9-46	0.90** Missing	1.07** BA 9-10-8	-

Note. The table shows the relative value (%), significance level, frequency band, cortical area, and 3 hits of position estimations reported as Brodmann areas (BA), for the deviances in spectra for each participant. Missing; Some of the position estimations could not be located with the use of independent component analysis in sLORETA. **p*<.05, ***p*<.01, ****p*<.001.

Table 3

Overview of individual significant deviances from the normative database in relative spectra and the location of those deviances for the EC condition, pre-treatment (N =13)

Frequency band	Cortical area	Fib001	Fib002	Fib003	Fib005	Fib006	Fib008	Fib009	Fib0010	Fib0011	Fib012	Fib0013	Fib0015	Fib0016
Theta	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	18.47*** BA 11-10-32	-	-	-	-	-	12.81*** BA 47-11-10	-	-	-	-	-	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	1.33* Missing
Alpha	Central	-	3.45** BA 1-43-40	-	1.79* BA 6-4-5	-	-	-	-	-	-	-	-	-
	Temporal	-	-	-	-	-	-	-	-	3.38* BA 39-19-40	-	-	-	-
	Frontal	-	-	-	-	-	-	-	10.33* BA 11-10-32	-	-	24.03*** BA 21-20-22	-	-
Beta	Central	-	-	-	1.00*** BA 8-9-6	1.27*** Missing	1.14** Missing	-	-	0.53* BA 10-11-32	0.52* BA 40-2-1	0.74*** BA 19-7-39	0.28** Missing	0.18* Missing
	Temporal	-	0.61* Missing	1.84*** BA 37-19-21	1.43*** BA 19-39-18	1.37*** BA 19-39-18	0.98** Missing	-	-	-	-	0.78** BA 7-5-4	1.96*** BA 13-41-40	-
	Frontal	-	0.99*** BA 24-31-43	-	-	0.53** Missing	-	0.89** Missing	-	0.48* Missing	-	-	-	0.49** Missing

Note. The table shows the relative value (%), significance level, frequency band, cortical area, and 3 hits of position estimations reported as Brodmann areas (BA), for the deviances in spectra for each participant. Missing; Some of the position estimations could not be located with the use of independent component analysis in sLORETA. *p<.05, **p<.01, ***p<.001.

Table 4

Overview of individual significant deviances from the normative database in relative spectra and the location of those deviances for the VCPT condition, pre-treatment (N =13)

Frequency band	Cortical area	Fib001	Fib002	Fib003	Fib005	Fib006	Fib008	Fib009	Fib0010	Fib0011	Fib012	Fib0013	Fib0015	Fib0016
Theta	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	11.52*** BA 39-19-40	-	-	-	-	-	-	-	-	-	-	-	-
	Frontal	9.03*** BA 47-11-10	-	-	-	-	-	-	-1.11* Missing	-	-	-	-	-
Alpha	Central	-	-	-	4.40* BA 6-4-3	-	-	-	-	-	-	-	-	-
	Temporal	-	-	-	-	-	-	-	-	-	-	-	2.87* BA 18-19-39	-
	Frontal	-	-	-	-	-	-	-	-	-	-	2.50* Missing	-	-
Beta	Central	-	0.92** BA 6-4-3	-	0.95*** BA 6-8-32	-	1.19** BA 1-3-2	-	-	-	-	0.79* BA 1-3-2	1.25** Missing	-
	Temporal	-	1.34* BA 21-20-22	0.96** BA 21-27-22	1.55** BA 19-18-17	-	0.50* BA 7-19-39	-	-	-	-	0.88** BA 37-19-39	-	-
	Frontal	-	0.72** Missing	-	-	-	-	-	0.94** BA 11-10-47	1.28* BA 10-46-47	1.10* BA 10-46-47	-	0.98* BA 9-10-46	0.23* Missing

Note. The table shows the relative value (%), significance level, frequency band, cortical area, and 3 hits of position estimations reported as Brodmann areas (BA), for the deviances in spectra for each participant. Missing; Some of the position estimations could not be located with the use of independent component analysis in sLORETA. *p<.05, **p<.01, ***p<.001.

3.1.3 Grand average of ERP analysis. Analysis revealed significantly stronger N1 amplitude compared to the normative database at all cortical sites relevant for the N1 component (T5, O1, O2, T6). Also, patients´ displayed a significantly stronger amplitude for the CNV component at both Cz and Pz. Additionally, analysis revealed that patients´ had a significantly stronger P3 NoGo early amplitude at both Cz and Fz (see Figures 4 and 5). There were no significant deviances for the P3 NoGo late amplitude.

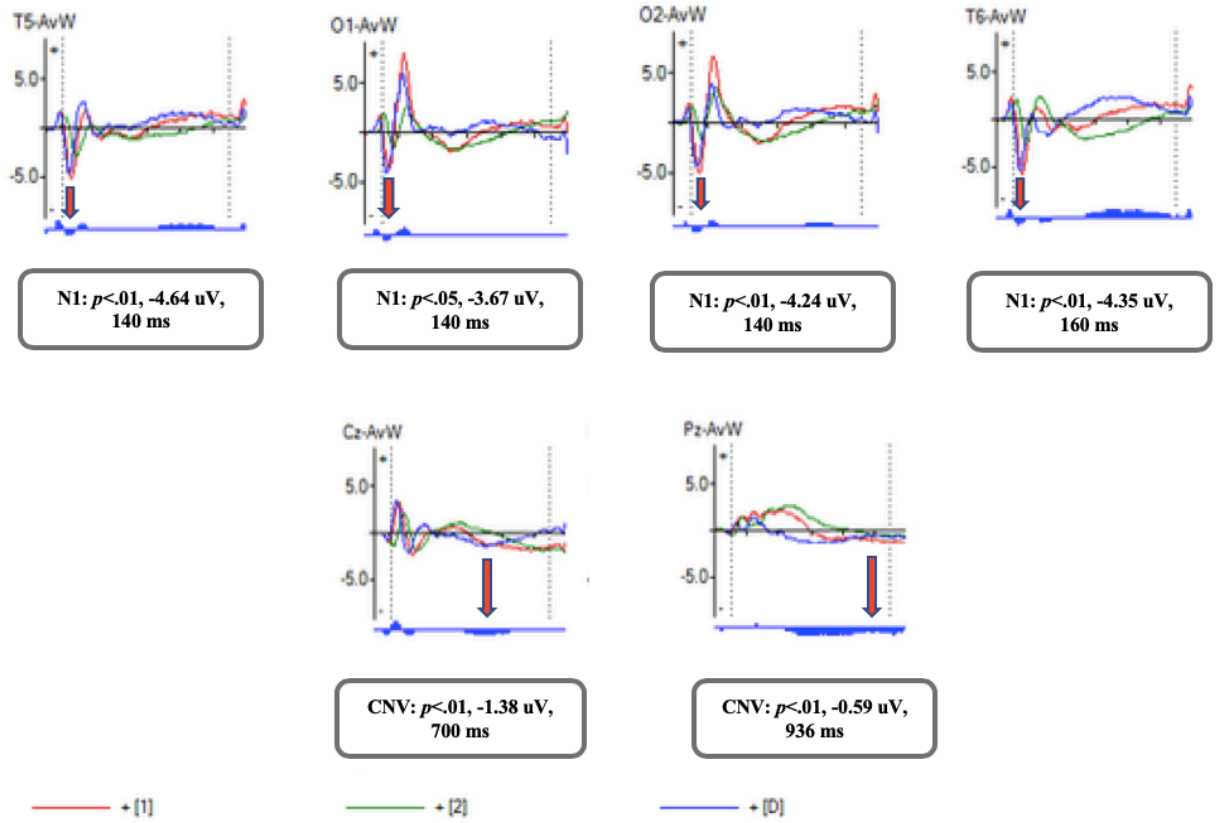

Figure 4. Patients´ grand average ERP analysis of significant deviances compared to the normative database, pre-treatment. The figure illustrates ERP components (N1 and CNV) with corresponding amplitude, latency, and significance level in the VCPT condition for all picture-stimuli starting with an animal.

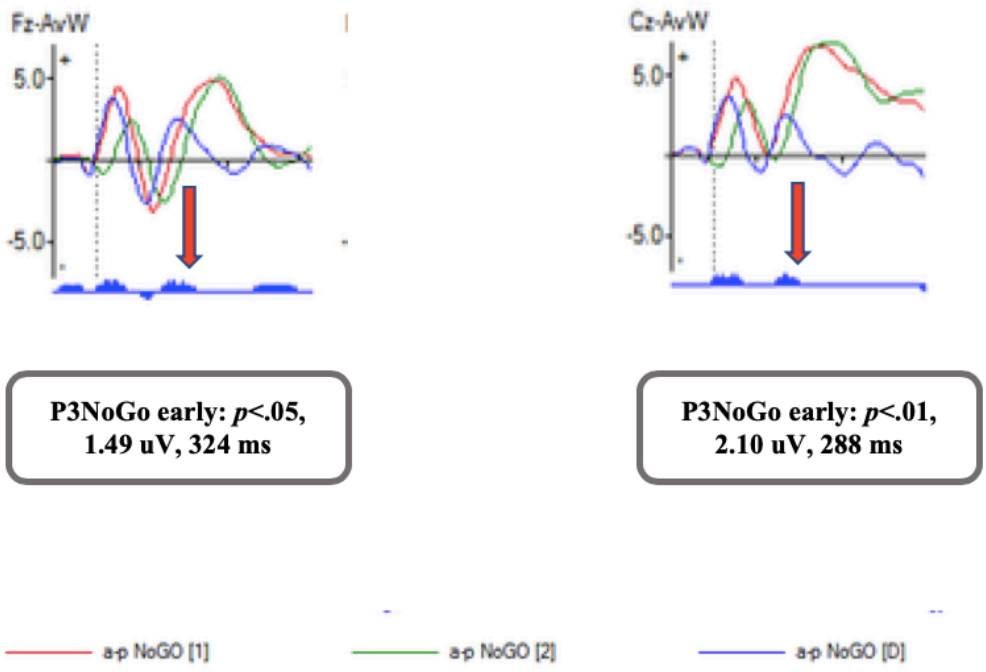

Figure 5. Patients´ grand average ERP analysis of significant deviances compared to the normative database, pre-treatment. The figure illustrates P3 NoGo early with corresponding amplitude, latency, and significance level in the VCPT condition for Go-NoGo stimuli.

3.1.4 ERP analysis of individual patients. Individual ERP analyses compared to the normative database revealed several significant deviances in mean amplitude for the ERP components. An overview of the significant deviances in amplitude for all ERP components between each patient compared with age-matched controls from the normative database are presented in Table 5 with associated significant level. Mean average µV for N1 was calculated for T5, O1, O2, and T6. Mean average µV for CNV was calculated for Cz and Pz. Mean average µV for P3 NoGo early and P3 NoGo late was calculated for Fz and Cz.

As seen in the table, all patients except Fib009 (no significant deviances in P3 NoGo early amplitude) showed significant deviances compared to the normative database for N1, CNV, P3 NoGo early, and P3 NoGo late amplitude. The ERP analysis showed approximately the same pattern among patients. 92.31 % of patients showed a significant stronger N1 amplitude and a significantly stronger CNV amplitude. One patient (7.69 %) showed a significant weaker N1 and CNV amplitude. 76.92 % of patients showed a significant stronger P3 NoGo early amplitude, while 15.38 % of patients showed a significant weaker P3 NoGo early amplitude. 61.54 % of patients showed a significant stronger P3 NoGo late amplitude. In contrast, 38.46 % of patients showed a significant weaker P3 NoGo late amplitude.

Table 5

Overview of individual significant deviances compared to the normative database for ERP components, pre-treatment (N =13)

	N1	CNV	P3 NoGo early	P3 NoGo late
	Mean average μV	Mean average μV	Mean average μV	Mean average μV
Fib001	-11.10***	-2.34***	7.11***	6.33***
Fib002	-8.56***	-1.14**	6.79***	7.82***
Fib003	-11.92***	-1.25**	4.81***	4.50***
Fib005	-4.99***	-0.06**	1.97***	-1.21**
Fib006	-3.70***	-2.63***	2.17*	2.12***
Fib008	-6.43***	-1.20**	6.48***	3.73***
Fib009	-5.92***	-1.50**	-	2.73*
Fib0010	0.78*	-1.85***	1.57***	-5.48***
Fib0011	-5.72**	-0.20***	-5.97***	-5.75***
Fib0012	-1.93*	-1.92***	0.68*	2.99***
Fib0013	-4.39***	-0.65*	-3.26*	-3.15*
Fib0015	-1.47**	-2.02***	1.20**	0.52*
Fib0016	-3.50**	-2.42***	1.14***	-1.69*

Note. The table shows individual significant deviances compared to the normative database for each component with corresponding mean amplitude. μV = amplitude. *p<.05, **p<.01, ***p<.001.

3.1.5 Source analysis of Brodmann areas. Source analysis indicated that patients showed deviances in all relevant Brodmann areas except BA 27 and BA 33 (see Table 6). Figures 6 and 7 illustrate cortical positions of the Brodmann areas displaying deviant brain activity, included in the salience network and default mode network, both in the left and right hemisphere. For a detailed description of each Brodmann area included in the dynamic pain connectome, see Appendix H.

Table 6

Percentage of patients with significant deviances in BAs, implicated in the DMN (N =13)

Brodmann areas	Percentage
9	57.14 %
10	92.86 %
13	57.14 %
21	71.43 %
23	57.14 %
24	35.71 %
27	0.00 %
28	7.14 %
29	21.43 %
30	71.43 %
31	71.43 %
32	85.71 %
33	0.00 %
36	21.43 %
37	71.43 %
39	92.86 %
40	78.57 %
44	14.29 %
45	78.57 %
46	92.86 %
47	92.86 %

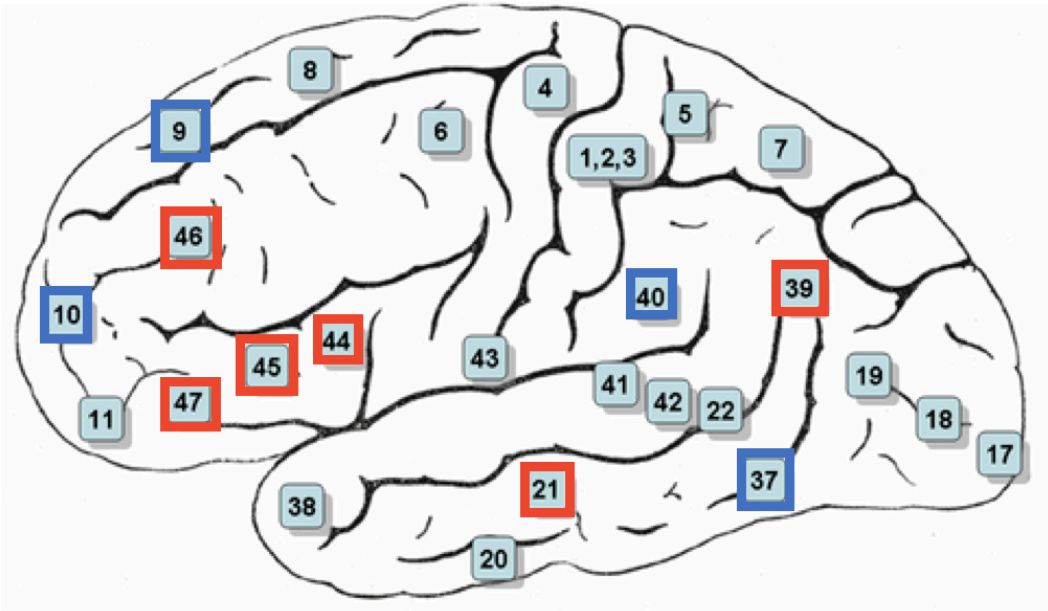

Figure 6. The figure shows patients´ activations in Brodmann areas located by sLORETA. Cortical areas marked with red are included in the salience network and cortical areas marked with blue are included in the default mode network. The figure displays the left hemisphere activation from a lateral view. This model is a modified version from the 20th U.S. edition of Gray´s Anatomy of the Human Body (Gray & Lewis, 2000).

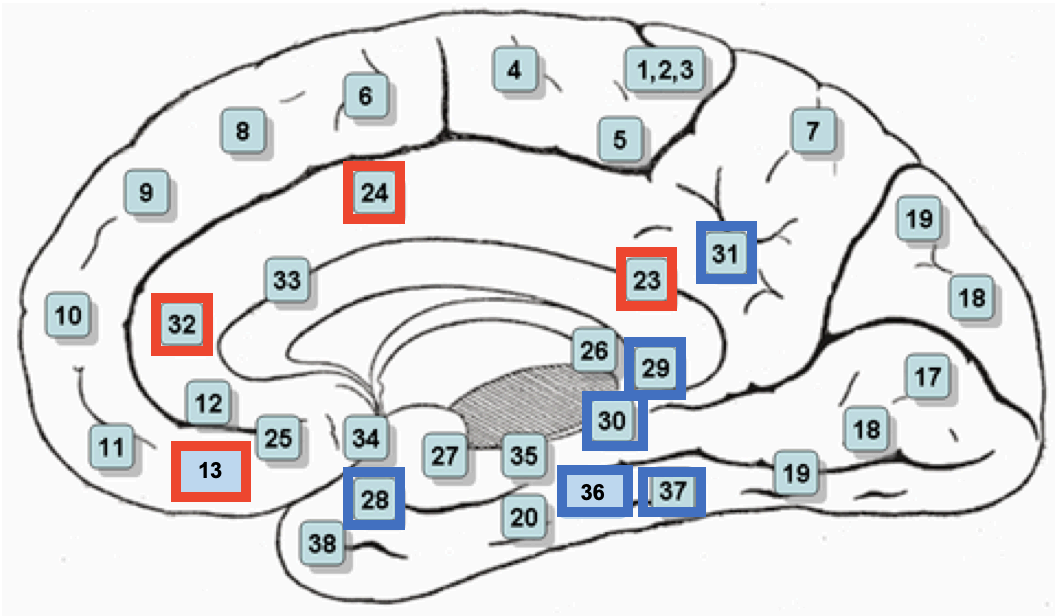

Figure 7. The figure shows patients´ activations in Brodmann areas located by sLORETA. Cortical areas marked with red are included in the salience network and cortical areas marked with blue are included in the default mode network. The figure displays the right hemisphere activation from a medial view. This model is a modified version from the 20th U.S. edition of Gray´s Anatomy of the Human Body (Gray & Lewis, 2000).

3.1.6 Correlation analysis. Kendall´s tau b (τ) and Spearman´s rho (r_s) correlation analysis revealed several significant correlations between the variables, pre-treatment. Correlation analysis between symptom score measures and brain frequency band amplitudes revealed a significant negative correlation between ACR-scores and theta frontally amplitude, τ =-.48, N =13, p =.027; r_s =-.59, N =13, p =.035. There were no significant correlations between the other symptom score measures and brain frequency band amplitudes. Correlation analysis between symptom score measures and ERPs indicated three significant relationships. Analysis revealed a significant positive correlation between fatigue-levels and N1 amplitude, τ =.67, N =13, p =.002; r_s =.83, N =13, p =.000, and between pain-levels and P3 NoGo late amplitude, τ =.45, N =13, p =.032; r_s =.58, N =13, p =.039. Analysis also revealed a significant positive correlation between pain-levels and P3 NoGo early latency, τ =.45, N =13, p =.032; r_s =.62, N =13, p =.023.

Analysis between behavioral measures and symptom score measures revealed a significant positive correlation between reaction time and fatigue-levels, τ =.49, N =13, p =.027; r_s =.60, N =13, p =.039. Correlation analysis between behavioral measures and ERP components revealed four significant relationships. There was a positive significant correlation between reaction time and N1 amplitude, τ =.46, N =13, p =.039; r_s =.60, N =13, p =.041, and between reaction time and CNV amplitude, τ =.74, N =13, p =.001; r_s =.88, N =13, p =.000. There was a significant negative correlation between reaction time and P3 NoGo late amplitude, τ =-.62, N =13, p =.006; r_s =-.79, N =13, p =.002. Additionally, analysis revealed a significant positive relationship between reaction time variability and CNV amplitude, τ =.53, N =13, p =.016; r_s =.63, N =13, p =.028. There were no significant correlations between behavioral data and brain frequency band amplitudes.

Correlation analysis revealed four significant correlations between ERP components and brain frequency band amplitudes. There was a significant positive correlation between CNV latency and alpha centrally amplitude, τ =.49, N =13, p =.020; r_s =.65, N =13, p =.017, and between CNV latency and theta centrally amplitude, τ =.43, N =13, p =.044; r_s =.58, N =13, p =.039. There was a significant negative correlation between N1 amplitude and theta frontally amplitude, τ =-.45, N =13, p =.032; r_s =-.57, N =13, p =.043, and a significant positive correlation between P3 NoGo late latency and theta centrally amplitude, τ =.44, N =13, p =.037; r_s =.59, N =13, p =.034.

3.2 The Effect of ILF NFT on Fibromyalgia Patients

3.2.1 ERP components. Patients showed a significant enhanced N1 latency from pre-treatment (*Mdn* =149.00) to post-treatment (*Mdn* =150.50), *z* =2.13, *p* =.033, *N* =13, *r* =.42 (see Figure 8). No other ERP component showed any significant increase or decrease from pre-treatment to post-treatment (see Appendix D).

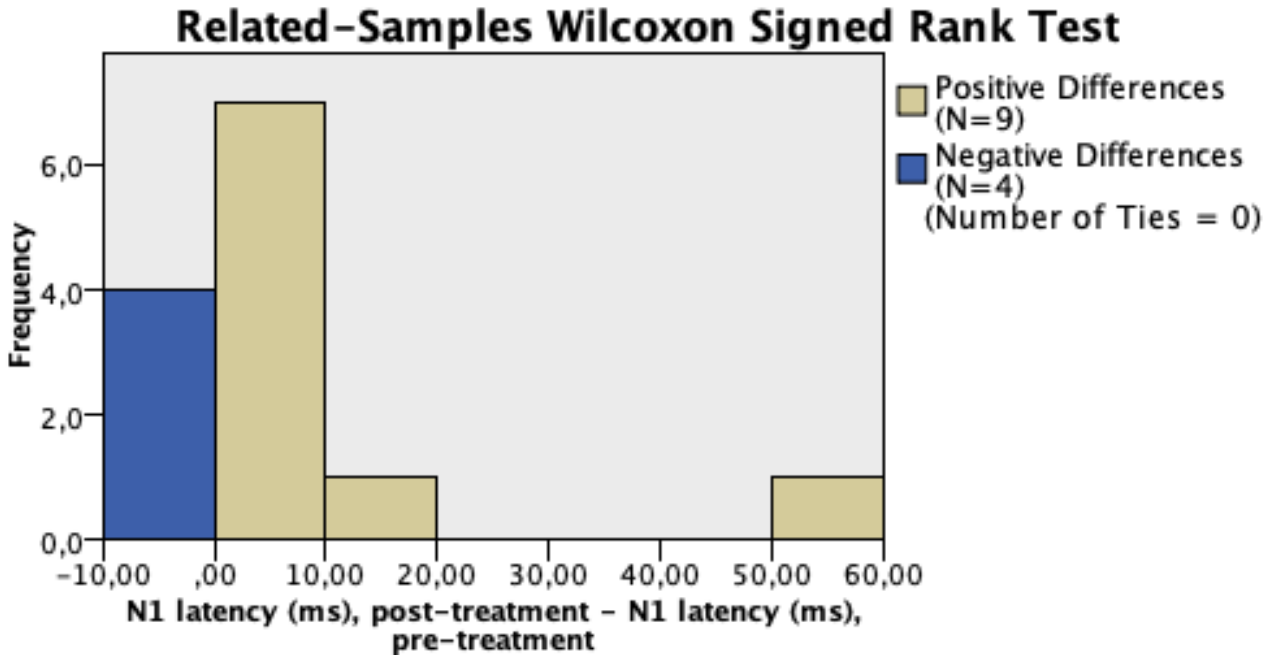

Figure 8. Histogram of Wilcoxon Signed-Rank Test for N1 latency pre-treatment versus post-treatment, indicating a positive difference in ranks. A positive difference in ranks emphasizes that the patients displayed a significant enhanced N1 latency post-treatment than pre-treatment. 9 patients displayed enhanced latency, while 4 patients displayed a decreased latency after ILF NFT.

3.2.2 Behavioural and symptom scores data. For VAS levels, patients showed a significant decline in fatigue-levels from pre-treatment (*Mdn* =70.83) to post-treatment (*Mdn* =41.00), *z* =-2.62, *p* =.009, *N* =13, *r* =-.51 (see Figure 9), and a significant decline in pain-levels from pre-treatment (*Mdn* =71.00) to post-treatment (*Mdn* =36.00), *z* =-2.45, *p* =.014, *N* =13, *r* =-.48 (see Figure 10). There was a significant decline in ACR-scores from pre-treatment (*Mdn* =22.00) to post-treatment (*Mdn* =17.00), *z* =-2.77, *p* =.006, *N* =13, *r* =-.54 (see Figure 11), and a significant decline in FIQ-scores from pre-treatment (*Mdn* =65.19) to post-treatment (*Mdn* =48.04), *z* =-2.62, *p* =.009, *N* =13, *r* =-.51 (see Figure 12). There were no significant differences for fibrofog-levels, reaction time, or reaction time variability (see Appendix D).

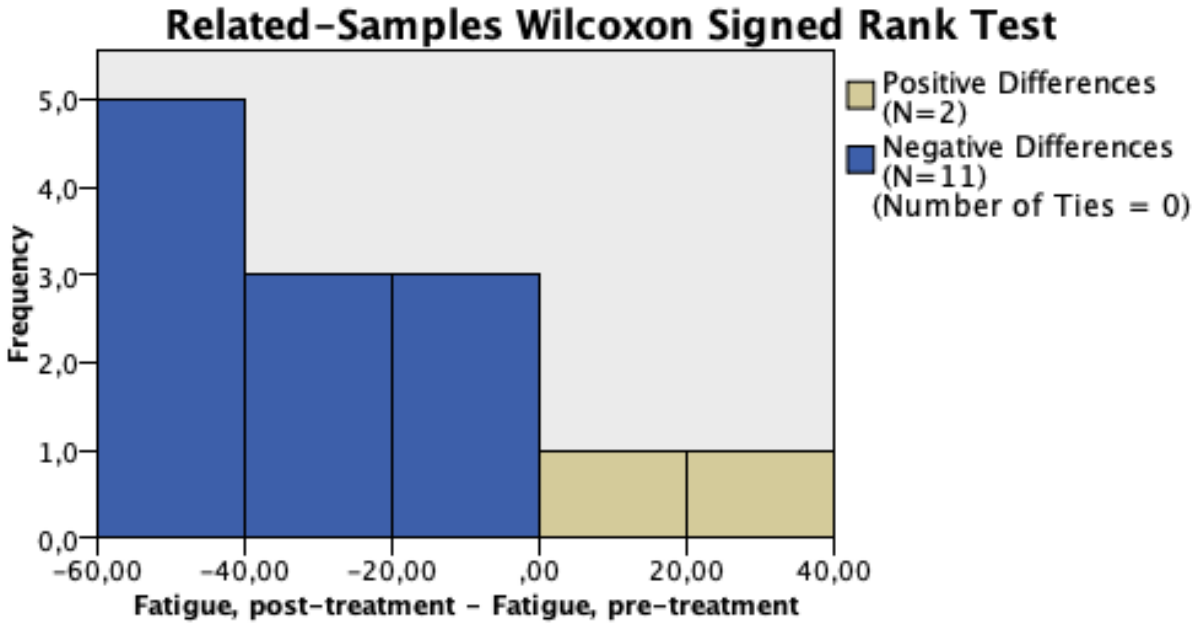

Figure 9. Histogram of Wilcoxon Signed-Rank Test for fatigue-levels pre-treatment versus post-treatment, indicating a negative difference in ranks. A negative difference in ranks emphasizes that the patients reported significant lower fatigue-levels post-treatment than pre-treatment. 11 patients reported a lower score, while 2 patients reported a higher score after ILF NFT.

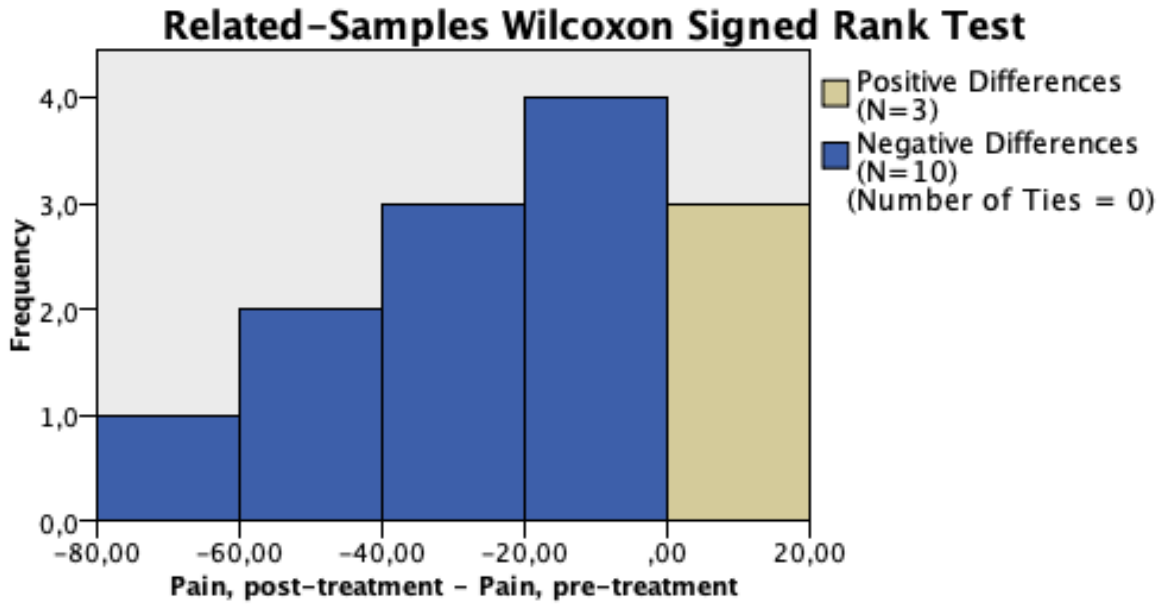

Figure 10. Histogram of Wilcoxon Signed-Rank Test for pain-levels pre-treatment versus post-treatment, indicating a negative difference in ranks. A negative difference in ranks emphasizes that the patients reported significant lower pain-levels post-treatment than pre-treatment. 10 patients reported a lower score, while 3 patients reported a higher score after ILF NFT.

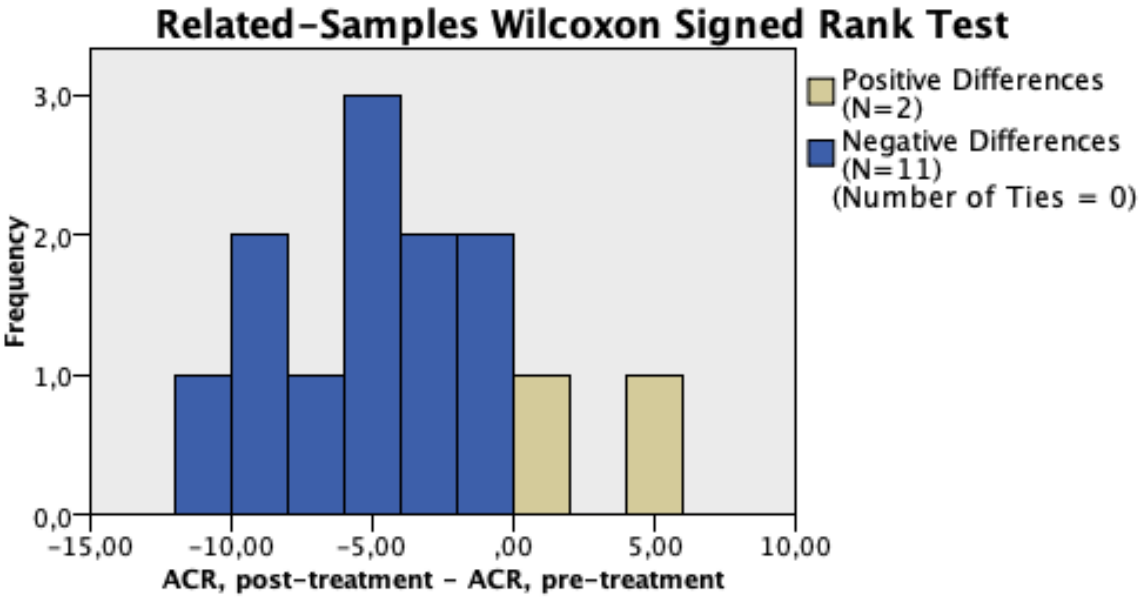

Figure 11. Histogram of Wilcoxon Signed-Rank Test for ACR-scores pre-treatment versus post-treatment, indicating a negative difference in ranks. A negative difference in ranks emphasizes that the patients reported a significant lower ACR-score post-treatment than pre-treatment. 11 patients reported a lower score, while 2 patients reported a higher score after ILF NFT.

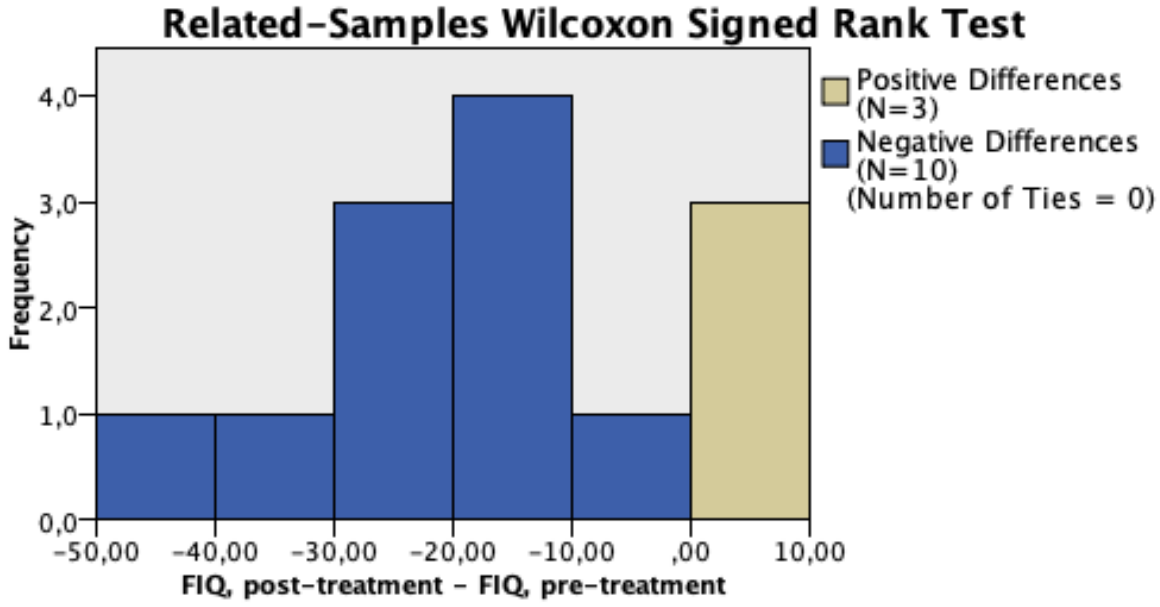

Figure 12. Histogram of Wilcoxon Signed-Rank Test for FIQ-scores pre-treatment versus post-treatment, indicating a negative difference in ranks. A negative difference in ranks emphasizes that the patients reported a significant lower FIQ-score post-treatment than pre-treatment. 10 patients reported a lower score, while 3 patients reported a higher score after ILF NFT.

3.2.3 Brain frequency band activity. Patients´ displayed a significant decrease in theta frontally amplitude from pre-treatment (*Mdn* =.94) to post-treatment (*Mdn* =.80), *z* =-2.13, *p* =.033, *N* =13, *r* =-.42 (see Figure 13). There were no significant differences between pre-treatment and post-treatment amplitude in the other frequency bands and corresponding cortical areas (see Appendix D).

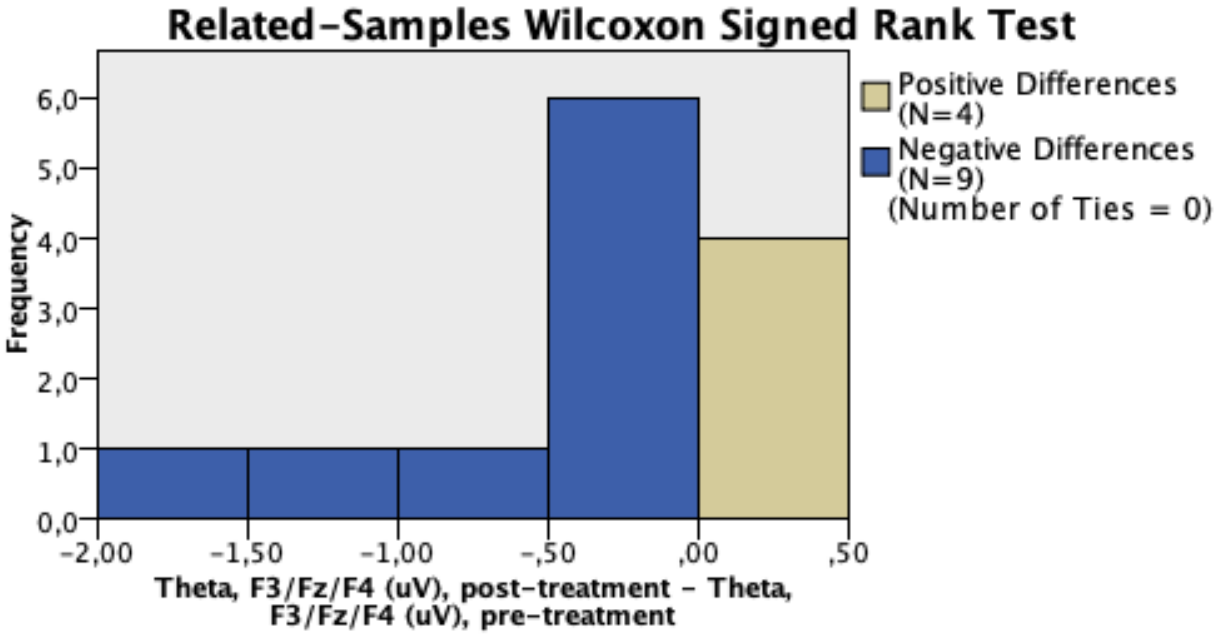

Figure 13. Histogram of Wilcoxon Signed-Rank Test for theta frontally amplitude pre-treatment versus post-treatment, indicating a negative difference in ranks. A negative difference in ranks emphasizes that patients displayed a significant lower theta frontally amplitude post-treatment than pre-treatment. 9 patients displayed a lower amplitude, while 4 patients displayed a higher amplitude after ILF NFT.

3.2.4 Pre-treatment post-treatment comparison of power spectra analysis. A comparison between individual power spectra pre-treatment and post-treatment indicated a decrease in the percentage of patients displaying deviances compared to the normative database, in almost all frequency bands and corresponding cortical areas. An overview of the significant deviances in power spectra between each patient compared with age-matched subjects from the normative database for all three conditions, post-treatment, is presented in Appendix F.

All conditions together, comparison indicated that fewer patients showed deviances, compared to the normative database, in theta, beta, and alpha frequency bands and corresponding cortical areas, after ILF NFT. Except, theta centrally and alpha frontally which

showed no changes in the percentage of patients with deviances, from pre-treatment to post-treatment (see Table 6 and Figure 14).

Table 6

Percentage of patients with significant deviances in power spectra, for all conditions (N =13)

Frequency band	Cortical area	Pre-treatment	Post-treatment
Theta	Total	45.15 %	15.38 %
	Central	0.00 %	0.00 %
	Temporal	23.08 %	15.38 %
	Frontal	30.77%	0.00 %
Alpha	Total	53.85 %	46.15 %
	Central	15.38 %	7.69 %
	Temporal	30.77 %	23.08 %
	Frontal	15.38 %	15.38 %
Beta	Total	100 %	92.31 %
	Central	84.62 %	69.23 %
	Temporal	53.85 %	38.46 %
	Frontal	76.92 %	46.15 %

Note. The table shows the percentage of patients displaying significant deviances, compared to the normative database, in theta, alpha, and beta frequency bands in all conditions together, in corresponding cortical areas separately, and total. Pre-treatment and post-treatment values are presented.

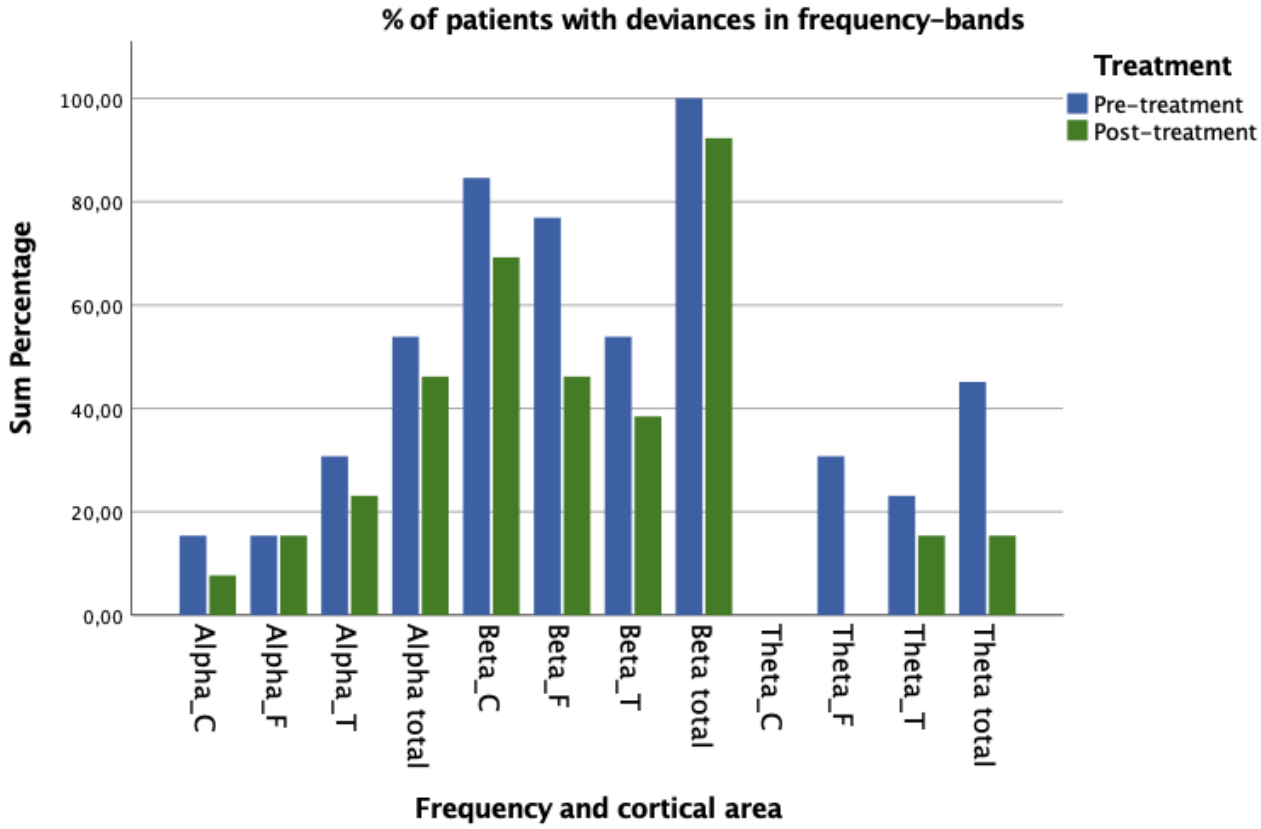

Figure 14. Bar-chart showing percentage of patients displaying deviances in frequency bands and corresponding cortical areas, pre-treatment versus post-treatment. _C = central; _F = frontal; _T = temporal.

3.2.5 Pre-treatment post-treatment comparison of ERP analysis. A comparison between ERP amplitude deviances from normal revealed several changes from pre-treatment to post-treatment. An overview of individually significant deviances compared to the normative database for each component with corresponding mean amplitude, post-treatment, is presented in Appendix G. For the N1 component, 30.77 % of patients showed enhanced amplitudes, and 61.54 % showed decreased amplitudes, after ILF NFT. Also, one patient (7.69 %) displayed a positive N1 amplitude pre-treatment which increased post-treatment (see Figure 15).

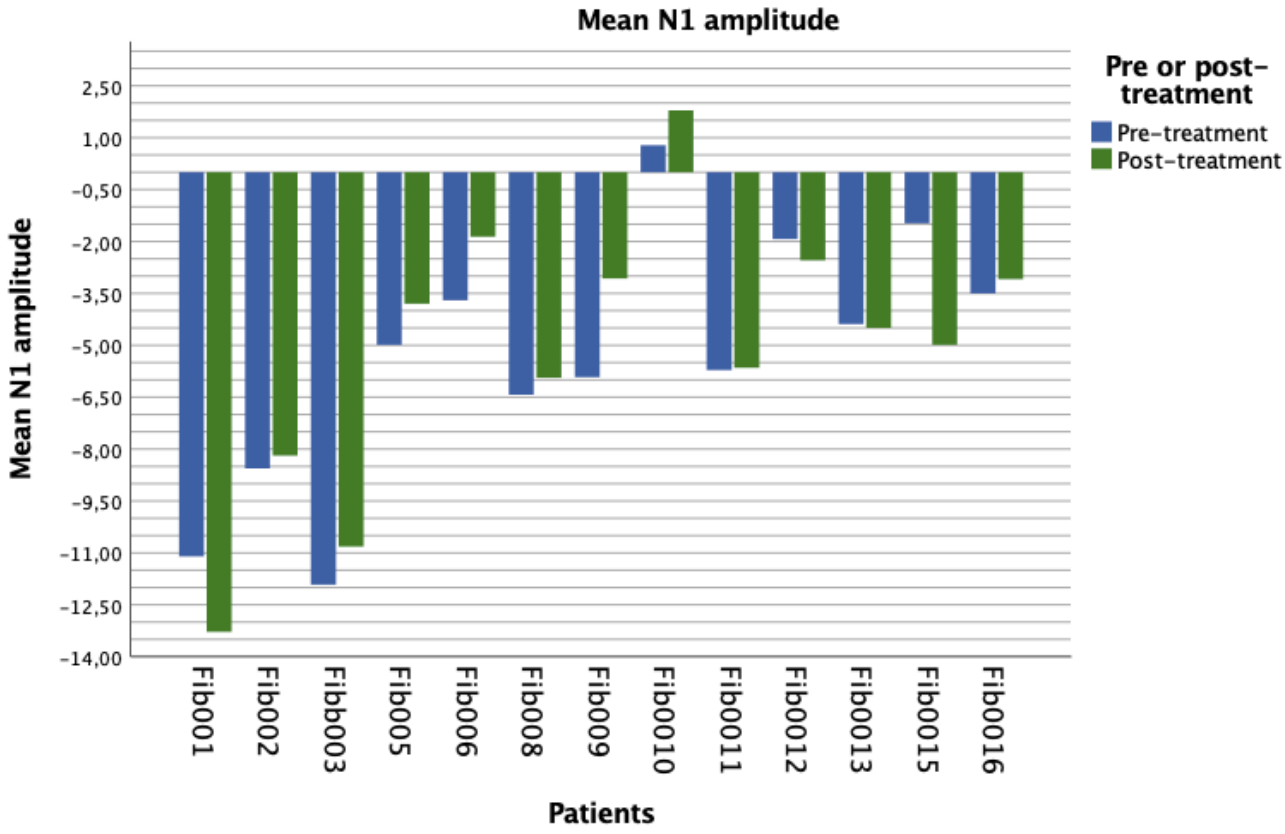

Figure 15. Bar-chart of individual significant deviances from normal, for N1 mean amplitude, pre-treatment and post-treatment.

For the CNV component, 38.46 % of patients showed enhanced amplitudes, while 53.85 % showed decreased amplitudes post-treatment. One patient (7.69 %) displayed a shift in polarity from pre-treatment to post-treatment. Pre-treatment, this patient showed an enhanced negative CNV amplitude. In contrast, this patient showed a decreased positive CNV amplitude post-treatment (see Figure 16).

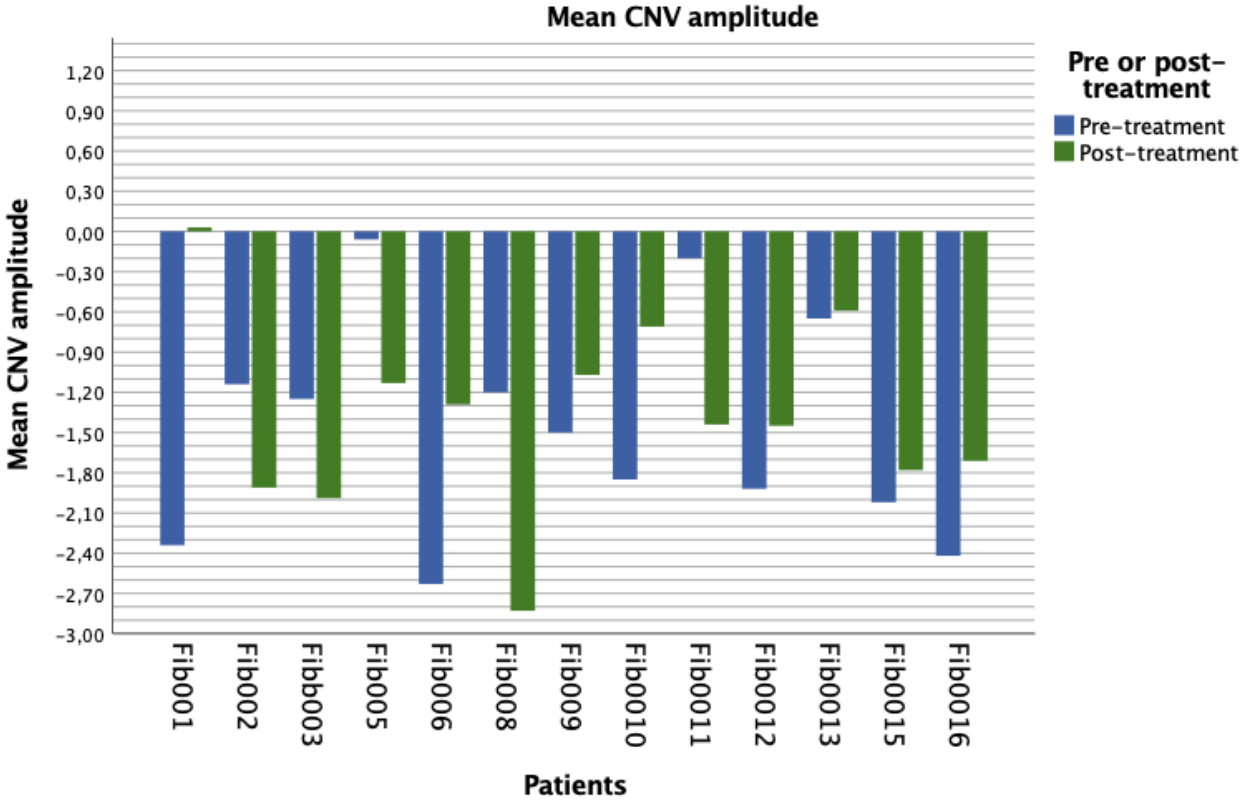

Figure 16. Bar-chart of individual significant deviances from normal, for CNV mean amplitude, pre-treatment and post-treatment.

For the P3 NoGo early component, 23.08 % of patients showed enhanced amplitudes, while 38.46 % showed decreased amplitudes post-treatment, compared to pre-treatment. Additionally, 15.38 % of patients displayed a shift in polarity from pre-treatment to post-treatment. These patients showed enhanced positive P3 NoGo early amplitudes pre-treatment. In contrast, the patients displayed enhanced negative P3 NoGo early amplitudes post-treatment. One patient (7.69 %) displayed no deviances compared to the normative database, pre-treatment. In contrast, this patient showed a negative P3 NoGo early amplitude, post-treatment. 15.38 % of patients displayed negative P3 NoGo early amplitudes, pre-treatment. These patients displayed enhanced negative P3 NoGo early amplitudes, post-treatment (see Figure 17).

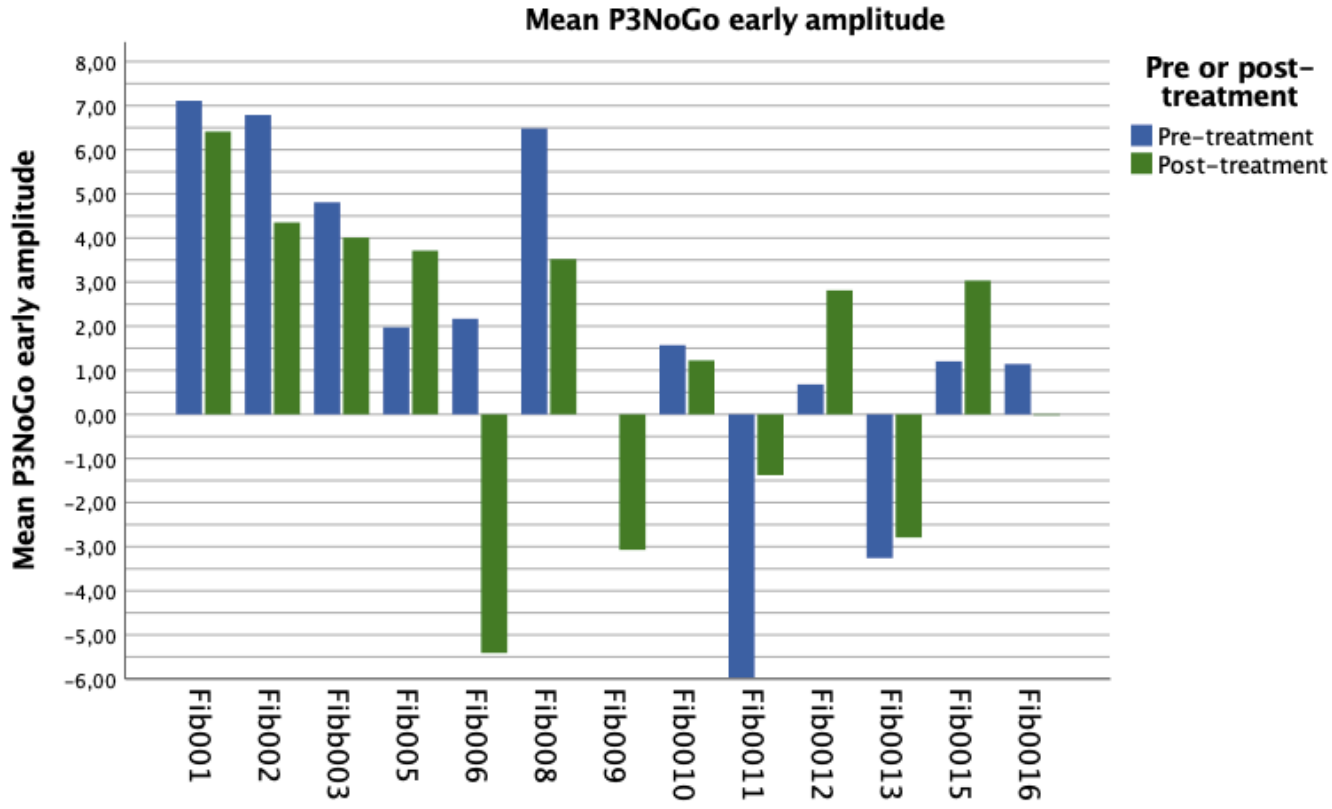

Figure 17. Bar-chart of individual significant deviances from normal, for P3 NoGo early mean amplitude, pre-treatment and post-treatment.

For the P3 NoGo late component, 23.08 % of patients showed enhanced amplitudes, while 23.08 % showed decreased amplitudes post-treatment, compared to pre-treatment. 15.38 % of patients showed a shift in polarity from negative P3 NoGo late amplitude (pre-treatment) to positive P3 NoGo late amplitude (post-treatment), while 15.38 % of patients showed a shift in polarity from positive P3 NoGo late amplitude (pre-treatment) to negative P3 NoGo late amplitude (post-treatment). 15.38 % showed a negative P3 NoGo late amplitude pre-treatment. These patients showed decreased negative P3 NoGo late amplitudes post-treatment. Also, one patient (7.69 %) showed a negative P3 NoGo late amplitude pre-treatment, and that patient showed an enhanced negative P3 NoGo late amplitude post-treatment (see Figure 18).

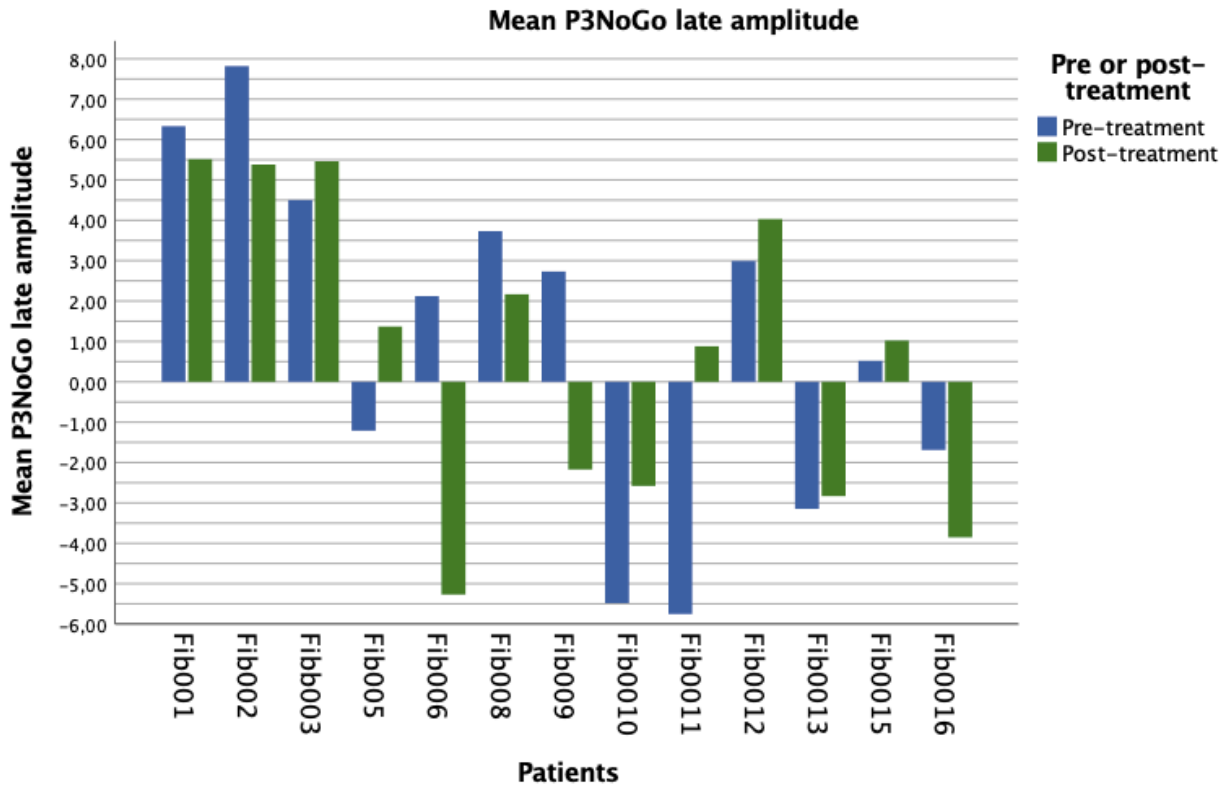

Figure 18. Bar-chart of individual significant deviances from normal, for P3 NoGo late mean amplitude, pre-treatment and post-treatment.

4. Discussion

4.1 Main Findings

This project had two objectives. The main objective was to investigate whether infra-low frequency neurofeedback (ILF NFT) could reduce fibromyalgia (FM) symptoms, measured by changes in symptom score measures and normalization of QEEG data. The second objective was to investigate whether the brain patterns of FM patients deviated from age-matched controls in the normative database and whether these deviances was located to brain regions implicated in the dynamic pain connectome. To further explore which cortical regions that may have the potential of uncovering neurobiological markers for FM disease.

4.1.1 Preliminary results. Grand average of power spectra revealed that FM patients showed increased theta temporally (μV) activity (p<.001) and increased beta centrally (μV) activity (p<.05), in the resting EC condition, compared to healthy controls. Also, patients showed increased theta frontally (μV) activity (p<.05) and increased theta temporally (μV) activity (p<.001), in the active VCPT condition. All conditions together, individual power spectra analysis showed that all patients displayed enhanced activity in the beta frequency band (100 %). 45.15 % of patients showed enhanced activity in the theta frequency band, except one patient who displayed reduced activity in theta temporally activity in the VCPT condition. 53.85 % of patients showed enhanced activity in the alpha frequency band.

Compared to the normative database, grand average of ERP revealed enhanced N1 amplitude (p<.05), CNV amplitude (p<.01), and P3 NoGo early amplitude (p<.001) among the FM patients. Individual ERP analysis revealed that 92.31 % of patients displayed enhanced N1 and CNV amplitude, and 76.92 % of patients displayed enhanced P3 NoGo early amplitude.

Source analysis revealed that patients displayed deviations in all Brodmann areas except BA 27 and BA 33. The most prominent Brodmann areas where most of the patients showed deviant activity were BA 10, 39, 46, and 47 (92.86 %), BA 32 (85.71 %), BA 40 and 45 (78.57 %), and BA 37, 31, 30 and 21 (71.43 %).

4.1.2 The effect of ILF NFT on FM symptoms. Wilcoxon Signed-Rank Tests revealed six significant changes from pre-treatment to post-treatment: *(a)* a significant moderate enhanced N1 latency from pre-treatment to post-treatment (p<.05, r =.42), with a moderate effect size; *(b)* a large significant decrease in fatigue-levels (p<.01, r =-.51), and a

moderate significant decrease in pain-levels ($p<.05$, $r=-.48$); *(c)* a large significant decrease in both ACR-scores ($p<.01$, $r=-.54$) and FIQ-scores ($p<.01$, $r=-.51$); *(d)* a significant moderate reduced theta frontally amplitude ($p<.05$, $r=-.42$).

A power spectra comparison of the percentage of patients showing deviances in frequency bands and corresponding cortical areas, pre-treatment versus post-treatment, revealed that fewer patients displayed deviations in all brain frequency bands and corresponding cortical areas after ILF NFT. Except for theta centrally and alpha frontally amplitude, which showed no change from pre-treatment to post-treatment.

An ERP comparison of ERPs´ amplitude pre-treatment versus post-treatment for each patient individually, compared to the normative database, showed a variety of results. For N1 amplitude, most of the patients (61.54 %) displayed a decreased N1 amplitude, after ILF NFT. For CNV amplitude, most of the patients (53.85 %) displayed a decreased CNV amplitude, after ILF NFT. The P3 NoGo amplitude showed different results. 38.46 % of patients displayed a decreased P3 NoGo early amplitude, while 23.08 % of patients showed enhanced amplitudes, after ILF NFT. 23.08 % of patients displayed a decreased P3 NoGo late amplitude, after ILF NFT. In contrast, 23.08 % of patients displayed enhanced P3 NoGo late amplitudes, after ILF NFT.

It is important to note that the changes in ERP comparison and power spectra comparison from pre-treatment to post-treatment is not the result of a significant test. Therefore, these changes are only interpreted as tendencies within the patient group, not significant changes from pre-treatment to post-treatment. The results from Wilcoxon Signed-Rank Tests are the only statistically significant results from pre-treatment to post-treatment.

4.2 Interpretation of Preliminary Results

4.2.1 Power spectra deviances. As expected, power spectra analysis revealed that all patients showed significant deviances from the normative database in relative power in one or more of the brain frequency bands. Grand average power spectra indicated that deviant activity in beta and theta frequency bands were most prevalent. Patients displayed a significantly enhanced theta frontally activity, which corresponds with earlier findings (Donaldson et al., 2003; Fallon et al., 2018; Lim et al., 2016). An interpretation for this finding is the relationship between theta frontally activity and activity within the default mode network (DMN). Scheeringa and colleagues (2008) found that increased theta frontally amplitude correlates with decreased DMN activity at rest. This decreased resting-state network activity may result from a difficulty with focusing their attention away from pain,

causing poor functional connections between the DMN and the pain-modulating antinociceptive system (Flodin et al., 2014; Kucyi & Davis, 2015). Besides, the enhanced theta frontally activity in this study was found in Brodmann areas within attentional networks (BA 47 and BA10). Which further support the idea that the enhanced theta frontally activity seen among the FM patients in this study could be explained by decreased DMN activity causing disruptive attentional processing of pain, and consequently reduced pain inhibition.

Grand average power spectra analysis also revealed that patients displayed a significantly enhanced beta centrally activity located in areas implicated in somatosensory processing (BA 1, 2, 3, and 5) and motor cortex (BA 4) which corresponds with earlier findings (González-Roldán et al., 2016; Hargrove et al., 2010). Earlier studies investigating cortical excitability in FM patients have revealed that this patient group display hyperexcitability in motor and somatosensory cortical regions (Mhalla, de Andrade, Baudic, Perrot, & Bouhassira, 2010), in addition to, reduced inhibition (Salerno et al., 2000). These findings are associated with a working hypothesis by Castillo-Saavedra and colleagues (2016) stating that motor cortex and primary pain circuits are connected in a feedback loop, such as the more pain a chronic pain patient experiences, the more excitable this neural network becomes (Castillo-Saavedra et al., 2016). A dysfunction in GABAergic transmission of interneurons could cause the enhanced excitability seen in the motor cortex. Further, this dysfunction might be produced by maladaptive neuroplasticity as a result of baseline alternations in neuronal circuits implicated in pain modulation. Hence, we suggest that the enhanced beta centrally activity (Rolandic beta rhythm) among FM patients in this study, could be interpreted as an increase of excitability in the sensory-motor strip due to the disinhibition of cortical areas that participate in pain processing. This notion is further supported by Kayiran and colleagues (2010) who used uptraining of the inhibiting sensory-motor rhythm in neurofeedback training on FM patients. This rhythm is believed to be associated with the suppression of sensory-motor gating and increases could lead to thalamic inhibition. They found that an increase in this inhibitory rhythm in motor cortex resulted in pain relief (Kayıran et al., 2010), which points to the primary cortex as a potential core region for neurotherapy focusing on pain relief among FM patients.

4.2.2 ERP deviances. As expected, ERP analysis revealed significant deviances in N1, CNV, and P3 NoGo amplitude among FM patients. Grand average ERP analysis revealed that patients displayed significant stronger N1, CNV, and P3 NoGo early amplitude, compared to the normative database. The enhanced N1 amplitude corresponds with Choi and

colleagues´ (2016) findings of enhanced auditory N1 amplitude among FM patients. In this study, correlation analysis revealed a significant positive relationship between N1 amplitude and fatigue-scores, indicating that patients displaying enhanced N1 amplitude also reported high levels of fatigue. Since N1 amplitude seems to reflect the intensity and localization of incoming sensory stimuli, the results may indicate that the enhanced N1 amplitude seen among FM patients is due to the hypersensitivity to sensory stimuli, caused by central sensitization. Central sensitization symptoms are prevalent in fatigue patients, including hypersensitivity to bright light, smell, sound, hot or cold sensations and touch (Nijs et al., 2012). Therefore, the enhanced N1 amplitude seen in this study could reflect a perceptual overload due to the patients´ hypersensitivity to sensory stimuli, which often results in fatigue due to the considerable amount of energy the body has to use on incoming sensory stimuli.

The enhanced CNV amplitude among FM patients in this study corresponds with earlier findings in migraine patients (Böcker et al., 1990; Siniatchkin et al., 1998), and experiments using induced pain (Stude et al., 2003) and expectation of pain (Babiloni et al., 2005). Moreover, CNV amplitude correlated positively with reaction time in this study, which corresponds with earlier findings (Brunner et al., 2015). Based on the fact that CNV amplitude seems to reflect energization, and that enhanced CNV amplitude is associated with prolonged reaction time, the results could indicate a degree of processing disruption in the time between the presentation of stimuli and the following motor response (pressing a button) (Macar & Vidal, 2004). Therefore, enhanced CNV amplitude might reflect disrupted attentional and arousal processes among FM patients. These disrupted attentional processes could further be caused by central sensitization mechanisms causing hypervigilance. FM patients may have difficulties with disengaging from hypervigilance and allocate attentional resources towards a reaction time task, indicated by the enhanced CNV amplitude discovered in this study.

Grand average ERP analysis also revealed a significant enhancement in P3 NoGo early amplitude compared to the normative database, which is inconsistent with earlier findings of reduced P3 amplitude among FM patients (Alanoğlu et al., 2005; Ozgocmen et al., 2003; Yoldas et al., 2003). These earlier findings used auditory stimuli, and this study used visual stimuli in a VCPT task, so it could be possible that the inconsistencies are caused by the use of different stimuli and conditions. Furthermore, P3 NoGo early and P3 NoGo late have different topographies, latencies, and reflect different cognitive processes. This fact was not taken into account in these earlier findings, consequently yielding inconsistent results. The enhanced frequency band activity over frontal and central areas could explain the significant

enhanced P3 NoGo early amplitude seen among the FM patients in this study. P3 NoGo displays a fronto-central distribution (Brunner et al., 2015). Power spectra analysis revealed that 85.71 % of patients showed deviant activity in the fronto-central cortical region BA 32, which corresponds to anterior cingulate cortex. Hence, enhanced frequency band activity in the anterior cingulate cortex could explain the significant enhancement in P3 NoGo early amplitude. This notion is further supported by the correlation analysis, revealing a significant negative correlation between P3 NoGo late amplitude and reaction time, indicating that fast responders exhibit a higher P3 NoGo amplitude, which corresponds with earlier findings (Brunner et al., 2013). Therefore, it may be possible that the enhanced P3 NoGo early amplitude could indicate an overactivation of attentional processes, causing difficulties with allocating attentional resources.

4.3 Interpretation of the Effect of ILF NFT on FM Symptoms

4.3.1 ERP components. A significant enhanced N1 latency was found after ILF NFT. Enhanced N1 latency is associated with more effort expended in processing stimuli (Callaway & Halliday, 1982). A short N1 latency may, therefore, reflect a failure to activate normal attentional capacities. The significant enhanced N1 latency, together with the tendency of weaker N1 and CNV amplitude among the FM patients after ILF NFT, is interpreted as an improvement in focused attention. The preliminary analysis indicated overactivation in frontal and central cortical areas. Moreover, comparison of pre-treatment and post-treatment individual power spectra analysis revealed that fewer patients displayed enhanced relative power in frequency bands at cortical sites implicated in attentional processes (central and frontal sites). This reduced over-activation could be related to the significant reduction in pain-levels, post-treatment. Pain has such an attention-demanding quality that it is challenging to focus attention away from pain during tasks. The observed enhanced N1 latency may, therefore, be a result of better attentional capabilities caused by a pain-reduction after ILF NFT, making it possible for patients to focus their attention on relevant incoming stimuli and away from pain.

4.3.2 Brain frequency band activity. The most striking finding in this study was the significantly enhanced theta frontally activity pre-treatment, and consequently a significant decrease in frontal theta amplitude after ILF NFT. This result corresponds with an earlier study using ILF NFT on patients with depression (Grin-Yatsenko et al., 2018). The enhanced theta frontally activity, pre-treatment, could be a result of thalamocortical dysrhythmia

(TCD). Deafferentation of excitatory inputs on thalamic cells results in cell membrane hyperpolarization, which in turn generates low-threshold calcium spike bursts at theta frequencies, caused by activation of calcium T-channels. These bursts of thalamic relay neurons exert oscillatory activity in thalamocortical loops, leading to over-production of theta activity in the cortex (Lim et al., 2016; Llinás, Urbano, Leznik, Ramírez, & Van Marle, 2005; Llinás, Ribary, Jeanmonod, Kronberg, & Mitra, 1999). The frontal cortical regions implicated in the DMN and the salience network (SN) receive projections from mediodorsal nucleus of the thalamus. Hence, these thalamic neurons directly influence frontal cortical activity, both structural and functional (Klein et al., 2010). Additionally, Scheeringa and colleagues (2018) observed a negative correlation between theta frontally amplitude and default mode network activity in their combined fMRI and EEG study. Which further supports a working hypothesis stating that frontal theta activity has close connections with the cortical regions implicated in the dynamic pain connectome and that enhanced frontal activity could be a result of TCD.

The decreased theta frontally amplitude seen after ILF NFT may be attributed to the renormalization of functional connectivity between the DMN, the SN, and the antinociceptive system (AS). In addition to decreased theta frontally activity, pre-treatment to post-treatment comparison indicated that fewer patients showed enhanced activity in alpha and beta frequency bands after ILF NFT, suggesting that uptraining of infra-low frequencies exerted a normalizing effect on several cortical brain-frequency bands. Spontaneous infra-low frequency fluctuations (<.01 Hz) during both resting state and active-task conditions are thought to reflect cyclic modulation of cortical excitability and long-distance neuronal synchronization (Legarda et al., 2011; Lőrincz et al., 2009). Research on how these infra-low oscillations affect faster thalamocortical frequencies are limited, and most of the research is derived from animal studies. Nevertheless, observations suggest an inverse relationship between infra-low frequencies below 1 Hz and faster frequencies above 1 Hz (Achermann & Borbely, 1997). This notion is supported by results of a pharmacological study where reduction of power in the theta frequency band induced by a benzodiazepine hypnotic was accompanied by an increase of power in the infra-low frequency band (Trachsel, Dijk, Brunner, Klene, & Borbély, 1990).

TCD could explain the inverse relationship between the infra-low frequency band and the theta frequency band. It is possible that decreased infra-low oscillation activity in the mediodorsal nucleus of thalamus leads to TCD by causing a deafferentation of excitatory input in thalamic cells. Consequently, TCD results in enhanced theta frontally activity in cortical regions implicated in the dynamic pain connectome. As mentioned earlier,

thalamocortical oscillations arise from a feedback loop within the thalamic relay nuclei (TRN). Reticular nucleus (RE) contributes to the inhibitory feedback control of the thalamocortical (TC) neurons which project to the cortex (Buzsáki, 2006). Infra-low oscillations might contribute to the inhibitory input of TRN by exerting inhibitory phases of infra-low oscillations in TC neurons due to the effect of ATP-derived adenosine (Hughes, Lőrincz, Parri, & Crunelli, 2011). When these infra-low frequencies are decreased, the consequent reduction of TRN inhibitory output results in bursts of thalamic relay neurons. Moreover, this reduction of inhibitory output results in TCD, characterized by persistent theta and beta overactivations in pain-associated cortical regions (Henderson et al., 2013).

Therefore, we suggest that uptraining of infra-low frequencies with ILF NFT normalizes the thalamocortical rhythm by contributing to more inhibitory input to thalamocortical neurons projecting to the cortex. Thereby, reducing overactivation of alpha, beta, and theta frequency bands in cortical areas implicated in the dynamic pain connectome. This reduction in brain frequency band activity together with an enhancement of DMN activity leads to symptom reduction among FM patients.

4.3.3 Symptom score measures. After ILF NFT, Wilcoxon Signed-Rank Tests revealed significant decreases in all symptom score measures (ACR, FIQ, VAS for pain, and VAS for fatigue), except VAS levels for fibrofog, indicating an overall symptom reduction and improvement of life quality after ILF NFT. This symptom reduction could be associated with the significant reduction in theta frontally amplitude, seen in this study. Even though this study found no significant positive correlations between theta frontally amplitude and symptom score measures pre-treatment, earlier findings have revealed positive relationships between theta frontally activity and fatigue (Fallon et al., 2018), and theta frontally activity and pain (Lim et al., 2016), among FM patients. Furthermore, Grin-Yatsenko (2018) and colleagues found improved mood and self-organization skills, in addition to, increased emotional stability and stress tolerance after ILF NFT, among patients with depression (Grin-Yatsenko et al., 2018). Based on these earlier findings and the fact that this study found no significant reduction in fibrofog after ILF NFT, it is possible that ILF NFT is more successful in treating symptoms of pain and fatigue than fibrofog.

Fibrofog is a more diffuse and a less investigated FM symptom than fatigue and pain, characterized by cognitive difficulties in working memory, executive functions, semantic memory, episodic memory and attention (Kravitz & Katz, 2015). Also, FM patients generally display increased alertness and decreased vigilance (measured as slowed reaction time),

which could be an important feature of fibrofog (Miró et al., 2011). This study showed no significant reduction in reaction time from pre-treatment (*Mdn* = 309.00, *SD* = 62.93) to post-treatment (*Mdn* = 326.00, *SD* = 62.12). Instead, patients showed a tendency of longer reaction time after ILF NFT. This result, together with no significant decrease in fibrofog VAS levels post-treatment could indicate that ILF NFT influence attentional networks that are more functionally associated with symptoms of pain and fatigue, than the memory- and cognitive difficulties implicated in fibrofog.

Another explanation could be the lack of fibrofog symptoms among the patients in this study. Mean VAS levels were larger for pain (*M* = 65.23, *SD* =19.84) and fatigue (*M* = 65.76, *SD* = 19.82), then for fibrofog (*M* = 52.07, *SD* = 27.46). Moreover, fibrofog (*Var* = 754.16) VAS levels displayed a larger variability than fatigue (*Var* = 392.83) and pain (*Var* = 393.75). Hence, an explanation for the lack of significant improvement in fibrofog VAS levels after ILF NFT could be that the patients included in this study did not experience severe fibrofog symptoms before the intervention, and consequently, displayed no symptom reduction in fibrofog after ILF NFT. Another explanation could lie in the diffuse definition of fibrofog. VAS for fibrofog only measured total fibrofog symptoms and not the different aspects, such as semantic memory, recall, focused attention, and episodic memory. Besides, FIQ and ACR did not include measures of attentional and cognitive difficulties. Hence, the lack of fibrofog symptoms and large variability among the patients could be due to the symptom score measures not being able to measure fibrofog symptoms properly.

4.4 Potential Neurobiological Markers for Fibromyalgia

As expected, sLORETA source analysis revealed that FM patients showed deviant brain frequency activity in several cortical areas implicated in the dynamic pain connectome. 92.86 % of patients showed deviant activity in the prefrontal cortex (BA 10, 46, and 47) and temporal parietal junction (BA 39). 85.71 % of patients showed deviances in the anterior cingulate cortex (BA 32). 78.57 % of patients showed deviances in inferior frontal gyri (BA 45) and inferior parietal lobule (BA 40). 71.43 % of patients showed deviances in the posterior cingulate cortex (BA 30 and 31), and temporal gyrus (BA 37, and 21). Hence, source analysis revealed that FM patients displayed deviances in areas implicated in both the default mode network: ventral medial prefrontal cortex (vMPFC), posterior cingulate cortex (PCC), inferior parietal gyri (IPL), lateral temporal cortex (LTC), and dorsal medial prefrontal cortex (dMPFC); and the salience network: dorsal anterior cingulate cortex (dACC), inferior frontal gyri (IFG), temporal parietal junction (TPJ), dorsolateral prefrontal cortex (dlPFC),

and mid-cingulate cortex (MCC). These results support earlier findings of deviant activity among FM patients in MCC (González-Roldán et al., 2016), ACC, mPFC, and dlPFC (Fallon et al., 2018; Lim et al., 2016). Moreover, the results support the notion that functional activity within the dynamic pain connectome modulates symptoms experienced by FM patients. Cortical regions within the dynamic pain connectome could, therefore, be core candidates for uncovering neurobiological markers for diagnosis. In addition to potential candidates for neurotherapy. It should be noted that these cortical areas are also implicated in other chronic pain diseases (dos Santos Pinheiro et al., 2016). Therefore, more research are needed, comparing activity in dynamic pain connectome regions with healthy controls and other related chronic pain diseases (such as fatigue, chronic back pain, and arthritis) to be able to find neurobiological markers for fibromyalgia, specifically.

4.5 Limitations of the Study and Future Recommendations

4.5.1 Design. A concern regarding the research design used in this project is the lack of a sham-condition and a follow-up. The project should have implemented a follow-up to investigate long term effects of ILF NFT. Unfortunately, this was not possible due to the time constraints of the master thesis, only covering 9 months. Even though this study revealed that ILF NFT lead to symptom reduction among FM patients, the results are difficult to replicate due to the probability that they could be a result of placebo effects. Since there are no available treatments for fibromyalgia leading to considerable symptom reduction, the patient group should be very motivated for the treatment to work. Thereby, the significant reduction in symptoms measured by the subjective symptoms score measures included in the project, could be a result of placebo effects. The study should, therefore, have used a randomized placebo-controlled design to be able to control for potential placebo effects. A placebo-controlled design would consist of a control condition where everything is identical, except that the feedback for NFT is not related to the brain activity of the participants. Using this design would also allow for the control of unspecific expectancy effects by blinding the intervention. This kind of research design would require a standardized protocol for ILF NFT as an intervention for fibromyalgia (Arns, Heinrich, & Strehl, 2014). Moreover, there are ethical issues that should be considered when implementing this type of design. By implementing a sham condition, there is a potential for withholding the best possible treatment from patients. Also, it would be unethical to implement a sham-condition in this project since most of the patients had a long way to travel and did not receive compensation for fuel expenses or compensation for participation in the project.

To this date, there is no published literature on the use of ILF NFT on FM patients, which made it challenging to implement standardized ILF NFT protocols in this project. More research has to be done to establish better guidelines for a protocol, which should entail an investigation of the number of training sessions and the type of electrode placement. Besides, a core element of neurofeedback training is individualization regarding the patients´ symptoms (Hammond, 2010). Individualization of NFT is an advantage when dealing with fibromyalgia, due to the variability of symptoms and variability in the severity of symptoms among the patients. Accordingly, more research has to be done before establishing a standard protocol for ILF NFT as an intervention for FM disease.

Nevertheless, it should be emphasized that this project used objective QEEG data, in addition to, subjective symptom score measures which yielded statistical significant results indicating symptom reduction. Therefore, the results in this study demonstrates that training with infra-low frequency neurofeedback leads to a significant symptom reduction among FM patients.

4.5.2 Participants and control group. A relevant limitation of this study is the lack of a control group. The use of a control group in this study would make it possible to compare the patient group with more appropriate age-matched healthy controls. The only control group in this project was the HBI normative database. This database provided a reasonable foundation for comparison. Nevertheless, there are some statistical limitations regarding the HBI database. There does not exist a record of the standard deviations in the database. The only statistical information obtained is the average mean for the whole group, no single values. Which makes it impossible for SPSS to make statistical comparisons. Hence, we had to rely on the internal t-test engine of the WinEEG software to look for significant deviances between the patients´ and controls in the HBI normative database.

Another limitation is the small sample size used in this study. 16 participants completed the pre-treatment EEGs and diagnostic measures. 15 patients proceeded with ILF NFT, but only 14 patients completed the training. Also, one participant was excluded from analysis due to gender, making a total sample size of 13 patients. Participants were recruited from the Fibromyalgia Association and self-help Facebook groups. It is not possible to know if those who are active in these forums are representative for FM patients in general. Some people with fibromyalgia may be so severely afflicted that they do not have the energy to engage in this kind of training, which require multiple sessions and traveling.

There are several reasons for the small sample size and lack of a control group. This project included a patient group where most of the patients receive disability benefits because the disease severely affects daily functioning. To participate in the project, patients had to travel to NTNU, Dragvoll 12-17 times which is challenging for a patient group that struggles with simple daily tasks. Besides, having a larger sample size and control group would have required a substantial amount of time to gather participants. As mentioned earlier, this was not possible due to the time constraints of the project.

4.5.3 Variables. A challenge concerning the diagnostic measures in this study was the lack of validated Norwegian versions of the questionnaires. The project decided to use Norwegian versions of the questionnaires due to potential language problems among the participants. Due to difficulties with accessing validated Norwegian versions of FIQ and ACR, the Norwegian versions used in this study were translated with the help of a translator. The Norwegian versions were scored according to original rules, and the same translated version was used pre-treatment and post-treatment; accordingly, the statistical results should not be affected. Nevertheless, the questionnaires are not empirically validated, making it difficult to replicate this study. Also, none of the questionnaires measured memory difficulties implicated in fibrofog, which could have influenced the results.

Another concern is the lack of control regarding possible confounding third variables which could have influenced the QEEG data, and consequently the results. There are many variables which may influence VCPT-results, such as age, sight/vision, other diagnoses, medication and time of the day. Moreover, the variables used for QEEG data could yield different experimental effects compared to earlier findings, due to different paradigms and protocols across studies. Brain imaging techniques, such as sLORETA, show that the brain sources of QEEG activity are not necessarily located in the tissue immediately below electrodes. Additionally, definitions of frequency bands vary somewhat across studies, affecting the cut-off point for frequency band ranges. Hence, low alpha can be reported as theta whereas high theta can be reported as low alpha. It should also be mentioned that ERP component analysis may yield different results across studies, as the ERPs are dependent upon the protocol used, which is guiding for the interpretations made from ERP analyses.

4.5.4 Analysis and statistics. The number of variables used in this project limited which statistical analyses that could be performed. Since this was a pilot study, several QEEG variables and symptom score measures were used, resulting in 24 independent variables. The

number of variables and the small sample size made it impossible to conduct multivariate analysis due to the increased chance of committing a Type 1 error, in addition to, the potential of low effect sizes for the significant results. The non-parametric version of the dependent t-test (Wilcoxon Signed-Rank Test) used in this study is not optimal to use in a pre-test post-test design. The ideal for a pre-test post-test design in one group is to do a RANOVA (repeated measures ANOVA). However, this analysis requires that the group are measured 3 times with an additional QEEG halfway into the training. Having an EEG measure half way would have demanded more time and effort from the patients, which would be unethical to request within such a small timeframe. Besides, a RANOVA would require a bigger sample size due to the number of variables used in this study. Based on time constraints and concern for the patients´ health, a repeated measures design was not possible to implement in this project.

Future studies with larger sample sizes will be able to conduct multivariate analysis. It would be interesting to divide the patient group in to high, moderate and low groups for the different symptoms (pain, fatigue and fibrofog), to investigate in more detail how ILF NFT influence symptom reduction, and to investigate whether the training has a more significant effect on the most severe cases of symptoms, compared to mild cases of symptoms. To make sure the effects are not due to an unspecific third variable, covariates such as age, number of years with the disease, and medications, should be implemented in future statistical analysis.

5. Conclusion

The objective of this pilot study was to investigate the effects of infra-low frequency neurofeedback training (ILF NFT) on fibromyalgia (FM) symptoms, to explore ILF NFT as a potential treatment option for fibromyalgia disease. Additionally, the project aimed to position estimate FM patients´ brain activity deviances to further investigate if the cortical regions implicated in the dynamic pain connectome (DPC) could be core regions for uncovering neurobiological markers for fibromyalgia.

To my knowledge, no other studies have investigated the effect of ILF NFT on FM patients. This study found a significant wider N1 latency, and a significant reduction in theta frontally amplitude and symptom score measures after ILF NFT, measured by Wilcoxon Signed-Rank Tests. Additionally, pre-treatment to post-treatment comparisons of individual QEEG deviances indicated decreased ERP component deviances among the patients. Also, fewer patients showed deviant beta, theta, and alpha frequency band activity after ILF NFT. These changes were not deemed statistical significant, yet they warrant support for the fact that ILF NFT intervention caused a normalization of brain activity, in addition to, symptom reduction. Based on these results, the present study found that ILF NFT normalized QEEG deviances, reduced fibromyalgia symptoms, and improved life quality among the participants. The study suggests that ILF NFT causes symptom reduction by improving functional connectivity and information processing within and between pain networks implicated in the DPC, presumably by working on a thalamocortical level.

Source analysis revealed complex patterns of QEEG deviances in areas implicated in the DPC, which corresponds with earlier studies. Our results strengthen the assumption that deviant activity within cortical regions in the DPC generate the symptoms experienced by FM patients, and that central sensitization mechanism and thalamocortical dysrhythmia may cause this deviant activity. Which points to these cortical regions as core regions for uncovering neurobiological markers. Nevertheless, more research comparing FM patients brain activity patterns with appropriate healthy controls and other chronic pain patients are needed to discover neurobiological markers for FM, specifically.

The limitations of this study have been addressed. More research with a larger sample size and an improved research design should be conducted. Despite the limitations in this study, it is possible to claim improvement in life quality and normalization of QEEG activity among the FM patients, after training with ILF NFT. Therefore, the results of this study points towards ILF NFT as a potential treatment option for fibromyalgia disea

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Appendix

A. Table for Shapiro-Wilk tests of normality for all variables, pre- and post-treatment

B. Table for kurtosis and skewness values for all variables, pre- and post-treatment

C. Table for descriptive statistics for all variables, pre- and post-treatment

D. Table for Wilcoxon Signed-Rank Tests for all variables

E. Table for Kendall´s tau correlation analysis, pre-treatment

F. Tables for individual power spectra analysis for all conditions, post-treatment

G. Table for individual ERP analysis, post-treatment

H. Table with description of Brodmann areas included in the dynamic pain connectome

I. Informed consent schema

J. FIQ questionnaire (Norwegian version)

K. ACR questionnaire (Norwegian version)

L. VAS questionnaire for pain, fatigue and fibrofog (in Norwegian)

Appendix A

Table A1

Shapiro-Wilk tests of normality for all variables, pre-treatment (N =13)

Variable	*W*	*df*	*p-level*
Fatigue	.96	12	.769
Fibrofog	.97	12	.934
Pain	.96	12	.764
ACR	.98	12	.972
FIQ	.95	12	.692
RT	.78	12	.006
RT_var	.70	12	.001
N1_a	.89	12	.127
N1_l	.95	12	.644
CNV_a	.98	12	.108
CNV_l	.95	12	.670
P3 NoGo_e_a	.70	12	.001
P3 NoGo_e_l	.90	12	.154
P3 NoGo_l_a	.93	12	.327
P3 NoGo_l_l	.95	12	.619
Alpha_C	.87	12	.056
Beta_C	.94	12	.466
Theta_C	.79	12	.006
Alpha_F	.90	12	.179
Beta_F	.94	12	.533
Theta_F	.65	12	.000
Alpha_T	.75	12	.003
Beta_T	.89	12	.011
Theta_T	.73	12	.002

Note. _a = amplitude; _l = latency; _e =early; _l = late; _C = central; _F = frontal; _T = temporal.

Table A2

Shapiro-Wilk test of normality for all variables, post-treatment (N=13)

Variable	*W*	*df*	*p-level*
Fatigue	.94	12	.516
Fibrofog	.98	12	.955
Pain	.91	12	.186
ACR	.99	12	1.000
FIQ	.93	12	.335
RT	.96	12	.745
RT_var	.87	12	.073
N1_a	.92	12	.306
N1_l	.84	12	.030
CNV_a	.95	12	.648
CNV_l	.95	12	.605
P3 NoGo_e_a	.96	12	.763
P3 NoGo_e_l	.94	12	.495
P3 NoGo_l_a	.94	12	.522
P3 NoGo_l_l	.96	12	.766
Alpha_C	.93	12	.420
Beta_C	.85	12	.032
Theta_C	.89	12	.112
Alpha_F	.94	12	.497
Beta_F	.97	12	.913
Theta_F	.63	12	.000
Alpha_T	.82	12	.014
Beta_T	.96	12	.805
Theta_T	.76	12	.003

Note. _a = amplitude; _l = latency; _e =early; _l = late; _C = central; _F = frontal; _T = temporal.

Appendix B

Table B1

Skewness and kurtosis values for all variables, pre-treatment (N=13)

Variable	*Skewness*	*Kurtosis*
Fatigue	-0.82	-0.54
Fibrofog	-0.56	-0.00
Pain	-0.65	0.35
ACR	0.73	-0.07
FIQ	-0.61	-0.74
RT	2.80*	2.35*
RT_var	4.03*	6.19*
N1_a	-1.16	-0.48
N1_l	-1.15	-0.14
CNV_a	-1.31	-0.11
CNV_l	-0.33	-0.31
P3 NoGo_e_a	-3.75*	4.69*
P3 NoGo_e_l	1.47	-0.20
P3 NoGo_l_a	1.08	-0.27
P3 NoGo_l_l	-1.19	1.49
Alpha_C	1.99*	1.07
Beta_C	0.63	-0.89
Theta_C	2.73*	1.79
Alpha_F	1.50	-0.16
Beta_F	1.17	1.13
Theta_F	4.19*	5.80*
Alpha_T	3.78*	5.73*
Beta_T	2.32*	0.98
Theta_T	3.66*	5.68*

Note. _a = amplitude; _l = latency; _e =early; _l = late; _C = central; _F = frontal; _T = temporal. * = at accepted value of +/- 1.96.

Table B2

Skewness and kurtosis values for all variables, post-treatment (N=13)

Variable	*Skewness*	*Kurtosis*
Fatigue	-1.26	0.44
Fibrofog	0.49	0.46
Pain	0.69	-0.61
ACR	-0.23	0.08
FIQ	1.64	2.09*
RT	0.83	0.20
RT_var	2.29*	3.33*
N1_a	-1.40	0.06
N1_l	2.28*	2.41*
CNV_a	-1.18	0.07
CNV_l	0.19	-0.81
P3 NoGo_e_a	-0.70	0.30
P3 NoGo_e_l	0.05	-0.70
P3 NoGo_l_a	0.35	-1.17
P3 NoGo_l_l	0.22	0.15
Alpha_C	1.01	-0.61
Beta_C	2.88*	3.35*
Theta_C	1.01	-0.93
Alpha_F	1.28	0.48
Beta_F	-0.37	-0.87
Theta_F	4.88*	8.35*
Alpha_T	2.39*	1.09*
Beta_T	1.08	-0.23
Theta_T	2.94*	2.25*

Note. _a = amplitude; _l = latency; _e =early; _l = late; _C = central; _F = frontal; _T = temporal. * = at accepted value of +/- 1.96.

Appendix C

Table C

Descriptive statistics for all variables, pre- and post-treatment (N =13)

	M		*SD*		*Range*		*Var*	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Fatigue	65.76	39.76	19.82	13.59	61.46	48.62	392.83	184.80
Fibrofog	52.07	38.70	27.46	27.80	100.00	93.00	754.16	772.82
Pain	65.23	44.41	19.84	20.57	76.04	70.54	393.75	423.00
ACR	21.92	17.08	4.66	4.35	17.00	16.00	21.74	18.91
FIQ	64.39	49.44	11.53	8.42	34.72	34.73	133.06	70.82
RT	329.50	339.62	62.93	62.12	218.00	224.00	3960.27	3858.39
RT_var	7.85	7.72	3.99	2.95	15.10	12.20	15.90	8.70
N1_a	-6.79	-6.79	3.71	3.61	11.42	12.25	13.74	13.04
N1_l	145.79	153.44	10.59	14.62	35.00	56.50	112.23	213.82
CNV_a	-1.60	-1.79	0.64	0.67	1.91	2.26	0.41	0.45
CNV_l	882.92	874.62	53.20	49.89	184.00	160.00	2829.74	2488.92
P3 NoGo_e_a	-0.85	0.25	5.25	3.69	18.86	13.98	27.56	13.61
P3 NoGo_e_l	280.31	304.62	61.61	48.99	184.00	160.00	3795.90	2399.59
P3 NoGo_l_a	10.13	9.73	7.08	5.29	22.84	15.58	50.19	27.96
P3 NoGo_l_l	367.08	377.54	35.19	35.94	142.00	132.00	1238.41	1291.44
Alpha_C	1.80	1.74	1.26	1.10	4.27	3.42	1.59	1.21
Beta_C	1.30	1.43	0.65	0.85	2.00	3.30	0.42	0.72
Theta_C	0.87	0.76	0.59	0.39	1.93	1.09	0.35	0.15
Alpha_F	1.76	1.70	1.12	0.97	3.38	3.43	1.25	0.95
Beta_F	1.53	1.41	0.77	0.61	2.91	1.97	0.60	0.37
Theta_F	1.37	1.00	1.23	0.80	4.47	3.11	1.51	0.64
Alpha_T	1.90	2.27	1.22	1.73	4.48	5.28	1.49	2.99
Beta_T	2.01	1.80	1.59	0.99	4.68	3.33	2.53	0.98
Theta_T	0.91	0.99	0.51	0.64	2.13	2.12	0.27	0.41

Note. _var = variability; _a = amplitude; _l = latency; _e = early; _l = late; _C = central; _F = frontal; _T = temporal.

Appendix D

Table D

Results from Wilcoxon Signed-Rank Test for all variables, pre- and post-treatment (N =13)

	Pre-treatment		Post-treatment		
	Mdn	*SD*	*Mdn*	*SD*	*z*
Fatigue	70.81	19.82	41.00	13.59	-2.62**
Fibrofog	55.21	27.46	38.54	27.80	-1.80
Pain	71.00	19.84	36.00	20.57	-2.45*
ACR	22.00	4.66	17.00	4.35	-2.77**
FIQ	65.19	11.53	48.04	8.42	-2.62**
Reaction time	309.00	62.93	326.00	62.12	0.86
Reaction time variability	7.00	3.99	7.70	1.95	-0.04
N1 amplitude	-6.13	3.71	-5.96	3.61	-0.18
N1 latency	149.00	10.59	150.50	14.62	2.13*
CNV amplitude	-1.56	0.64	-1.69	0.67	-1.36
CNV latency	888.00	53.20	870.00	49.89	-0.39
P3 NoGo early amplitude	1.45	5.25	0.78	3.69	-0.11
P3 NoGo early latency	264.00	61.61	296.00	48.99	1.73
P3 NoGo late amplitude	9.41	7.08	9.75	5.29	-0.04
P3 NoGo late latency	364.00	35.19	380.00	35.94	0.73
Alpha central	1.24	1.26	1.57	1.10	-0.04
Beta central	0.98	0.65	1.27	0.85	1.18
Theta central	0.63	0.59	0.64	0.39	1.36
Alpha frontal	1.45	1.12	1.64	0.97	-0.25
Beta frontal	1.50	0.77	1.39	0.61	-0.18
Theta frontal	0.94	1.23	0.80	0.80	-2.13*
Alpha temporal	1.76	1.22	1.59	1.73	0.42
Beta temporal	1.42	1.59	1.58	0.99	0.11
Theta temporal	0.81	0.51	0.90	0.65	-0.11

Note. *p <.05, **p <.01, ***p <.001.

Appendix E

Table E

Kendall's tau correlation analysis for all variables, pre-treatment (N=13)

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. Fat	-	.21	.14	.35	.54*	.49*	.41	.67**	.00	.23	-.23	.41	-.10	-.31	-.25	.03	-.15	-.37	-.05	.04	-.27	.15	-.27	-.05
2. Fib		-	.04	.28	.41	.09	.17	.23	.28	.05	-.10	-.08	.28	.03	-.07	.15	.23	-.27	.13	.30	.07	.28	.19	.13
3. Pain			-	-.07	.27	-.30	.03	-.09	-.01	-.22	-.19	-.14	.45*	.45*	.00	.17	.19	.34	-.07	-.18	.10	.04	-.03	-.17
4. ACR				-	.35	.02	.28	.33	.04	.01	-.30	.22	.04	-.07	-.24	-.20	-.17	-.40	-.20	-.18	-.48*	.01	.21	.07
5. FIQ					-	.12	.17	.26	.05	-.03	-.13	.05	.36	.00	-.09	.18	.05	-.07	.26	.09	.09	.41	-.07	.31
6. RT						-	.54*	.46*	.12	.74***	.19	.25	-.40	-.62**	-.11	.22	.03	-.26	.12	.30	-.23	.28	-.14	-.12
7. RT_var							-	.35	.38	.53*	.20	.17	-.08	-.29	-.09	.14	.17	-.06	-.14	.03	-.43	.20	.15	-.20
8. N1_a								-	-.18	.21	-.21	.44*	-.23	-.39	-.22	-.21	-.33	-.37	-.13	-.01	-.45*	.08	-.25	-.03
9. N1_l									-	.15	.31	-.08	.03	-.08	.04	.26	.23	.07	-.08	.07	-.04	-.08	.07	-.03
10. CNV_a										-	.08	-.05	-.26	-.51*	-.22	.13	.15	-.30	.21	.30	-.17	.21	.04	-.31
11. CNV_l											-	.05	-.05	-.21	.30	.49*	.41	.43*	.21	.09	.14	.21	.40	.15
12. P3 NoGo_e_a												-	-.39	-.39	-.22	.00	-.28	-.19	-.13	-.30	-.40	-.03	-.27	.18
13. P3 NoGo_e_l													-	.54*	-.01	.26	.33	.27	.18	.19	.40	.18	.22	.08
14. P3 NoGo_l_a														-	.25	.00	.13	.27	-.13	-.17	.25	-.08	.25	.23
15. P3 NoGo_l_l															-	.04	.14	.44*	.01	-.16	.13	.25	.16	.30
16. Alpha_C																-	.46*	.37	.46*	.25	.25	.46*	.09	.15
17. Beta_C																	-	.19	.39	.37	.37	.28	.43*	.03
18. Theta_C																		-	.04	-.18	.23	.19	.03	.14
19. Alpha_F																			-	.58**	.53*	.59**	.07	.03
20. Beta_F																				-	.42	.27	.08	-.27
21. Theta_F																					-	.22	.00	-.04
22. Alpha_T																						-	.17	.23
23. Beta_T																							-	.09
24. Theta_T																								-

Note. _var = variability; _a = amplitude; _l = latency; _e = early; _l = late; _C = central; _F = frontal; _T = temporal. *p <.05, **p <.01, ***, p <.001.

Appendix F

Table F1

Overview of individual significant deviances compared to the normative database in relative spectra and the location of those deviances for the EO condition, post-treatment (N =13)

Frequency band	Cortical area	Fib001	Fib002	Fib003	Fib005	Fib006	Fib008	Fib009	Fib0010	Fib0011	Fib012	Fib0013	Fib0015	Fib0016
Theta	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	5.17*** Missing	-	-	-	-	-	-	-	-	-	-	-	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	-
Alpha	Central	-	-	-	-2.14* Missing	-	-	-	-	-	-	-	-	-
	Temporal	-	-	-	-	-	-	-	5.37** BA 19-39-7	-	5.07** Missing	-	-	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	Central	1.21** BA 4-3-6	2.15** BA 6-4-3	-	1.51*** BA 11-10-32	1.28** BA 9-8-6	2.13*** BA 20-21-38	0.79*** Missing	-	1.06*** BA 6-8-32	-	1.39*** BA 40-39-2	-	-
	Temporal	-	-	-	2.22*** BA 17-18-19	-	-	-	-	-	-	-	-	-
	Frontal	-	0.78** BA 45-47-46	0.60* Missing	-	1.17* Missing	-	-	1.14** BA 10-11-47	-	-	-	1.40** BA 45-47-46	0.58* BA 47-11-10

Note. The table shows the relative value (%), significance level, frequency band, cortical area, and 3 hits of position estimations reported as Brodmann areas (BA), for individual deviances in power spectra. Missing; Some of the position estimations could not be located with the use of independent component analysis in sLORETA. *p<.05, **p<.01, ***p<.001.

Table F2

Overview of individual significant deviances compared to the normative database in relative spectra and the location of those deviances for the EC condition, post-treatment (N =13)

Frequency band	Cortical area	Fib001	Fib002	Fib003	Fib005	Fib006	Fib008	Fib009	Fib0010	Fib0011	Fib012	Fib0013	Fib0015	Fib0016
Theta	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	14.80*** BA 21-20-22	-	-	-	-	-	-	-	-	-	-	-	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	-
Alpha	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	-	-	-	-	-	-	-	-	-	-	-	-	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta	Central	0.51* Missing	2.99*** BA 2-40-1	-	1.10*** BA 11-10-47	-	1.51*** BA 11-10-47	-	-	0.84*** BA 2-5-40	0.70* BA 40-7-2	1.26*** BA 40-7-5	-	-
	Temporal	-	-	0.99** Missing	1.60*** BA 18-19-17	1.32*** BA 37-20-19	-	-	-	-	-	-	-	1.03* BA 21-20-22
	Frontal	-	0.75*** Missing	-	-	1.78*** Missing	-	-	-	-	-	-	-	0.64** Missing

Note. The table shows the relative value (%), significance level, frequency band, cortical area, and 3 hits of position estimations reported as Brodmann areas (BA), for individual deviances in power spectra. Missing; Some of the position estimations could not be located with the use of independent component analysis in sLORETA. *p<.05, **p<.01, ***p<.001.

Table F3

Overview of individual significant deviances compared to the normative database in relative spectra and the location of those deviances for the VCPT condition, post-treatment (N =13)

Frequency band	Cortical area	Fib001	Fib002	Fib003	Fib005	Fib006	Fib008	Fib009	Fib0010	Fib0011	Fib012	Fib0013	Fib0015	Fib0016
Theta	Central	-	-	-	-	-	-	-	-	-	-	-	-	-
	Temporal	11.12*** BA 18-19-17	6.02*** BA 40-22-39	-	-	-	-	-	-	-	-	-	-	-
	Frontal	-	-	-	-	-	-	-	-	-	-	-	-	-
Alpha	Central	-	-	-	3.75* BA 1-2-3	-	-	-	-	-	-	-	-	-
	Temporal	-	-	-	-	-	-	-	-	-	2.16* Missing	-	4.81* BA 39-40-19	-
	Frontal	5.36*** BA 47-11-10	-	-	-	-	-	-	-	-	-	1.88* Missing	-	-
Beta	Central	0.67* BA 4-1-6	0.75* BA 1-3-2	-	1.09** Missing	-	1.59*** BA 40-2-39	-	-	0.48* Missing	-	0.82* Missing	-	-
	Temporal	-	-	1.10* BA 37-19-39	1.67* BA 39-19-40	-	-	-	-	-	-	1.09* BA 21-20-22	-	-
	Frontal	-	0.46** Missing	-	-	0.99** BA 10-11-47	-	-	-	-	-	-	1.72** BA 47-45-46	-

Note. The table shows the relative value (%), significance level, frequency band, cortical area, and 3 hits of position estimations reported as Brodmann areas (BA), for individual deviances in power spectra. Missing; Some of the position estimations could not be located with the use of independent component analysis in sLORETA. *p<.05, **p<.01, ***p<.001.

Appendix G

Table G

Overview of individual significant deviances compared to the normative database for ERP components, post-treatment (N =13)

	N1	CNV	P3 NoGo early	P3 NoGo late
	Mean average µV	Mean average µV	Mean average µV	Mean average µV
Fib001	-13.28***	0.03*	6.41***	5.51**
Fib002	-8.19***	-1.91**	4.35***	5.38***
Fib003	-10.82***	-1.99**	4.01***	5.46***
Fib005	-3.80**	-1.13*	3.71***	1.37***
Fib006	-1.86***	-1.29***	-5.41***	-5.27***
Fib008	-5.94***	-2.83***	3.52***	2.17***
Fib009	-3.07**	-1.07***	-3.07**	-2.17*
Fib0010	1.79**	-0.71*	1.22*	-2.58***
Fib0011	-5.65***	-1.44***	-1.38*	0.88*
Fib0012	-2.54*	-1.45***	2.81***	4.03***
Fib0013	-4.50***	-0.59*	-2.79**	-2.83*
Fib0015	-4.99***	-1.78***	3.03**	1.02**
Fib0016	-3.09*	-1.71**	-0.02**	-3.85***

Notes. The table shows individual significant deviances compared to the normative database for each component with corresponding mean amplitude. µV = amplitude. *p<.05, **p<.01, ***p<.001.

Appendix H

Table H

Description, localization and function of Brodmann areas implicated in the dynamic pain connectome (Bernal & Perdomo, 2008)

Brodmann area	Localization	Function	Description
13 (SN)	Associational cortex (insular cortex)	Associational information processing	Associational cortical area in the anterior part of the insula. This area is not visible in medial and lateral views of the hemisphere. Insula is involved in somatosensory processing, pain perception, emotion and language processing, among other information processing.
21 (SN)	Lateral temporal lobe (middle temporal gyrus)	Involved in processing visual information and language, among other temporal associational functions	Associational cortical area in the middle temporal gyrus. This area participates in the analysis of visual signals related to object form and motion. In addition, this area is involved in a rather complex level of language processing.
23 (SN)	Medial parietal lobe (posterior cingulate cortex)	Participates in limbic associational integration	Associational cortical area in the posterior part of the cingulate gyrus. This area is a cortical component of the limbic system and participates in language and emotional processing.
24 (SN)	Medial frontal lobe (anterior cingulate gyrus)	Involved in emotional and cognitive processing	Associational cortical area in the anterior part of the cingulate gyrus. This area is a cortical component of the limbic system, which is involved in emotional processing, the control of facial expressions, motor organization, and the affective dimensions of pain.
32 (SN)	Medial frontal lobe (anterior cingulate cortex)	Involved in emotional and cognitive processing	Associational cortical area in the medial prefrontal region of the frontal lobe. This area participates in prefrontal cortical networks that governs personal and social behavior, emotion and decision making.
33 (SN)	Medial frontal lobe (anterior cingulate gyrus)	Involved in emotional and cognitive processing	Associational cortical area in the anterior part of the cingulate gyrus. This are is involved in emotional processing, pain perception, and other executive functions.

39 (SN)	Inferior parietal lobe (angular gyrus)	Involved in cross-modal association among different sensory modalities	Associational cortical area in the angular gyrus at the interface between the posterior parietal, temporal and occipital lobes. The area is involved in a number of processes related to language, cognition and somatosensory information.
44 (SN)	Inferior frontal lobe (Broca´s area)	Involved in speech-language production	Associational cortical area in the orbital part of the inferior frontal gyrus. This area is involved in language production. In addition, this area includes mirror neurons for expressive movements.
45 (SN)	Inferior frontal lobe (Broca´s area)	Involved in speech-language production and processing	Associational cortical area in the inferior frontal gyrus. This area is involved in complex verbal functions, cognitive control of memory and reasoning.
46 (SN)	Lateral frontal lobe (dorsolateral prefrontal cortex)	Participates in prefrontal associational integration	Associational cortical area in the anterior middle frontal gyrus and anterior part of the inferior frontal gyrus. This area participates in prefrontal cortical networks that govern executive functions, such as motor planning, organization and regulation.
47 (SN)	Inferior frontal lobe (inferior prefrontal gyrus)	Participates in prefrontal associational integration and language processing	Associational cortical area in the anterior-ventral part of the inferior frontal gyrus. This area participates in prefrontal cortical networks that govern executive functions. In addition, this area is involved in semantic processing and encoding.
9 (DMN)	Prefrontal cortex (middle frontal gyrus)	Participates in prefrontal associational integration and memory processing	Associational cortical area in the anterior dorsal-lateral prefrontal region of the frontal lobe. This area participates in prefrontal cortical networks that govern executive functions, and participation in memory processing, such as memory encoding and retrieval.
10 (DMN)	Prefrontal cortex (middle frontal gyrus)	Participates in prefrontal associational integration and memory processing	Associational cortical area in the anterior dorsal-lateral prefrontal region of the frontal lobe. This area participates in prefrontal cortical networks that govern executive functions, and participation in memory processing, such as memory encoding and retrieval.
27 (DMN)	Medial temporal lobe	Participates in emotion and memory processing	Hippocampal area in the medial temporal lobe. This area participates in a wide variety of memory processes, including; working memory, episodic memory, and memory retrieval.

Appendix I

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

qEEG, Transkraniell Likestrømsstimulering og Nevrofeedback på Fibromyalgipasienter

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke hjerneaktivitet hos fibromyalgipasienter, samt å utprøve behandlingsmetodene Nevrofeedback (treningsmetode) og Transkraniell Likestrømsstimulering (tDCS), og vurdere deres effektivitet. Prosjektet uføres i forbindelse med vår masteroppgave og hovedoppgave ved Psykologisk Institutt (NTNU, Dragvoll), i samarbeid med førsteamanuensis Stig Hollup og psykiater Egil Fors.

HVA INNEBÆRER PROSJEKTET?

For å måle hjerneaktiviteten, vil vi bruke en målemetode kalt ElektroEncefalografi (EEG). Denne teknikken måler hjernebølger i ulike områder av hjernen, og man får mulighet til å se om noen hjerneområder skiller seg ut i forhold til høy eller lav aktivitet. I tillegg vil deltager gjennomføre noen spørreskjemaer som måler ulike aspekter ved fibromyalgi.

Videre vil deltagere bli tilfeldig fordelt på to grupper. Man vil få tilbud om enten Nevrofeedback eller tDCS. Nevrofeedback er en treningsmetode som krever minimalt med fysisk innsats, hvor man skal sitte foran en dataskjerm med 3 elektroder på hodet i ca. 30 minutter. Man skal etter instrukser konsentrere seg om bildet på skjermen som er tilbakemelding på egen hjerneaktivitet. Metoden går ut på at hjernen skal trene seg selv opp til ønsket hjerneaktivitet ut i fra resultatene vi får på EEG-målingen gjort i forkant. Denne treningsmetoden er uten ubehag og bivirkninger. I dette prosjektet vil det være ca. 15 økter per deltaker. Det er ingen begrensning på hvor ofte man kan utføre treninger, og hvor raskt vi blir ferdig med alle behandlingene kommer ann på den individuelle tidsplanen vi legger opp. Vi ser for oss ca. 2-3 økter i uka over en periode på ca. 10 uker.

Transkraniell likestrømsstimulering er en ikke-invasiv elektrisk hjernestimulering som involverer veldig små mengder strøm (0.5-2.0 mA) gjennom 2-3 elektroder plassert på hodet. For å opprette bedre kontakt mellom elektrodene og hjernen vil vi bruke saltholdige svamper som er festet til elektrodene. Teknikken krever minimalt med fysisk innsats, og man skal sitte avslappet med elektrodene på hodet i ca. 20 minutter. For at behandlingsmetoden skal ha effekt vil det bli utført repeterte økter, og i dette prosjektet vil det være ca.5 økter per deltager. Vi ser for oss at disse 5 øktene blir utført over en uke. Metoden er uten særlig ubehag og bivirkninger.

Etter behandlingen vil vi utføre en ny EEG-måling samt gjennomføring av samme spørreskjemaer på nytt. Dette gjør vi for å kunne se om behandlingene har hatt en effekt.

MULIGE FORDELER OG ULEMPER

Behandlingene i dette prosjektet krever minimalt med fysisk aktivitet, og er trygge teknikker med lav risiko og ubehag. Sjeldne bivirkninger i tDCS behandlingen kan være forbigående lett hodepine og tretthet, og en stikkende følelse under elektroden.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Sigrid Hegna Ingvaldsen (tlf: 915 13 022, e-post: sigrihi@stud.ntnu.no) eller Line Luckman (tlf: 984 48 015, e-post: lineolu@stud.ntnu.no).

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Navnelisten vil være oppbevart innelåst ved NTNU, og det er kun prosjektleder som har tilgang til den.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, (2015/1745).

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Appendix J

Fibromyalgia Impact Questionnaire (FIQ)

Retningslinjer: For spørsmål 1-11, sett en ring rundt tallet som best beskriver hvordan du total sett klarte å fullføre disse handlingene *i løpet av den siste uken*. Hvis du normalt ikke gjør noe det blir spurt om, kryss spørsmålet ut.

	Alltid	For det meste	Noen ganger	Aldri
Klarte du og:				
Dra på shopping?.....	0	1	2	3
Vaske klær?.....	0	1	2	3
Lage mat?.....	0	1	2	3
Vaske opp kjeler for hånd?..	0	1	2	3
Støvsuge et teppe?.....	0	1	2	3
Re opp senga?.....	0	1	2	3
Gå på asfalt?.....	0	1	2	3
Besøke venner/slektninger?..	0	1	2	3
Gjøre hagearbeid?.....	0	1	2	3
Kjøre bil?.....	0	1	2	3
Gå trapper?.....	0	1	2	3

12. I løpet av de 7 dagene den siste uken, hvor mange dager følte du deg bra?

0 1 2 3 4 5 6 7

13. Hvor mange dager den siste uken, klarte du ikke å jobbe, inkludert husarbeid, på grunn av fibromyalgi sykdommen?

0 1 2 3 4 5 6 7

Retningslinjer: For de siste spørsmålene, marker punktet på linjen som best indikerer hvordan du følte det totalt i løpet av den siste uken.

14: Når du jobbet, i hvor stor grad påvirket smerten eller andre symptomer relatert til fibromyalgi din evne til å arbeide, inkludert husarbeid?

Ikke noe problem ☐☐☐☐☐☐☐☐☐☐ Stort problem

15: Hvor kraftig har smerten din vært?

Ingen smerte ☐☐☐☐☐☐☐☐☐☐ Veldig kraftig smerte

16: Hvor trøtt har du vært?

Ingen trøtthet ☐☐☐☐☐☐☐☐☐☐ Veldig trøtt

17: Hvordan har du følt deg når du har stått opp om morgen?

Våknet opplagt ☐☐☐☐☐☐☐☐☐☐ Våknet veldig trøtt

18: Hvor kraftig har stivheten din vært?

Ingen stivhet ☐☐☐☐☐☐☐☐☐☐ Veldig stiv

19: Hvor nervøs eller engstelig har du følt deg?

Ikke engstelig ☐☐☐☐☐☐☐☐☐☐ Veldig engstelig

20: Hvor deprimert eller trist har du følt deg?

Ikke deprimert ☐☐☐☐☐☐☐☐☐☐ Veldig deprimert

Appendix K

AMERICAN COLLEGE OF RHEUMATOLOGY (ACR): DIAGNOSTISK KRITERIA FOR FIBROMYALGI

DEL 1: VIDT-SPREDT SMERTE INDEKS

Identifiser områdene du har hatt vondt i løpet av den siste uken

- ☐ Skulderbelte, venstre
- ☐ Skulderbelte, høyre
- ☐ Øvre arm, venstre
- ☐ Øvre arm, høyre
- ☐ Nedre arm, venstre
- ☐ Nedre arm, høyre
- ☐ Hofte (rumpe), venstre
- ☐ Hofte (rumpe), høyre
- ☐ Øvre ben, venstre
- ☐ Øvre ben, høyre
- ☐ Nedre ben, venstre
- ☐ Nedre ben, høyre
- ☐ Kjeve, venstre
- ☐ Kjeve, høyre
- ☐ Bryst
- ☐ Mage
- ☐ Nakke
- ☐ Øvre del av ryggen
- ☐ Nedre del av ryggen

DEL 2A: SYMPTOMERS ALVORLIGHETSGRAD

Indiker hvor stort problem de følgende symptomene har vært for deg i løpet av den siste uken. Velg kun et alternativ for hver av de tre kategoriene.

Fatigue

- ☐ Ikke noe problem
- ☐ Litt eller milde problemer; generelt milde eller periodiske
- ☐ Moderate problemer; betraktelig problemer; ofte til stede og/eller på et moderat nivå
- ☐ Alvorlig; forstyrrer livskvaliteten

Ikke våkne opplagt

- ☐ Ikke noe problem
- ☐ Litt eller milde problemer; generelt milde eller periodiske
- ☐ Moderate problemer; betraktelig problemer; ofte til stede og/eller på et moderat nivå
- ☐ Alvorlig; forstyrrer livskvaliteten

Kognitive symptomer

- ☐ Ikke noe problem
- ☐ Litt eller milde problemer; generelt milde eller periodiske
- ☐ Moderate problemer; betraktelig problemer; ofte til stede og/eller på et moderat nivå
- ☐ Alvorlig; forstyrrer livskvaliteten

DEL 2B: ANDRE SYMPTOMER

Har du hatt problem med noe av det følgende, i løpet av de tre siste månedene? Velg alle alternativer som er passende.

- ☐ Muskel smerte
- ☐ Muskel svakhet
- ☐ Nummenhet i kroppen
- ☐ Irritabel tarmsyndrom (IBS)
- ☐ Smerte/kramper i magen
- ☐ Diare
- ☐ Forstoppelse
- ☐ Halsbrann
- ☐ Oppkast
- ☐ Kvalme
- ☐ Hodepine
- ☐ Svimmelhet
- ☐ Kortpustet
- ☐ Nervøsitet
- ☐ Depresjon
- ☐ Fatigue/trøtthet
- ☐ Insomni/søvnproblemer
- ☐ Dårlig appetitt
- ☐ Utslett
- ☐ Elveblest
- ☐ Sol-sensitivitet
- ☐ Tåkesyn
- ☐ Endring/tap av smak
- ☐ Hørselsvansker
- ☐ Ringing i ørene
- ☐ Få lett blåmerker
- ☐ Hyppig urinering
- ☐ Blære spasmer
- ☐ Smertefull urinering
- ☐ Hjerneslag
- ☐ Feber
- ☐ Brystsmerte
- ☐ Hårtap

Appendix L

VISUELL ANALOG SKALA (VAS)

Smerte

Hvor kraftig er smerten din? Sett et kryss på linjen.

Ingen smerte _____ Utholdelig smerte

Fatigue/trøtthet

Hvor kraftig er din fatigue/trøtthet? Sett et kryss på linjen.

Ingen fatigue _____ Kraftig fatigue

Fibrotåke

Hvor kraftig er din fibrotåke? Sett et kryss på linjen.

Ingen fibrotåke _____ Kraftig fibrotåke

Sigrid Hegna Ingvaldsen

QEEG and Infra-Low Frequency Neurofeedback Training in Fibromyalgia: A Pilot Study

NTNU
Norwegian University of
Science and Technology