Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Social and Educational Sciences
Department of Psychology

Jasmin Stølevik Eide

The effects of infra-low frequency neurofeedback on fibromyalgia symptoms

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Supervisor: Stig Arvid Hollup
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Preface and acknowledgements

Going head into such an important topic and complex field has been challenging and exciting. The amount of knowledge and skills I have acquired over the course of 2 years has been overwhelming and unpredictable. Fibromyalgia, being a disabling disease with unknown cause, generated a keen interest in the field. I am ever so grateful for the opportunity to write my thesis about fibromyalgia and potentially generate more knowledge. This could not have been done without some key contributors.

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Lastly, I would like to dedicate my appreciation to some of my family members. To my beloved Grandfather Reidar Edvald Stølevik, Grandmother Wenke Stølevik and Father Einar Stølevik: thank you for keeping me curious and teaching me the wonders of science. To my dear Mother Elisabeth Eide and Grandmother Synnøve Dahl: thank you for believing in me and the supportive conversations throughout this process.

Sammendrag

Bakgrunn: En av de hyppigste årsakene til at man oppsøker helsehjelp er smerte. Fibromyalgia er en kronisk smertelidelse preget av konstante og diffuse smerter, utmattelse og kognitive vansker (fibrotåke), noe som affiserer livskvaliteten til svært mange mennesker. Per i dag finnes det ingen adekvat forklaring på hvorfor noen individer får fibromyalgia. Dette skaper ringvirkninger gjennom lite tilstrekkelig diagnostiske verktøy, mangelfull behandling og mye usikkerhet for pasienten. Litteraturen peker mot forklaringsmodeller som omfavner en sensitivering i sentralnervesystemet og unormal hjerneaktivitet i kortikale områder knyttet til «the Dynamic Pain Connectome (DPC)» og default-modus-nettverket.

Mål: Hensikten med denne studien er todelt. Den første delen *(1)* har som mål å undersøke hvordan hjernens temporale dynamikk skiller seg mellom mennesker med fibromyalgi og en kontrollgruppe, og hvorvidt disse avvikene kan knyttes til DPC. Videre er prosjektets andre mål (2) å granske effekten av infra-low frekvens nevrofeedback-trening (ILF-NFT) på symptomer assosiert med fibromyalgi.

Metode: Pasienter som har fått påvist fibromyalgi mottok ILF-NFT, og det ble gjennomført. undersøkelser (EEG-opptak) og selvrapporterte symptomer (spørreskjema) før og etter behandling. Hjerneaktivitet ble målt via en 19-kanals EEG, og frekvensanalyse ble utført av EEG aktivitet ble i theta, alpha og beta frekvens, lokalisert i frontale, sentrale og temporale of parietale områder.

Resultater: En Wilcoxon Signed-Rank Test indikerte at symptomer assosisert med fibromyalgia hadde en signifikant reduksjon etter å ha mottatt ILF-NFT. Dette tyder på at treningen påvirket kortikalt aktivitetsmønster som bidrar til symptomer som smerte, fibrotåke og utmattelse. Flere av deltakerne hadde avvik i nøkkelområder knyttet til DPC. Begrensninger ved studien diskuteres.

Nøkkelord: Fibromyalgi, sentral sensitivering, hjerneaktivitet, EEG, dynamic pain connectome,

Abstract

Background: One of the main motives for why individuals seek medical attention is pain. Fibromyalgia (FM) is a condition characterized by chronic pain, fatigue, and cognitive complaints, which severely disrupts an individual's quality of life. Medical providers and researchers have not been able to find a There is no cohesive theory of why some individuals have fibromyalgia. Consequently, there is a lack of adequate diagnostic tools, unsatisfactory treatment, and uncertainty amongst patients. Previous studies have found fibromyalgia patients to display significant alterations in central mechanisms, functional connectivity in the resting-state networks and cortical areas identified as the Dynamic Pain Connectome (DPC).
Aims: This study consists of two parts. It aims to (1) identify whether individuals suffering with fibromyalgia significantly differ in the temporal dynamics of the brain, and if this is related to cortical areas involved in the DPC. The second part wishes to (2) investigate the clinical benefits of infra-low frequency neurofeedback treatment (ILF-NFT) on fibromyalgia symptoms.
Method: FM patients received ILF-NFT, which included pre- and post-treatment clinical measures with a 19-channel EEG recording and self-reports of symptom severity. Power spectra analysis was conducted to look for deviations in the theta, alpha and beta frequency, derived from frontal, central, temporal, and parietal electrodes.
Results: A Wilcoxon Signed-Rank Test found significant decreases in symptoms following ILF-NFT, indicating that the treatment targets cortical activity associated with pain, fatigue, and cognitive complaints. Several of the participants had deviations which were source localized in key DPC-nodes. The limitations of this study are further discussed.

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Introduction

Extensive attempts to decipher the pain code has been made, as chronic pain is one of the largest health concerns facing our society today (Bushnell et al., 2013). Approximately 19% of the adult population in the European Union (EU) suffer from chronic pain, which negatively influences their quality of life. Norway ranks as one of the countries who are greatest affected, with nearly 30% of the population (Breivik et al., 2006). Fibromyalgia (FM) is an idiopathic rheumatic pain disorder, with unknown pathophysiology, defined by the presence of musculoskeletal pain (Baliki et al., 2008; Wolfe et al., 2010). It is estimated to affect 4.7% of the European population (Branco et al., 2010). Pain often manifest as widespread and diffuse and include hyperalgesia and allodynia. Apart from pain-symptoms, FM-patients will generally display affective and cognitive symptoms (Ceko et al., 2013; Staud, 2006; Verbunt et al, 2008; Wolfe et al., 2013).

Understanding how information is processed in our brains is key to our understanding of complex phenomena such as chronic pain. The human brain comprises of billions of neurons that are functionally wired through synchronised firing-patterns in different time scales (Kropotov, 2008). Researchers have found chronic pain patients to display irregularities in the temporal dynamics and cross-network communication in the brain. The default mode network, the salience network and the antinociceptive system is hypothesised to be of significance in the search for underlying biomarkers of chronic pain. Together, these networks make up the dynamic pain connectome (DPC) (Kucyi & Davis, 2015). Functional connections between these areas are assumed to be fundamental to self-regulation and maintenance. Since the main goal of our brain is the maintenance of self-regulatory processes (Fox & Raichle, 2007; Sitaram et al., 2017), it is hypothesised that fibromyalgia and other chronic pain disorders can be linked to abnormalities in cortical areas associated with these processes. Such deviations can potentially explain the continuous experience of pain in the absence of a driving force.

Tools like an electroencephalogram (EEG) can reveal deviations in the temporal dynamics of the brain related to pain processing. By applying technologies such as quantitative EEG (qEEG), one can compare patients with FM to healthy age-matched controls, revealing significant cortical alterations contributing to the long-lasting symptoms seen in chronic pain patients. Interventions such as neurofeedback are hypothesised to renormalize these deviations to a more appropriate activation pattern.

Nociception

The International Association for the Study of Pain (IASP) describes pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage" (IASP Task Force on Taxonomy, 1994). Pain is created in our brain as an integrative function between sensory input and modulatory top-down factors. The experience of pain is an evolutionary adaptation to protect an organism from harmful stimuli and agents, thus important to our survival. Examples of such agents are extreme temperature, chemical substances, and mechanical force (Baliki & Apkarian, 2015; Latremoliere & Woolf, 2009). By nature, pain is related to aversion and behavioural changes, like a motor response to withdraw from the triggering stimuli (Mouraux & Iannetti, 2018; Schulz et al., 2012; Wiech et al., 2010). The sensory experience of pain engages both complex temporal and spatial activation patterns in our brain. Spatially it involves distinct cortical networks, and temporally it engages different frequencies of oscillations (Ploner & May, 2018). Hence, pain is the result of an interplay between ascending and descending cortical pathways and involves a complex signalling cascade (Ploner et al., 2017).

Understanding pain. Nociception is the term used for the physiological translation of cutaneous-damaging pain stimulus (Millan, 2002; Ploner et al., 2017). Nociceptors are unspecialized free nerve endings, classified by with their cell body diameter and axons. The Aδ fibres are myelinated with oligodendrocytes and have a low threshold to generate action potentials. These fibres transduce nociceptive stimuli rapidly, compared to the unmyelinated C-fibres (Dubin & Patapoutian, 2010; Meeus & Nijs, 2007). The distinct sensation of dull and sharp pain occurs due to differences in conduction time depending on myelinization and cell body diameter (Apkarian et al., 2005; Julius & Basbaum, 2001). However, nociceptors are complex by nature. Their diverse repertoire of transduction mechanisms and modifiable receptive properties give rise to a complex primary afferent signal (Julius & Basbaum, 2001).

From the ascending nociceptive pathway, nociceptors synapse with second-order neurons in the dorsal horn (DH) of the spinal cord. The spinal cord is divided in anatomically distinct laminae (Basbaum, Bautista, Scherrer & Julius, 2009), and the Aδ fibres can synapse in laminae III-VI (Millan, 2002) whilst the C-fibres synapse in laminae I and II (Basbaum et al., 2009). Postsynaptic responses occur through presynaptic exocytosis of glutamate and are modulated by neurotransmitters and peptides, such as substance P, calcitonin gene-related peptide and somatostatin (Harte et al., 2018; Meeus & Nijs, 2007). Projection neurons transmit the stimuli contralaterally from the DH to the brain, through the modulation of excitatory interneurons, inhibitory interneurons, and neurochemical substances. (Basbaum et

al., 2009; Millan, 2002). From the DH, nociceptive input transmits onto different cortical structures mediated and gated by the thalamus (Lim et al., 2016; Ploner et al., 2017). For instance, sensory-discriminative factors of pain relay through the spinothalamic pathway, synapsing in the thalamus before projection to cortical areas like the somatosensory cortex. Signals which synapse in the brainstem travel through the spinoreticulothalamic tracts and give rise to more poorly localizable signals. Emotional aspects of pain involve structures such as the anterior cingulate gyrus and the insular cortex (Basbaum et al., 2009).

***Pain in the brain*.** Pain is subjective due to its intrinsic and dynamic nature (Kucyi & Davis, 2015; Apkarian et al., 2011). The experience of pain does not solely depend on the transduction of nociceptive stimuli (Julius & Basbaum, 2001). Our brains have no specific pain loci, instead, it is hypothesised to be a consequence of temporal and spatial coding. Pain is created and modulated by contextual factors: which includes the attentional, affective, and cognitive networks (Kucyi & Davis, 2017). Therefore, it is a dissociation between ascending noxious stimuli and perceived pain (Nickel et al., 2017).

A complex phenomenon like pain involves activity in several cortical structures. Examples of pain-relevant areas are the somatosensory cortices (S1 and S2), the insula (INS), anterior cingulate cortex (ACC), thalamus (Th), amygdala (Am) and the prefrontal cortex (PFC) (Bushnell et al., 2013; Davis & Moayedi, 2013; Nickel et al., 2017). While the somatosensory areas are involved in stimulus localization, baseline activity in the posterior ACC and the bilateral INS positively correlated with higher pain ratings of acute pain (Boly et al., 2007). This multinetwork engagement can seemingly constitute the distinct perceptual aspects of pain.

Individuals can experience pain even in the absence of tissue damage. Pain is considered maladaptive when pain no have a biological significance or protective function (Latremoliere & Woolf, 2009; Yamamotove, 2019). Malfunctions in the nociceptive system can be caused by trauma, chemotherapy, diabetes, autoimmune disorders, or infections. Disruption in this system can give rise to allodynia and hyperalgesia, pain due to sensory stimuli and heightened sensitivity to pain stimuli respectively (Harte et al., 2018; Latremoliere & Woolf, 2009; Staud, 2006). Therefore, it is wrongful to assume that pain is uniquely related to tissue damage.

Chronic pain and the brain. Pain is considered chronic when it has no protective function, persisting longer than expected healing time (Apkarian et al., 2005; Apkarian & Baliki, 2015). Living with chronic pain has a severe impact on the quality of life and is known to be comorbid with mood disorders, such as anxiety and depression (Baliki et al., 2006;

Mouraux & Iannetti, 2018). There is no consensus upon the driving forces behind the various types of chronic pain, but findings indicate both functional and anatomical abnormalities within pain-related brain structures. Anomalies in the ascending pathway can occur with both a central and/or peripheral locus (Basbaum et al., 2009). Nevertheless, chronic pain is complex and is often accompanied by abnormalities in mood and memory (Apkarian et al., 2016).

Researchers believe pain to comprise of a sensory-discriminative and affective-motivational component. The latter compose the emotional and cognitive facets of pain, such as unpleasantness. Newer research indicates that patients suffering from chronic pain display abnormalities in cortical networks associated with both cognitive and emotional aspects of pain (Bushnell et al., 2013), in addition to resting-state networks (Kucyi & Davis, 2015). Cognitive implications can often manifest as lowered information processing time. On average, chronic pain populations have slower reaction times on cognitive tests compared to healthy controls, in addition to poorer learning and memory functions (Moriarty et al., 2011). It is therefore suggested a hippocampal involvement (Baliki & Apkarian, 2015; Baliki et al., 2006).

However, simply viewing pain as a static neuromatrix of ascending and descending modulation, do not include the dynamic and intrinsic nature of the brain (Kucyi & Davis, 2017). The complex interplay between pain-related areas does not solely rely on anatomical connectivity, but also their temporal dynamics (Davis & Moayedi, 2013; Kucyi & Davis, 2017). Pre-existing brain state has shown, through electrophysiological studies, to be a precursor pain intensity (Boly et al., 2007). Researchers have made extensive efforts to identify potential contributing factors to the ongoing and chronification of pain. Newer research has been dedicated to the dynamic pain connectome and functional connectivity within and between resting-state networks (Kucyi & Davis, 2015).

The Dynamic Pain Connectome

Pain and attention are naturally linked due to the evolutionary mechanisms of pain (Kucyi & Davis, 2015; Legrain et al., 2009). Attention will naturally fluctuate, but the salience of pain can redirect attentional demands and interfere with thought process and working memory (Baliki & Apkarian, 2015; Kravitz & Katz, 2015), consequently changing behaviour (Kucyi & Davis, 2015). Studies upon the modulatory effects of attention upon pain explicitly manipulate attentional and cognitive states of the participants. Kucyi & Davis (2012) have

criticised this methodology because it ignores the natural and spontaneous intrinsic fluctuations of attention, as it biases attention towards pain (Kuvyi & Davis, 2017). When viewing pain within the framework of the Dynamic Pain Connectome (DPC), these spontaneous fluctuations and pre-existing brain states are integrated in the explanation of intraindividual variability of pain. The DPC postulates that perception of pain depends on intrinsic fluctuations between a brain-wide network. Mainly, integration of pain aspects is derived from the spatiotemporal signature of three key cortical networks: the *(1)* default mode network, *(2)* the salience network and *(3)* the antinociceptive system (Kucyi & Davis, 2015, 2017).

The Default Mode Network. The Default mode network (DMN) comprises of cortical structures that coherently display attenuated activity during an active state. Consequently, enhancing activity and functional connectivity during a passive state, as revealed through BOLD-studies (Buckner et al., 2008; Fox & Raichle, 2007; Greicius et al., 2003). The DMN was accidentally discovered through early observation deploying the Kety-Schmidt nitrous oxide technique. The researcher found there no difference in global metabolism rates in the brain between active and passive states (Kety & Schmidt, 1948), prompting investigations of the spontaneous activity and the resting-state of the brain. Gordon Shulman identified a set of cortical areas which decreased their activity in task- and attentional demanding situations (Raichle, 2015b; Shulman et al., 1997). In 2001, Raichle and colleagues contribute with empirical support of the DMN. Conformingly, they found task-induced metabolic changes to be small compared to a resting state (Raichle el al., 2001).

The electrical correlations of fMRI BOLD signal were found to correlate with activity in a low frequency range of approximately 0.01-5 Hz (Raichle, 2015b). Resting-state BOLD-studies has found the DMN to oscillate at an infra-low frequency of 0.01-0.1 Hz (Fox & Raichle, 2007, Raichle et al., 2001). These slow oscillations were initially treated as noise and removed by averaging fMRI-data (Raichle, 2015). However, researchers found the default mode system characterized by these low frequency oscillations (Broyd et al., 2009; Greicius et al., 2013; Kropotov, 2016). It is hypothesised that the low frequencies are associated with temporal binding of information, cortical excitability, and intrinsic brain activity, therefore important to overall brain function (Broyd et al., 2008; Raichle, et al., 2001; Raichle, 2015b).

Grossly, the DMN can be subdivided into three key areas: the ventral medial prefrontal cortex (VMPC), the dorsal medial prefrontal cortex (dmPFC), and the posterior cingulate cortex (PCC). Also important is the precuneus (PCun) and lateral parietal cortex (LPC). The entorhinal cortex (EC) has also been linked to the DMN (Kucyi & Davis, 2015;

Raichle, 2015). These areas oscillate in a coherent fashion when an individual is at rest and in a state of introspection (Kropotov, 2016). Indeed, our brain is active even when environmental and bodily derived stimuli are abolished, due to its self-organizing nature (Buzsáki, 2006).

The VMPC is associated with sensory-visceromotor linkage, as a node in the circuitry of conveying externally and bodily related information through the orbitofrontal cortex. Further relying information onto key structures such as the hypothalamus, amygdala, and midbrain structures. Acting as a node in this network, the VMPC is hypothesised to be important in mood control and motivational drive. The VMPC is also thought to be key in anxiety responses related to task difficulty and performance; with decreased anxiety levels being correlated with greater activity reduction in the VMPC (Raichle, 2015b).

The dmPFC is hypothesised to be linked to self-referential judgements, whilst the posterior parts of the DMN are related to memory and experiences (Raichle, 2015). Parenthetically, the DMN is usually anticorrelated with the salience network (Hemington et al. 2015) and it is associated with mind-wandering (Kucyi & Davis, 2015; 2017). A various of neuropsychological illnesses such as autism, ADHD and depression display abnormal finding within the DMN (Baliki et al., 2008). Therefore, the DMN is key to our understanding of brain organization, function and potentially pathology (Raichle, 2015).

Table 1

Cortical structures and key nodes in the default mode network

Cortical structure	Brodmann areas
Ventral medial prefrontal cortex (vMPFC)	10, 14, 25, 32
Posterior cingulate (PCC)	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, 27, 36, 37, 30
Anterior cingulate cortex	24, 32, 33

The Salience Network. The Salience Network (SN) is a large-scale and highly intrinsically connected network comprising of nodes that is activated thought various form of salience, thus often referred to as a task-positive network (Raichle, 2015; Menon, 2015). It involves subcortical structures related to emotion and affection and is thought to be relevant

in emotional pain processing (Seeley et al., 2007). The discovery of the SN derives from resting-state fMRI-studies and analysis techniques such as independent component analysis (ICA); where spatially and statistically independent signal generators can be identified (Fox & Raichle., 2007). ICA can thus reveal clusters of cortical areas that are functionally connected through BOLD-oscillations and is a technique aimed at solving the blind source separation problem accordingly (Kropotov, 2008

The SN comprises of core nodes including the anterior insula (aINS), dorsal anterior cingulate cortex (dACC) and dorsolateral prefrontal cortex (dlPFC) (Peters et al., 2016; Seeley). These nodes are interconnected with subcortical regions like the thalamus, caudate nucleus, and brainstem nuclei. Ultimately, creating a cortico-striatal-thalamic loop (Peters et al., 2016; Seeley et al., 2007). An extensive voxel-based morphometry meta-analysis of six mental illness groups (*N*=892) found grey matter atrophy (GMA) in SN nodes, like the bilateral insula. Suggesting an underlying and shared endophenotype across neuropsychiatric diagnostic groups (Goodkind et al., 2015).

The SN increases its activity positively in accordance with the attentional demands of the environment and in the presence of pain. Structures like the aINS and right TPJ has been related with sustained attention directed towards pain stimuli (Kucyi & Davis, 2015). Activity in the SN appears to be intrinsically anticorrelated with DMN activity (Fox et al., 2005), prompting researchers to believe that interconnections between these networks are linked to a shift from introspection to a more stimulus-focused state (Kucyi & Davis, 2015; Menon, 2015; 2017 Peters et al., 2016). Specifically, the connection between the aINS and the ACC have been suggested to important in the attentional transition between central executive and a more internally oriented state (Craig, 2009; Menon, 2015)

The aINS is believed to play a role in human awareness, and it is observed to be abnormal in conditions like depression, anxiety, post-traumatic stress disorder (PTSD) and schizophrenia (Craig, 2009). Pre-nociceptive activation of the aINS has been associated with increased subjective reports of pain, thus pre-existing brain state can influence perception. In addition, expectancy of pain increases the functional connectivity between the left portion of the aINS and the mid-cingulate cortex (Wiech et al., 2010). In general, the SN has been linked to psychopathology where salience detection is affected, like schizophrenia and social anxiety disorder (Menon, 2015). It is possible that disruption in the SN leads to hypervigilance to pain.

Table 2.

Component of the Salience Network (SN)

Cortical structure	Brodmann area
Anterior right insula (aINS)	13
Mid-cingulate cortex (MCC)	23, 24, 32
Temporoparietal junction (TPJ)	39
Inferior frontal gyri (IFG)	44, 45, 45, 47
Dorsolateral prefrontal cortex (dlPFC)	46
Dorsal anterior cingulate cortex (dACC)	24, 32, 33

The Antinociceptive System. Lastly, the antinociceptive system (AS) consists of cortical structures like the periaqueductal grey (PAG) and is considered a descending modulatory system. It is involved in the pain-attention dynamics and attentional fluctuations away from pain. The PAG is localized in the brainstem and contains mu-opioid-receptors. Hence, it is linked to top-down analgesic modulation of pain stimuli (Kucyi & Davis, 2015; Millan, 2002). The AS is also associated with prefrontal activation; it is therefore assumed that the anterior cingulate cortex is involved in descending pain modulation (Bushnell et al., 2013; Davis & Moayedi, 2013; Jensen et al., 2009).

The PAG has descending connectivity with the rostroventromedial medulla (RVM), which terminates in the spinal cord. The RVM contains ON- and OFF-neurons: with the former being associated with the promotion of nociception and secondary hyperalgesia, whilst the latter is linked to antinociception. Antinociception can therefore occur with through inhibition of the ON-cells and excitation of the OFF-cells, which occurs in the context of opioid-administration. Activity in the ON- and OFF-neurons are mutually exclusive, therefore these neurons are associated with a "pain-on" state or a "pain off" state. Connections between the PAG and RVM are modulated with GABAergic input, which in turn can affect the ON- and OFF-cells as well. Hence, PAG-RVM connectivity is key in understanding both pain and antinociception (Morgan et al., 2008).

When the mind wanders away from pain, the functional connectivity (FC) between the PAG and the DMN increases. Specifically, connectivity between the PAG and the mPFC was associated with interindividual variability in attending to a noxious stimulus (Kucyi & Davis, 2015; 2017). Hence, flexibility in the resting state FC between AS and DMN can reflect a

predisposition of redirection attention away from pain (Kucyi et al., 2013; Kucyi & Davis, 2015).

Table 3.

Key nodes in the antinociceptive system (ANS)

Cortical area	Brodmann area
Periaqueductal gray (PAG)	-
Anterior cingulate cortex (ACC)	24, 32, 33
Rostroventromedial medulla (RVM)	-

Brain dynamics

Electroencephalogram. Electroencephalogram (EEG) can provide insight into the temporal dynamics of the brain. An EEG measures the coherent and joint activity derived from neural assemblies. Synaptic and transmembrane potentials are the fundamentals of the EEG signal, reflecting rhythmic fluctuations and dynamic neuronal activity (Kropotov, 2016; Nunez & Srinivasan, 2006). Specifically, extracellular changes in postsynaptic dendrites occur due to the neuron's excitable membranes and ionic movement. The ionic movement measured by one electrode, deriving from the surrounding tissue, is named local field potentials (LFP) and is a consequence of the continuous interplay between excitatory- and inhibitory post-synaptic potentials (Kropotov, 2016; Pevzner et al., 2016).

Generation of the EEG-signal. Pyramidal cells along the cortex are assumed to be the main source of the EEG signal. During excitation, the postsynaptic neuron will have a negative voltage near the dendrites compared to the rest of the neuron. Regions with positive change are named source, whilst the negative areas are called sink. Scalp electrodes can measure the sum of these negative and positive charges. Depending on electrode placement, a signal of electrical charge can be obtained with a specific polarity (+/-). An electrode near the dipole gives rise to a positive deflection, electrodes at an equidistance will be neutral and being near the sink gives a negative deflection (Buzsaki et al., 2012; Jackson & Bolger, 2014; Kropotov, 2016; Pevzner et al., 2016).

Pyramidal cells can either be oriented tangential/perpendicular or radial/parallel. Measurable signals are obtained when pyramidal cells are parallel arranged and synchronously active. The polarity of the signal depends on the pyramidal dipole orientation. If an EPSP occurs at the apical dendrite, LFP will have a negative deflection due to the influx of positively charged extracellular ions. Hence, EEG measures voltage shifts in the

extracellular fluid. EEG signals deriving from the extracellular fluid propagates through the skull due to tissue volume conduction and the electroconductive cerebrospinal fluid (CSF) (Buzsaki et al., 2012;2013; Jackson & Bolger, 2014; Kropotov, 2016; Kropotov, 2008; Pevzner et al., 2016).

Quantitative EEG (qEEG) is a method allowing for EEG processing through, for instance, spectral and wavelet analysis (Buzsaki, 2006). It quantifies raw EEG data by decomposing the signals to a sinusoidal function (Evans and Abarbanel, 1999), through algorithms like the Fast Fourier transformation (FFT). This allows for the extraction of parameters such as EEG coherence, power spectra and peak amplitude (Fallon et al., 2016; Fallon et al., 2018; Hargrove et al., 2010). qEEG has clinical benefits as it can provide insight into potential underlying mechanisms of certain diseases and responsiveness to pharmacology (Gunkelman & Johnstone, 2005)

Oscillations

Oscillations are coherent and rhythmic patterns of brain activity measured in a temporal scale (Ploner et al., 2017). They are fundamental for brain functioning and thought to allow for cross-network communication between spatially distributed networks. The various oscillatory frequencies are associated with different functions. When an individual is in an engaged state, changes in the oscillatory pattern appear. Yet, different oscillations can coexist during the same brain state (Buzsaki et al., 2013; Kropotov, 2016). The various brain waves are defined by cycles per seconds (Hz), and it is hypothesised that disorders and clinical questions can be inferred from deviations in these brain rhythms. The oscillations can be divided into frequency bands, namely delta, theta, alpha, beta, and gamma (Buzsaki, 2006; Urigüen & Garcia-Zapirain, 2015).

***Delta rhythms*.** The delta-band includes frequencies from 1-4 Hz (Kropotov, 2008). Delta waves are high in amplitude and commonly associated with slow-wave sleep, therefore more prominent during sleep and drowsiness. Frontal delta waves in wakefulness have been associated with cortical plasticity (Malik & Amin, 2017; Kropotov, 2008). One can differentiate between the cortical and thalamic delta, depending on its origin. Whilst the generation of the cortical delta is unknown, the latter is generated in the thalamus by thalamocortical neurons. The genesis of the thalamic delta is the consequence of the polarity of thalamocortical neurons. Specifically, hyperpolarization of these neurons which in turn causes a burst mode. This is a consequence of both excitatory and inhibitory ion currents,

resulting in Ca2+ spikes (Kropotov, 2008). Interpretation of the functional meaning of delta waves are challenging, as EEG measures is prone to artifacts.

Theta rhythms. The theta waves comprise of the oscillatory frequencies between 4-8 Hz. Theta can be observed in healthy subjects during rest, REM-sleep and during mental effort. However, theta-waves are most prevalent during a state of relaxed focus and is linked to working memory and attention (Choe et al., 2018; Buzsaki, 2002; Kropotov, 2008). High theta is considered abnormal when being observed in adult wakefulness in the lack of mental effort (Malik & Amin, 2017). There is no consensus upon its behavioural correlates, but it is assumed to be generated subcortically in the septo-hippocampal-entorhinal system (Buzsaki 2002; Buzsaki et al., 2013). Theta frontal midline has been associated with the metabolic activity in the anterior cingulate cortex and other frontal areas. It should thus be expected to see some theta in the frontal midline during tasks related to engaged focus as it is associated with cognitive load (Gevins et al., 1997; Kropotov, 2008, 2016).

***Alpha rhythms*.** The frequency band of alpha ranges from 8-13 Hz and is generated in the thalamocortical system (Buzsaki et al., 2013). Alpha is thought to exhibit the role of a sensory gating mechanism, regarding signal detection threshold and stimulus relevancy. Phases of the alpha wave are hypothesised to reflect an online-or offline-state, influencing perceptual threshold and consequently the likelihood of signal detection (Frölich, 2016; Kropotov, 2008, 2016). Hence, an association with alpha and allocation of cognitive resources has been made (Gevins et al., 1997; Sigvaldsen, 2019). Mainly, alpha can be localized posteriorly, centrally, and mid-temporally. Posterior alpha is prominent in occipital- parietal areas, especially when a subject is at rest with eyes closed. It is hypothesised that the occipital alpha is generated in the calcarine fissure and occurs due to inhibition of occipital activity. Hence, occipital alpha is suppressed in the presence of visual stimuli. (Kropotov, 2008, 2016).

Alpha can also be identified centrally, over the sensorimotor strip. This is referred to as mu- or sensory motor rhythm and is considered a resting rhythm of the sensorimotor strip. Lastly, the tau-rhythm can be localized in the auditory cortex and is generated in the Sylvian fissure. Following an auditive input, the tau-rhythm will desynchronize. It is plausible to assume that alpha rhythms are negatively correlated with metabolic activity, considering the reduction of occipital-posterior alpha when removing sensory input (Kropotov, 2008, 2016).

Beta rhythms. The beta band can grossly be subdivided into low (13-20 Hz) and high (21-30 Hz). In general, beta is related to focused attention (Buzsáki, 2006), but researchers have hypothesised there to be multiple neuronal mechanisms associated with beta such as decision making and novelty stimuli. In healthy subjects, one will normally identify beta in

frontal and central areas, especially compared to posterior areas. During resting-state observations one can identify the Rolandic beta rhythm over the sensorimotor areas, namely the basal ganglia. This rhythm is modulated by motor-related tasks and originates in the primary somatosensory cortex (Hari & Salmelin, 1997; Kropotov, 2008, 2016). Its most prominent feature is movement-induced desynchronization during voluntary motor activity (Frölich, 2006; Kropotov, 2016).

Most of the known mechanisms of beta oscillations stem from observations following gamma-aminobutyric acid (GABA)-agonist administration, such as benzodiazepines. Benzodiazepines will modulate the global beta by increases its power and decreasing its frequency (Blume, 2006; Frölich, 2006). The Rolandic beta is also modulated by dopamine and can in some cases be associated with pathology. Increased beta in the basal ganglia-thalamocortical motor loop, due to the lack of dopamine, is associated with bradykinesia as seen in Parkinson's disease (Kropotov, 2016)

Gamma rhythms. Frequencies above 30 Hz are named gamma waves and are linked to cognitive processes and conscious perception (Malik & Amin, 2017). Gamma has been suggested to play a role in the binding problem: namely the mechanisms that are contributing to the perception of coherence deriving from different sensory features (Kropotov, 2008). Gamma waves can be measured in various regions of the brain, but these high frequencies are usually more local and transient compared to its lower frequency counterparts. The gamma waves are challenging to record due to low energy, small amplitude, and proneness to muscle-artifact distortion. Gamma is typically induced following a coherent visual percept, in accordance with the binding problem (Kropotov, 2008, 2016; Urigüen & Garcia-Zapirain, 2015).

Even though gamma waves are difficult to record, studies indicate that gamma oscillations are important in both attentional mechanisms and memory (Jensen et al., 2007). For instance, retention of visual percepts in short-term memory has been associated with an increase in gamma oscillation over the occipital areas of the brain (Tallon-Baudry et al., 1999). Furthermore, gamma is related to pain intensity (Ploner, 2017), while a reduction in gamma-power has been linked with the neurogenerative disorder Alzheimer (van Deursen et al., 2008). In pain research, gamma is linked to the sensorimotor transformation of pain related to behavioural changes like withdrawal (Schulz et al., 2012). Gamma rhythms are therefore of interest in pain research, but its relevance is difficult to detect due to contamination from muscle-artifacts (Urigüen & Garcia-Zapirain, 2015; Puce & Hämäläinen, 2017).

Slow oscillations. Considering the fact what the mammalian brain constitutes 2% of the total body mass and utilizes 20% of total body energy consumption, interest in the spontaneous cortical activity arose (Fox & Raichle, 2007; Raichle, 2015a). Infra slow oscillations (ISO) were discovered in animals by Nina Aladjalova and Valentina Ilukhina in Russia during 1970-1980. It was not until much later that fMRI resting-state studies found that the mammalian brain displays blood oxygenated level-dependent (BOLD) fluctuations in a timescale at approximately 0.1 Hz (Fox & Raichle, 2007). Temporal dynamics under 0.1 Hz have usually been treated as noise in EEG and fMRI data acquisition (Hughes et al., 2011; Raichle, 2011). Conventional EEG applies low pass filters that typically excludes fluctuations beneath 0.5 Hz. ISO, or direct current potentials, require specific amplifiers to be measured and are prone to artifact-contaminations (Raichle, 2015a, Raichle, 2015b; Kropotov, 2008). Low frequencies are therefore often excluded from EEG-studies.

ISO has been observed in humans through full-band EEG (fbEEG) (Hughes et al., 2011; Vanhatalo et al., 2004). Is hypothesised that both the BOLD ISO and infra-slow fluctuations (ISF) reflect underlying neuronal dynamics (Hiltunen et al., 2014) and metabolic processes. Also, they are assumed to involve coordination of activity within the brain (Raichle, 2015a). ISO also display interactions with other brain waves, as they have been shown to modulate faster oscillations (Buzsáki, 2006; Buzsaki et al., 2013) and is also correlated with psychophysical performance. Researchers now believe that ISO can be related to cortical excitability (Kropotov, 2016**;** Vanhatalo et al., 2004.). In general, infra-slow fluctuations are important in advancing our understanding of the brain.

In chronic pain research, these slow waves have been related to resting-state networks, like the DMN. Disruptions within the infra-low frequencies can potentially have a cascade of effects upon higher frequency oscillations, as they cross-couples with each other Buzsáki, 2006; Buzsaki et al., 2013. Overall, various oscillatory frequencies and the engagement of different cortical structures provide the dynamic basis of complex phenomena like pain (Ploner et al., 2006, 2017).

Generation of thalamocortical oscillations. Peripheral sensory stimuli, apart from olfaction, travels directly into the thalamus before being relayed onto the cortex. Hence, the thalamus serves as a gatekeeper: directing when and where external information can be distributed to cortical networks (Buzsáki, 2006). Generation of oscillation can occur due to factors such as the dynamic relationship between excitation and inhibition, pacemaker cells and resonance. In addition, it is plausible that pathology can be revealed when questioning how, when and where oscillation has been generated (Pevzner et al., 2016). The thalamus is a

key structure in the genesis oscillatory activity.

Specifically, in thalamocortical interactions there are three main types of neurons involved: *(1)* reticular neurons (RE), *(2)* thalamocortical neurons (TC) and *(3)* deep lying cortical neurons. The thalamus receives input from both the periphery and the cortex (corticothalamic neurons). Both TC and CT neurons are glutaminergic, whilst the RE neurons are GABAnergic (Niedermeyer & Lopes da Silva, 2005). RE are interconnected and display inhibitory actions on thalamocortical neurons (Buzsaki, 2006; Jackson & Bolger, 2014).

Thalamocortical relay neurons can fire trains of action potentials depending on their membrane potential. They display two firing modes in accordance with their membrane potential. In a state of depolarization, tonic discharge can be observed. Giving rise to a train of action potentials, which relays to the cortex. In a hyperpolarized state, the thalamocortical relay neurons de-inactivate thalamocortical neurons because of calcium influx from low-threshold Ca2+ channels. When RE are repeatedly activated, they fire a rhythmic burst with inhibitory synaptic potentials (IPSP), consequently this hyperpolarization causes calcium to influx through low-threshold Ca2+ channels, and in turn depolarize the TC neuron. This creates spindles, as the TC neurons generates excitatory synaptic potentials (EPSP) which affects the RE in addition to corticothalamic neurons, causing a feedback loop. The intrinsic activity between TC, RE and corticothalamic neurons is key in the genesis of oscillations (Pevzner et al., 2016; Timofeev & Bazhenov, 2005). In summary, hyperpolarization of thalamocortical neurons occurs due to the effect of reticular neurons. Consequently, the hyperpolarization causes generation of action potential due to activation of low-threshold Ca2+ channels. In turn, thalamocortical neurons creates a burst firing (Pevzner et al., 2016; Sigvaldsen, 2019).

Our understanding of how the brain generates pain perception is derived from the knowledge of large-scale brain organization and intrinsic activity (Greicius et al., 2003). Advances in technology allow for the mapping of brain activity associated with cognitive states and underlying mechanisms of the pain experience. Expanding research-focus on large scale networks and their contribution to dysfunction fills a gap previously missing in neuropsychology (Menon, 2011). Our knowledge of chronic pain must for that reason include an understanding of intrinsic activity linked with psychological factors that influence pain perception.

The placebo response

The placebo effect is a positive response of symptom relief following administration of a treatment without any therapeutic value (Arnstein et al., 2011). Placebo is a complex phenomenon, and its biological underpinnings are poorly understood (Amanzio & Benedetti, 1999; Benedetti et al., 2005). One can differentiate between the placebo response and effect. Whereas the former is the individual reduction of symptoms, the latter is a populational based response. There is great heterogeneity in the placebo response, often associated with individual differences in psychological factors like the expected degree of pain relief (Bingel et al., 2011; Price et al., 2008). What is known, is that pre-existing brain state and ongoing intrinsic neural activity influence the interpretation of environmental stimuli (Buzsaki, 2006; Kucyi & Davis, 2017).

The psychological and neurobiological aspects of placebo. The human brain generates information based on context and learned experiences. Therefore, brain and environment make up an intricate and dynamic coupled system (Buzsáki, 2006). Factors known to influence the placebo response are open or close administration, verbal suggestion, expectancy, memory, and avoidance goal (Price et al.m2008). Additionally, psychological factors including pain catastrophizing are known for affecting the degree of symptom relief (Darnall & Colloca, 2018).

Since attentional and affective networks are involved in pain modulation, it is hypothesised that attentional and emotional state can affect pain perception and hence be important in placebo. The attentional system is related to pain intensity, hence involving cortical structures such as the anterior and mid-cingulate areas for silence detection. However, distraction away from pain has shown to be related to the insula and superior parietal cortex. The affective network is thought to be related to the unpleasantness of pain, including the insula. Negative emotional evaluation of pain is additionally thought to involve the ACC-fronto-PAG circuitry. (Bushnell et al., 2013; Davis & Moayedi, 2013), which are important areas in the DPC (Greicius et al., 2004; Kucyi & Davis, 2015).

Preliminary studies conducted by Levine and colleagues (1978) defined the field of analgesic placebo. Levine found placebo-responses to trigger endogenous opioid responses. Patients receiving oral surgery were treated with either morphine, placebo, or an opioid antagonist (naloxone). The group administered naloxone reported significantly higher levels of pain compared to the placebo group, which suggest that analgesic placebo involve an opioid-like mechanism (Levine et al., 1978). However, the effect of the opioid agonist remifentanil can be reversed depending on the degree of negative expectations of pain. Pain-

related BOLD responds found a significant change in brain activity in the thalamus, the MCC, INS and the S1. Additionally, activity in the hippocampus, MCC and mPFC predicted individual changes in increased perceived pain intensity (Bingel et al., 2011).

In contrast, positive expectancy in the presence of remifentanil revealed activity in the dlPFC, ACC, striatum, and frontal operculum (Bingel et al., 2011). Hence, positive, and negative expectancy of drug effectiveness influence degree of analgesic effects and involve different cortical structures in the DPC (Bingel et al., 2011; Bushnell et al., 2015)

***Chronic pain and placebo*.** Attempts to identify and predict individual variability in placebo response can benefit patients and chronic pain populations, due to a more individualized therapeutic approach (Tétreault et al., 2016). Patients suffering from chronic pain is hypothesised to display alterations in morphology and neurochemistry in areas involved in pain-modulation. Consequently, this can alter the degree of placebo responses obtained.

Morphological changes include significant lowered total grey matter, with localized changes in the IC, ACC and dlPFC (Apkarian et al., 2004; Moriarty et al., 2011). A study from 2009 linked altered pain processing in FM patients to the abnormal inhibitory activity from the rostral ACC (Jensen et al., 2009). All these areas are associated with pain, like the dlPFC that is associated with cognitive-affective modulation of pain (Lim et al., 2016). Chronic back pain patients have been found to exhibit reduced grey matter density (GMD) in the bilateral dlPFC and the thalamus (Apkarian et al., 2004). A meta-analysis of voxel-based morphometry studies on FM patients found grey matter atrophy in the mPFC and the dPCC, areas that are key nodes in the DMN (Lin, Lee & Weng, 2016). This suggests a faulty top-down pain modulation amongst chronic pain patients.

Neurochemical deviances have been identified through an in vivo proton magnetic resonance spectrometry study. FM and chronic back pain patients demonstrated an increase of glutamate and/or decrease of N-acetyl aspartate in the frontal areas of the brain. Researchers hypothesis that GM atrophy can be a result of excitotoxicity (Bushnell et al., 2013). Other studies find abnormally low dopamine levels in the frontal regions, and others display opioidergic dysfunctions. Altogether, these changes indicate that chronic pain and FM patients display morphological and neurochemical alterations which ultimately can placebo analgesia (Bushnell et al., 2013).

Chronic pain, rumination, and pain catastrophizing. Thinking negatively about pain can influence pain perception (Baliki & Apkarian, 2015; Kucyi et al., 2014). Hence, psychological factors are known to influence the experience of pain and can either facilitate or

inhibit pain perception. Attention to pain is also thought to be related to the degree of pain catastrophizing, as it predisposes individuals to difficulty of shifting focus away from pain (Gracely et al., 2004; Kucyi & Davis, 2015; Kucyi et al., 2013; Sullivan et al., 2005). For instance, pain rumination in patients suffering of temporomandibular disorder (TMD) were found to have an association to the functional connectivity in crucial DMN-nodes, like the mPFC and PAG (Kucyi el al., 2014). The degree of pain catastrophizing correlates with clinical pain, which analysis relate to activity in the dlPFC, anterior cingulate gyrus and the parietal cortex. Thus, pain catastrophizing can be related to areas associated with pain, attentional and emotional pain processing (Gracely et al., 2004). An EEG study comprising of 52 healthy college students found nocebo effects to be linked to an increase in the alpha band (ca. 8-10 Hz). The enhancement of alpha power was correlated with the psychometric scale of pain catastrophizing (Albu & Meagher, 2016). This suggest that individual variability in the susceptibility for increased pain perception can potentially be identified through functional connectivity in the DPC.

However, there is a need of meta-studies upon the effects of placebo and the psychological factors that influence pain perception. Due to experimental design weaknesses, there are no clear answers to which factors influence perceived symptom relief. Change in symptoms might occur because of natural history and not the administration of treatment (Price, 2008; Tétreault et al., 2016).

Fibromyalgia

Fibromyalgia is considered a rheumatic idiopathic pain disorder, primarily defined by widespread and diffuse musculoskeletal pain. The generalized pain is often distributed in 18 tender points (Wolfe et al., 2010, 2011). Additional clinical symptoms include sleep disturbances, fatigue, mood disorders and psychological distress. Symptom severity tends to vary over timespans of days to months (Clauw, 2014; Staud, 2006; Mork & Nilsen, 2012; Sluka & Clauw, 2016; Verbunt et al., 2008; Wolfe et al., 2013). Moreover, patients every so often reports a decline in memory, concentration, vigilance, and mental clarity; commonly referred to as fibro-fog. Forgetfulness and diminished mental clarity are often linked with dysfunction in working-, semantic- and episodic memory (Kravitz & Katz, 2015).

Fibromyalgia and chronic pain can severely disrupt an individual’s quality of life (Baliki et al., 2008; Wolfe et al., 2013). It is estimated that 4.7% of the western population suffers from fibromyalgia (Branco et al., 2010). Even though FM is a common diagnosis, it is

both broadly defined (Wolfe et al., 2019) and complex, which has caused controversy (Cohen, 2017; Rahman et al., 2014).

Its aetiology and pathophysiology are currently unknown (Fallon et al., 2018; Wolfe et al., 2010, 2011). Patients suffering from FM often have a history of endometriosis, headaches, and gastrointestinal issues. These are chronic pain syndromes with similar and overlapping clinical features, suggesting a common underlying mechanism (Caspi et a., 2014; Hudson & Pope, 1994; Sluka & Clauw, 2016). The lack of evidence of the aetiology of fibromyalgia compromises the quality of treatment, consequently affecting individual symptom reduction (Rahman et al., 2014).

Diagnostic criteria. The very first validated diagnostic tool of FM was published in 1990 by the American College of Rheumatology (ACR). These criteria have since then been revised. Today, FM diagnosis is given based on the following criteria: (1) Generalized pain, defined as pain, in at least 4 of 5 regions, (2) symptoms have been present at a similar level for at least 3 months, (3) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4-6 and SSS score ≥ 9, (4). A diagnosis of fibromyalgia is valid irrespective of other diagnoses and will therefore not exclude the presence of other clinically important illnesses (Wolfe et al., 2010, 2011, 2013). Since the diagnosis is prompted by self-report, there is a potential for both under- and overdiagnosis of the disease (Häuser et al., 2019; Wolfe et al., 2019).

A Norwegian study reveals that FM is one of the conditions physicians rank to have the lowest prestige (Album et al., 2017). This might be a consequence of the lack of biomarkers, which provides an unsteady fundament for the development of diagnostic criteria. The ambiguity of its pathophysiology is represented in the degree of both over- and misdiagnosing of patients. The latter might occur in the presence of other rheumatic diseases, such as rheumatoid arthritis (RA), which typically presents with overlapping symptoms as FM. Clinical cues for FM are often prompted from patient's anamnesis and family history of chronic pain, especially in early age (Häuser et al., 2019).

FM is currently being treated as an exclusion diagnosis. Differential diagnosis includes autoimmune connective tissue disease, hypothyroidism, myositis, and malignancies (Cohen, 2017). Patients will on average spend 2.3 years in the healthcare system before receiving a fibromyalgia diagnosis, which involves consulting 3.7 physicians on. It is plausible that spent in the healthcare system without receiving satisfactory treatment can increase psychological distress average (Choy et al., 2010). A diagnosis can contribute to the legitimatizing of the patients' experience, which is associated with better coping strategies

(Häuser et al., 2019). The diagnosis can be acquired through a primary healthcare provider, but many aims towards a multidisciplinary approach in the healthcare system (Clauw, 2014).

***Current treatment options*.** Adequate treatment for FM patients is currently not available and approximately 19% of chronic pain patients in Europe report not receiving satisfactory pain management (Breivik et al., 2006). The standard approach in treating fibromyalgia include the usage of analgesic, cognitive and psychotherapy, exercise, and patient education (Clauw, 2014; Rahman et al., 2014). Physical activity is considered crucial. A Norwegian study identified an association between body mass index (BMI), physical exercise and risk of FM. Where a high BMI and lack of exercise was positively correlated with an increased risk of developing FM (Mork et al., 2010). Analgesic therapy includes non-steroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, tramadol (opioid), pregabalin (anticonvulsant) and cyclobenzaprine (Crofford et al., 2005). Nevertheless, pharmacological treatments display great variety in efficacy and pose the risk of adverse effects (Kropotov, 2016). Since fibromyalgia is a highly individual disorder, individualized treatment is of great importance to increase the chances of symptom reduction.

Plausible explanations of fibromyalgia. Researchers have suggested a variety of neurobiological, psychological, and physiological explanations. Widespread pain is thought to stem from alterations in the spinal cord or the transduction threshold of nociceptors (Julius & Basbaum, 2001). However, FM patients rarely display peripheral sensitizations, as nociceptive afferent receptors usually are not affected. The clinical presentation of widespread and poor spatial localization of pain suggests a central mechanism (Meeus & Nijs, 2007). As we gain a deeper and extensive understanding of chronic pain, it is now evident that chronic pain results from both changes in anatomical structures and functional connectivity. Not exclusively in pain circuits, but also in areas associated with cognition and affective processes (Bushnell et al., 2013).

The hypothesis of central sensitization suggest that hyperalgesia and allodynia occur due to amplification of supraspinal mechanisms (Cagnie et al., 2014). Innocuous and subthreshold nociceptive stimuli trigger nociceptive pathways in the central nervous system (CNS); consequently, pain perception is disproportionate to the nociceptive input (den Boer et al., 2019). Dorsal root ganglion (DRG) displays increased excitability due to molecular changes and neural circuit reorganization (Baliki & Apkarian, 2015; Clauw, 2014). Prolonged and repeated activation of DRG by noxious stimuli can increase their receptive fields, ultimately giving rise to temporal summation and increased pain. These effects can become long-lasting due to plasticity. (Meeus & Nijs, 2007).

The excitatory neurotransmitter glutamate is released from the primary afferent presynaptic terminal and binds to AMPA and NMDA receptors on DRG postsynaptic terminals (Latremoliere & Woolf, 2009). The increased influx of Ca^{2+} causes an intracellular signalling cascade, including synthesis of nitric oxide (NO), leading to the increased release of neuropeptides such as substance P. Higher intracellular concentration of substance P lowers excitability threshold of the DRG. This can expand their receptive fields thereafter. Changes in gene expression and neural plasticity can plausibly explain long lasting pain because of cellular mechanisms (Farmer et al., 2012; Latremolier & Woolf. 2009; Meeus & Nijis, 2007).

Functional connectivity and chronic pain. Chronic pain patients suffer from continuous background pain, even in the absence of a noxious driving force. It has been suggested that this derives from abnormalities in the resting state networks (RSN) of the brain due to cortical reorganization and functional connectivity (Baliki & Apkarian, 2015). Deviances in resting state rhythms have therefore been suggested to play a crucial role in chronic pain genesis and maintenance (Kropotov, 2016). Several studies find chronic pain patients to present with irregularities in the DMN, SN and AS (e.g. Baliki & Apkarian, 2015; Baliki et al., 2008; Ceko et al., 2020). For instance, one study found chronic pain patients to exhibit increased connectivity between the mPFC and IC, and the mPFC and PCu, compared to healthy controls (Baliki et al., 2014). It is possible that these cortical reorganizations come from the pain persisting over a longer period (Ceko et al., 2020).

In response to pain, relevant cortical areas can display oscillatory behaviour in the theta, alpha, beta, and gamma frequencies. Often, implications in the frontal regions are identified (Apkarian et al., 2005; Baliki et al., 2008; Kucyi & Davis, 2015; Peng et al., 2018; Ploner, et al., 2005; Ploner, 2017). Resting-state EEG studies have found that those who suffer from neuropathic pain presented with overactivation of both beta- and theta-waves. For beta, the overactivation was source located to midprefrontal areas, the dlPFC, the insular cortex and the ACC. Theta overactivation was source located to the parietal cortex, insular cortex and the ACC as well (Sarnthein et al., 2006; Stern et al., 2006). It is unclear whether changes in power spectra is specific in neuropathic pain or chronic pain in general.

Stimulus encoding and pain intensity is associated with different mechanisms. A study comprising of 51 healthy participants, with 39 used in analysis, investigated the differentiation in stimulus encoding and pain intensity, through the application of noxious heat stimuli. The researcher found alpha and beta to be negative correlated with stimulus intensity in the contralateral sensorimotor areas, whilst gamma in the mPFC was positively

correlated with pain intensity. This finding showed no relation to stimulus location. Hence, the researcher finds it plausible that the bridge between sensory stimuli and pain perception is caused by switching to a more spatially independent stimuli encoding (Nickel et al., 2017). On the other hand, a study of 12 healthy participants that received a clinical noxious stimulus found a suppression of sensorimotor beta power following pain (Ploner et al., 2005). For FM patients, suppression of the INS and S2 beta activity have been related to allodynia (Fallon et al., 2013).

***Functional connectivity and fibromyalgia patients*.** There are inconsistent findings across FM-studies. One consistent finding is alteration within the frontocentral beta band (Fallon et al., 2013; Fallon et al., 2016; Hargroves et al., 2010; Lim et al., 2016). Several studies also find FM patients to present with increased low frequency and increased high-frequency oscillations (González-Roláand et al., 2016; Fallon et al., 2018; Sarnthein et al., 2005; Stern et al., 2006). It is suggested that thalamocortical dysrhythmia (TCD) contributes to this deviant oscillatory pattern. The theoretical framework of TCD suggest that neurological and neuropsychiatric diseases stems from the slowing of resting state alpha waves down theta, which increases the amount of theta. Consequently, theta cross-frequency couples with high-frequency oscillations (e.g. beta), resulting in a disrupted cross network communication (Vanneste et al., 2018; Llinas et al., 1998).

Fallon and colleagues (2018) conducted an EEG resting state (EC) where they found FM patients compared to healthy controls display higher frontal theta. Increased theta was found in frontocentral areas, including mPFC, dlPFC and ACC. These deviations correlated with both tiredness, tenderness, and pain scores (Fallon et al., 2018). Contrary, another study found lowered power increase of theta waves over structures like the mPFC in FM patients during working memory tasks. The researchers hypothesised this reduced increase to covary with fibro-fog scores (Gonzalez-Villar et al., 2017). Another study identified an abnormal frontal theta (Lim et al., 2016).

Lim and colleagues (2016) found FM patients to display increased theta, beta and gamma localized in the left dlPFC and orbitofrontal cortex (OFC) during resting state MEG. Increased beta power over in the dlPFC was positively correlated with affective dimensions of pain ratings. In addition, FM patients displayed overactivation of beta in the insular cortex, S1, S2 and M1. Increased gamma was also localized in the S1, S2 and M1. Plausibly due to changes in cortical excitability over the sensorimotor strip (Lim et al., 2016). The research group hypothesized that these findings indicate a resting state hypervigilance to spontaneous pain in FM patients.

Several studies have found abnormalities between the insula and DMN in FM patients, which points towards a possible neuromarker (Cifre et al., 2012; Napadow, Kim, Clauw & Harris, 2012; Napadow et al., 2010; Hsiao et al., 2017). A resting state eyes closed EEG found FM patients to display reduced delta in the right insula, in addition to the superior and middle temporal gyri. Increased beta was localized in the right frontal, midcingulate and motor areas. This latter finding is also suggested to stem from a cortical hyperexcitability (González-Roláⁿd, 2016.). A later study found decreased INS-DMN connectivity in the theta band amongst FM patients. This finding was also negatively correlated with tenderness-scores (Hsiao et al., 2017). Another study found increased resting state connectivity of the ACC with the basal ganglia and the INS. The ACC also displayed a reduced resting state connectivity with the PAG (Cifre et al., 2012).

Some studies suggest that changes in DMN activation and oscillatory power might not be a unique feature of chronic pain, but merely pain itself. A study conducted by Ceko and colleagues (2020) investigated resting state functional connectivity in the DMN in FM-patients. These patients were divided into two groups and had a matched control group each. In one of the groups, the patients received clinical pain during the scans. In the latter, they received no such stimulus (pain-free group). The results revealed no significant difference in the group with no stimulus compared to their controls. However, a significant change in the DMN-l-INS connectivity was shown in the pain-stimulus group, with the change being correlated to the level of clinical pain. The researchers suggest the exitance of a difference between pain state and pain trait on FM patients. Whereas changes in the DMN connectivity results from clinical pain during scans rather than the chronic pain diagnosis itself (Ceko et al., 2020).

A recent study conducted by Alshelh and colleagues (2018) injected intra-muscular hypertonic saline infusion in healthy controls, lasting between 5-20 minutes. The findings revealed a decreased connectivity between the PCC and mPFC, and the PCC and IPL. In addition, lowered oscillatory power in the PCC, precuncus, MPFC and IPL (Alshelh et al., 2018; Ceko et al., 2020). The changes seen in clinical pain in healthy controls can therefore be thought of the same activation pattern seen spontaneously in FM-patients (Ceko et al., 2020). The research groups find it possible that DMN changes can occur because of pain at the time of scanning (Ceko et al., 2020).

Early-life stress. Early-life stress (ELS) has been linked to an increased susceptibility to chronic pain conditions (Burke, Finn, McGuire & Roche, 2017). Patients suffering of FM tend to present with increased pain hypervigilance, catastrophizing, and maladaptive coping

strategies. Researchers have suggested that these psychological factors partake in a cognitive central sensitization process (Meeus & Nijs, 2007). Indeed, pain catastrophizing is suggested to act as a risk factor for developing FM (Sluka & Clauw, 2016). This vulnerability can stem from alterations in DMN connectivity caused by early life stressors. A recent study found that ELS can impair DMN connectivity in both mother and child. The resting state MEG-study found abnormalities in the mothers' alpha-band and children's theta-band. Compared to controls, the children displayed a lower DMN connectivity between the right angular gyrus (RAG) and PCC, RAG-PCC, RAG-dmPFC and RAG- left inferior temporal gyrus (LITG) (Zeev-Wolf et al., 2019). The angular gyrus is hypothesised to be involved in mental representation during mind-wandering (Seghier, 2013), hence important to the functioning of the DMN.

Long lasting effects of stress on the DMN are thought to affect hypervigilance, intrinsic and extrinsic attention, in addition to self-referential mental activity (Zeev-Wolf et al., 2019). The mothers displayed lower DMN connectivity between left angular gyrus (LAG) and the dmPFC, PCC-vMPFC, PCC-LITG, vMPFC-LITG and dmPFC-LITG. The researchers imply that theta is a potential marker of the developmental processes that occurs in a young brain, like synaptic plasticity. As humans mature, there is a change from dominant theta to alpha oscillation. It is suggested that development causes a shift from theta to alpha as a default rhythm (Kropotov, 2016). It is plausible that this shift is interfered with due to ELS, causing an abnormal brain maturation affecting the functional connectivity of the DMN.

Neurofeedback

Neurofeedback is a type of biofeedback, which provides an observer insight to real-time information about their physiological processes. Biofeedback can derive a signal from e.g. heartrate and blood pressure. Neurofeedback specifically derives information from brain activity, mainly EEG-electrodes. The aim of neurofeedback is for an individual to gain self-regulatory control over neuronal mechanisms related to behaviour (Sitaram et al., 2017). In neurofeedback an individual manipulates a chosen parameter voluntarily or involuntarily, an example being beta/theta ratio (Kropotov, 2016). The EEG signal is typically fed back to the participant through either auditive or visual stimuli (Sitaram et al., 2017). By allowing the brain to obtain more salient information about its own processes, the brains capacity to self-regulate in a proper manner improves accordingly. It is assumed that operant conditioning underlies the effects of neurofeedback, through adaptation of self-regulatory processes

(Othmer et al., 2013; Othmer & Othmer, 2016, 2017). However, the mechanisms which underpins the effect of neurofeedback has been a topic of debate (Ioannides, 2018)

The human brain is both highly unitary and integrated. Higher order brain functions are less reliant on ingoing sensory stimuli, and in a sense the perception of pain is created in the brain (Buzsáki, 2006). Self-maintenance and regulation are core functions of the human brain. Self-organizing and intrinsic activity is adjusted to external stimuli to create the sense of an external world, merely a type of calibration. It is plausible to assume that disruptions within the regulatory mechanisms and the RSN consequently affect an individual during active states. If chronic pain is caused by maladaptive plasticity within RSN and disruptions in ISO, neurofeedback which aims to renormalize the abnormal resting state rhythms might decrease symptom severity (Othmer et al. 2013, 2016, 2017). Researchers have used sensory motor rhythm neurofeedback with positive outcomes on pain and fatigue in FM patients (Kayiran, et al., 2010). Though during the latest years, more focus has been redirected to the infra-slow fluctuations of the brain (Kropotov, 2016).

The Othmer method. The Othmer method was presented in the 21st century by Sue and Siegfried Othmer. It utilizes the infralow frequency (ILF) below 0.1 Hz (Kropotov, 2016). Since infra-low neurofeedback treatment (ILF-NFT) targets the infra low frequencies known to characterize the temporal dynamics of the RSN, it may have direct implications on chronic pain. As slow oscillations cross-couples with higher frequencies (Buzsaki, 2002) and RSN subserves many cortical functions, it is possible that multisymptomatic disorders like FM originates from a cascade of effects, due to disruptions in the infralow frequency-range and in the RSN. As the DMN is important in self-regulatory mechanisms, aiming to normalize the infralow frequencies in the resting state networks can potentially be beneficial in FM and reduce symptom severity (Othmer et al, 2013; Niv, 2013; Ploner et al., 2017; Sigvaldsen, 2019). A small study with three patients suffering of depression, found participant to present with a significant decrease in theta in frontocentral areas of depressive participants during both resting and active state. This was accompanied by a reduction of excessive alpha over the entire scalp. All three patients reported improvements in mood and stress tolerance following treatment (Grin-Yatsenko et al. 2018).

The goal of ILF-NF is to lower symptom severity, which is accomplished by identifying individual optimal response frequency (ORF). ORF is situations where the patient experiences both calmness and alertness. IFL-NFT uses a bipolar montage, targeting two cortical sites and their relationship. Specific electrode placement is individualised by the clinician based on the symptoms and clinical presentation. It is recommended that one should

initiate treatment with a bipolar montage with a T3-T4 placement, as this display both strong effect and broader clinical efficacy (Othmer & Othmer, 2016, 2017; Othmer et al., 2013).

In ILF-NFT, the subject will naturally adjust to the signal through the brain's gradual discovery of its agency over the dynamic feedback. In contrast to other neurofeedback protocols, ILF-NFT does not utilize the principles of operant conditioning (Kropotov, 2016). The Othmer method does not require the subject intentionally pursuit any specific activity other than relaxation and is more related to the principles of skill learning (Dobrushina el al., 2020; Othmer & Othmer, 2016, 2017; Sigvaldsen, 2019).

The importance of this study

Alleviation of pain is more readily obtained in the presence of an acute injury (Mansour et al., 2014). For those affected by Fibromyalgia and chronic pain, it causes severe disruptions upon their quality of life as it effects both psychological and physical wellbeing. Currently, there are no treatment options targeting all symptoms of fibromyalgia. Rather, treatment comprises of non-specific pharmacological interventions and patient-education, which involves illness-acceptance. A consequence of this is dissatisfactory symptom relief. The unknown aetiology of fibromyalgia has a cascade of effects on both treatment, time spent in the healthcare system and psychological wellbeing. Understanding the underlying generators of chronic pain, like fibromyalgia, will benefit both patients and the healthcare system. For the patient, identifying a neuromarker will contribute to legitimization of the disease, decrease in psychological distress and more effective treatment. Having a potential multisymptomatic treatment of fibromyalgia can also increase quality of life and have societal benefits as more people can potentially return to work.

Aim of the study and hypothesis

The present study comprises of two sections. The first part aims to investigate the clinical effects of infra-low frequency neurofeedback (ILF-NFT) on symptoms associated with fibromyalgia: pain, fatigue, and cognitive issues. The second section focuses on identifying possible biological markers of fibromyalgia. This is attempted through investigating coherent deviations in QEEG power spectra in areas associated with the dynamic pain connectome.

Previous research has found FM patients to display several deviations in different

frequencies (e.g. Cifre et al., 2012; Hargrove et al., 2010; Lim et al., 2016) Based on previous research, deviations in brain frequencies vary from study to study. In this study the focus was on qEEG parameters derived from frontal (F3, Fz, F4), central (C3, Cz, C4), temporal (T3, T4) and parietal (P3, Pz, P4) regions. Fp1/Fp2 and O1/O2 electrodes were excluded from this study due to their proneness to artifacts (Kropotov, 2008, 2016; Urigüen & Garcia-Zapirain, 2015). There are indications that infra-low neurofeedback can possibly be beneficial for fibromyalgia patients who present with diffuse and widespread pain, in addition to many other symptoms (Kayrian). This study wishes to investigate the following statements:

1. If fibromyalgia is caused by a functional reorganization of the brain, patients should display coherent and significant deviations from healthy controls in power spectra analysis.
2. If fibromyalgia is caused by functional reorganization of the DPC, position estimation and source location (sLORETA) should identify deviances in Brodmann areas in accordance with the DPC
3. If ILF-NFT is effective for reducing symptom severity in fibromyalgia patients, these effects should be identifiable in power spectra analysis through normalization of power spectra deviances

Method

Subjects and selection strategy.

The subject basis was patients diagnosed with fibromyalgia by a health care provider. Participants were mainly recruited through self-help forums on Facebook and the Fibromyalgia Association (Fibromyalgiforeningen) in Trondheim, Norway. Patients who were interested in participation received an e-mail with information regarding the project and an informed consent schema (see Appendix G).

A total of 25 females agreed to partake in this study. 15 participants were recruited during July of 2019 and received neurofeedback during the fall of 2019. Whilst the remaining 10 patients were recruited in December 2019 and received training during the spring of 2020. 2 participants from the first group withdrew from the study before ILF-NFT were initiated.

Sigrid Hegna Sigvaldsen assisted on the neurofeedback sessions for the first group. The second group received ILF-NFT from 10 bachelor students, as a bachelor project were a part of this study. All students underwent a mandatory course to fully ensure quality of

treatment.

Originally, the present study comprised of 23 patients for pre- and post-treatment comparisons. Due to the SARS-COVID-2 pandemic, a lot of data was lost due to governmental restrictions. The second group of recruited participants (N = 10) was not able to conduct the post-test EEG following the neurofeedback treatment. Therefore, only 13 patients are available for pre- and post-test EEG comparisons. As access to the university was restricted, some patients in group 2 were not able to fill out the post-test questionnaires. A total of 20 patients conducted their post-test questionnaires. The result section of this study is therefore subdivided in accordance with available data. Reports will be made for all patients on pre-test and preliminary analysis, on 20 patients for pre- and post-test clinical self-reporting measures, and 13 patients for pre- and post- EEG comparisons, and 23 patients for pre-test analysis.

The study was originally designed as a placebo-controlled double-blinded study. Due to a syntax error in the CygNet software, all patients received active treatment. This was not discovered until the end of treatment. Therefore, it is assumed that some of the expectancy effects are reduced in this study, compared to an informed all-active study.

All patients fulfilled the ACR diagnosis criteria for FM (Wolfe et al., 2010). Several patients suffered of comorbid diseases such as other rheumatic disorders and mood disorders. Patients were not instructed to discontinue any medication they were currently on. Some patients were consuming pharmacological medicine known to influence the EEG recordings. (Blume, 2006; Kropotov, 2008, 2016; Niedermeyer & Lopes de Silva, 2005) A full overview of medicine consumed by patients are to be found in table 4.

Table 4.

Medication usage mapped during pre-test EEG, N=23

Therapeutic subgroup	Medicine	*N*	%
Antiflogistikum	Vimovo	3	13.04%
Opioidanalgetikum	Tramagetikk	1	4.34%
	Nobligan	2	8.69%
Analgetikum	Paracetamol	5	21.73%
	Tramadol	2	8.69%
	Pinex	2	8.69%
Sedativum/hypnotikum	Melatonin	2	8.69%
	Vallergan	1	4.34%
	Stilnoct	1	4.34%
	Imovane	1	4.34%
	Zopiclone	2	8.69%
Antidiabetikum	Metformin	2	8.69%
	Victoza	1	4.34%
Sympatomimetikum	Aduvanz	1	4.34%
	Elevanse	1	4.34%
Adrenergikum	Ventolin	2	8.69%
Antihistamine	Kestine	1	4.34%
	Cetrizin	3	13.04%
	Aerius	2	8.69%
Tromboseprofylaktikum	Albyl-E	1	4.34%
NSAID	Ibuprofen	3	13.04
Opioid/alcohol dependence	Naltreksone	1	4.34%
Muscarinic receptor antagonist	Detrocitol	1	4.34%
Thyreoidea hormone	Levaxin	2	8.69%
Antidepressants	Cymbalta	2	8.69%
	Sarotex	5	21.73%

	Cipralex	1	4.34%
Angiotensin	Atacand	1	4.34%
Contraception	Cerazette	1	4.34%
Corticostereoid	Prednisolon	1	4.34%
Estrogen	Vagifem	1	4.34%
	Estradot	1	4.34%
Lipid modification Agent	Lipitor	1	4.34%
Immunosuppressive	Methotrexate	1	4.34%

Note. % = the percentage of all patients that administered the specific drug.

All patients completed EEG recordings before treatment, and 13 patients completed EEG post treatment. A total of 10 patients did not have an EEG recording following neurofeedback training. Only 1 of these 10 patients finished their neurofeedback trainings before governmental restrictions, whilst the remaining participants did not. In addition to EEG, all patients completed five self-reporting symptom measures of symptom severity both prior and midway in the treatment. Following treatment, 20 patients completed these questionnaires. All participants received a gift-card of 1000 NOK and the study was approved by The Regional Committee of Medical Research Ethics. All participants gave written consent to partake in this study (See appendix E).

Apparatus

***EEG data acquisition*.** EEG was recorded pre- and post-treatment using tin (Sn) electrodes from Elecro-Cap (Elecrocap International Inc.) and a 19-channel digital amplifier from Mitsar (St. Petersburg, Russia). The EEG data was processed by WinEEG xxxx software and stored on an offline computer. Electrodes were allocated in accordance with the 10-20 international system, with respect to the anatomical landmarks of the nasion and inion. The complete electrode placement included frontal regions (Fp1, Fp2, F3, Fz/, F4, F7, F8), central regions (C3, Cz, C4), parietal regions (P3, Pz, P4), temporal regions (T3, T4, T5, T6) and occipital regions (O1, O2). Reference electrodes were positioned on the patient's earlobes and was grounded at FpZ.

Impedance was below 10 kOhm and maintained by applying conductive gel in all

electrodes. 100 microvolts (uV) was set as the exclusion threshold, and pass filters were applied for both slow and high waves. High pass filter for the former was set to 0.53 Hz, whilst low pass filter for the latter was set to 30 Hz. To reduce the influence of electrical noise and disturbances, a notch filter set at 45-55 Hz was applied during trials (Kropotov, 2006). Sampling rate of the recordings were fixed on 500 Hz. Amplifiers had input impedance set at 200 MOhm, with A/D of 14-bit precision (Sigvaldsen, 2019). All EEG recordings were visually examined for artifacts.

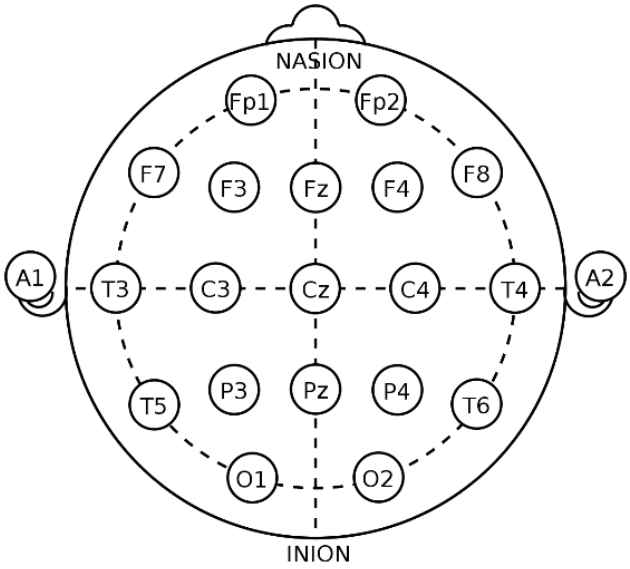

Figure 1. 10-20 system montage of electrode placement.

ILF-NFT. Cygnet Software with the NeuroAmp II amplifier (BeeMedic) was applied to conduct the infra-low neurofeedback training (ILF-NFT). Skin was carefully prepared with NuPrep abrasive paste, and Ag/AgCl electrodes were placed with conductive paste. The signal was amplified through NeuroAmp, with DC to 100 Hz frequency range, and processed through Cygnet biofeedback software (BEE medic GmbH). Patients freely choose between the available animation in CygNet (Somatic Vision Inc.).

VAS. Key symptoms of fibromyalgia are pain, fatigue, and cognitive issues. As these variables are subjective experiences, researchers can use the psychometric self-assessment tools such as Visual Analogue Scale (VAS) to gain further insight into the experienced symptoms (Ohnhaus & Adler, 1975). VAS comprises of three continuous lines at 100 mm, each assessing the key symptoms of fibromyalgia. This includes pain- fatigue- and fibro-fog-levels. The extremities of each line were indicated with “no pain/fibro-fog/fatigue” on one end and “worst possible pain/fibro-fog/fatigue” on the opposite end. Patients were requested to mark the line at the experienced level of each symptom during the last week. The visual

analogue scale (VAS) were given to patients before neurofeedback, midways during neurofeedback training and prior to the last session. Patients were encouraged to either fill out the form at the laboratory or at home (see appendix H).

ACR. The American College of Rheumatology (ACR) criteria have been revised since its original publishing in 1990 (Wolfe et al., 2010). The current diagnostic criteria consist of a mapping of widespread pain (WPI) and symptom severity (SS). The ACR criteria for fibromyalgia is satisfactory when a patient meet the following criteria: (1) WPI 7 and SS scale score , 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 (Wolfe et al., 2010).

The ACR consists of two sections. The first section aims to map WPI and comprises of a 19-point checklist of body areas which represents all four quadrants. Patients are asked to mark which areas they have experienced pain in during the last week. WPI is scored from 0-19. The second section maps symptom severity and consist of a (a) and (b) section. Section (a) asks the participant to indicate the severity of fatigue, tiredness, and cognitive symptoms during the last weeks on a 4-point Likert: where 0 indicated no issues and 3 indicates sever disruption of quality of life. Section (b) lists 33 somatic symptoms, and patients are requested to check which symptoms they have experienced during the last week. The researcher scores section 2b by categorizing scores into 0 (no symptoms) to 3 (a great deal of symptoms) (See appendix I) (Sigvaldsen, 2019).

FIQ. The fibromyalgia impact questionnaire (FIQ) aims to map the total spectrum of how fibromyalgia affects an individual (Bennet, 2005). FIQ comprises of three sections. The first section includes a total of 11 questions regarding the ability to perform task related to the large muscle groups (Bennett, 2005). Participants are asked to rate each task on a 4-point Likert scale, ranging from 0 = Always, 1 = Mostly, 2 = Sometimes, and 3 = Never. Patients were asked to delete items if the activity was not included in their daily life. Scores were obtained through summing the scores and averaging them by the amount of tasked scored by the participant. The next section comprises of a question regarding amounts of days (0-7) the previous week one felt good, in addition to how many days the previous week one missed work/housework due to fibromyalgia. The former was scored inversely, consequently a higher number on this item indicate greater amount of disability. The latter was scored 0-7. The last section comprises of a 10-increment scale on which patients were to mark severity of fatigue, pain, tiredness, stiffness, anxiety, and depression (Bennet, 2005). Marks between increments

were treated as an additional 0.5 points (Sigvaldsen, 2019). The questionnaire was translated to Norwegian and is supplemented in the appendix (appendix J).

Procedure

EEG acquisition. The EEG acquisition protocol involved a 26-minute recording with a 19-channel EEG in both a resting- and active-state. Patients were instructed to sit up-right in a comfortable chair in a soundproof room, at approximately 1.5 meters from a 22-inch computer screen during EEG recordings. This results in a visual angle of 5 degrees. Patients were reminded to relax their shoulders and jaw during recordings to reduce the number of muscular artifacts. EEG sessions were initiated with 180 seconds recording in resting state with eyes open (EO), directly followed by 180 seconds recording with eyes closed (EC). The limit of 180 seconds is applied to give a reliable spectrum with 4 s epochs (Kropotov, 2016). Thereafter, 20 minutes of behavioural sustained attention task (VCPT) was conducted.

VCPT. Visual continuous performance task (VCPT) was conducted using the software tool PsyTask (Mitsar, St. Petersburg, Russia). VCPT is a visual behavioural GO/NO-GO task, comprising of imaging pairs presented on a computer screen. Two images are presented for 100 milliseconds, with an inter-stimulus interval of 1000 milliseconds, and an inter trial interval of 3500 milliseconds. A total of 400 imaging pairs were displayed for a total 20 minutes, divided in four separate sequences of five minutes. Each sequence includes a total of 100 trials. Patients were given a short break between each sequence to reduce tiredness.

The visual stimuli can be divided in three categories: animal, plant and human. The VCPT comprised of four experimental conditions with image pairings: animal-animal (GO), animal-plant (NoGo), plant-plant (ignore) and plant-human (novel). In the last condition, stimuli of a human were paired with a sound calibrated at 60 dB SPL. Pictures in the GO and ignore condition were identical. The stimuli are illustrated in figure 2.

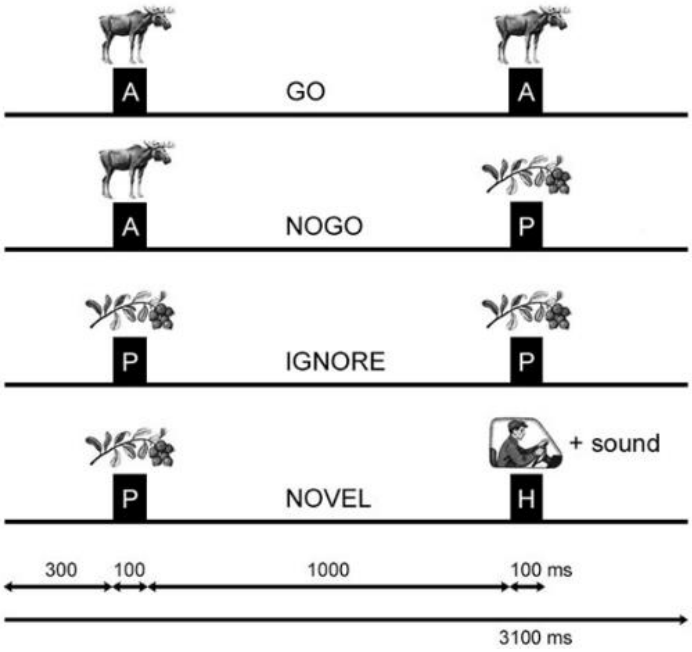

Figure 2. Stimulus conditions in VCPT.

Participants were instructed to rest their arm on a computer mouse, and to click with their right index finger at the animal-animal (GO) condition. Further on, participants were instructed to withhold a respond during the animal-plant (NoGo) condition. The remaining conditions were instructed to be ignored. Each participant underwent a trial in the presence of the examiner, to ensure fully understanding of the task to avoid effects of error. Both speed and accuracy were emphasized as of importance. In addition, the examiner stressed that the participant should try to relax their jaw and shoulders to avoid muscle artifacts.

ILF-NFT. Treatment sessions were initiated with a short conversation about how the patient was feeling. EEG-electrodes were places on T3-T4, with reference electrodes on Cz and forehead, in accordance with the 10-20 system. This positioning of the electrodes is a good starting point according to the literature (Othmer & Othmer, 2017). EEG signal was recorded with NeuroAmp DC-amplifier and processed by the Cygnet software (BEE medic GmbH). The patients were sitting in a comfortable chair resting both feet and their neck. Patients were provided with a headset, set at a comfortable volume. The feedback-animations were chosen by the patient each session (Somatic Vision Inc.). The animation changes in accordance with real-time amplitude changes in individual ILF, and training aimed at 0.05 Hz, varying in accordance with individual optimal response frequency (ORF) (Sigvaldsen, 2019*).* Treatment sessions lasted between 20-25 minutes, and during sessions each patient were prompted to give subjective reports of the experience. Originally, each patient was

aimed to receive a total of 15 trainings. Due to COVID-19, patients vary in the amount of completed sessions, which is reported in section 3.

EEG analysis

EEG data was acquired through WinEEG by Mitsar Inc. software version 2.81.25, and also used to perform QEEG analysis offline (Mitsar, St.Petersburg, Russia). Pre-processing included artifact correction and independent component analysis.

Artifact correction. Eyeblinks, eye movements and muscle movements produce noncerebral voltage changes in the EEG (Kropotov, 2016; Urigüen & Garcia-Zapirain, 2015). These ocular and muscular contaminations were treated as artifacts and corrected by the independent component analysis (ICA). Eye blinking is often related to Fp1 and Fp2 activity, whilst saccades are typically shown in F7 and F8. Myogenic, muscle, activity typically displays in Fp1 and Fp2 (forehead movement) and T3/T4 are related to jaw tension. In cases where cardioballistic artifacts were observed, they were removed as well (Kropotov, 2016). Residual data was visually inspected for artifacts not corrected by ICA and manually removed if needed.

***Independent component analysis*.** ICA is a correcting and separating technique applied to raw EEG data. ICA aims to extract independent spatial and temporal components in an EEG dataset, by utilizing a sophisticated algorithm based on blind source separation. Independent components include statistically independent, linear, and instantaneous sources, and those having a non-Gaussian probability density function are decomposed and sources of noise can be identified (Fox & Raichle, 2007; Kropotov, 2016). This allows for artifact correction. Residual data was visually inspected for artifacts not corrected by ICA and manually removed if needed.

Power spectra analysis. To analyse raw EEG data, it was processed by the algorithm Fast Fourier transform (FFT), to decompose the EEG signal into a rhythmic, sinusoidal pattern (Kropotov, 2016). Quantification of EEG data can be obtained through scores like spectral analysis, with power spectra indicating signal power at a temporal scale. Both absolute and relative power scores were computed for all patients (Dressler et al., 2004). However, this study focused on relative power (%) analysis, as this is preferred over absolute power estimation due to smaller error margins caused by the elimination of error sources like skull thickness (Kropotov, 2008, 2016) and has superior test-retest reliability (Salinsky et al., 1991; Sigvaldsen, 2019). Both grand average and individual power spectra analysis was

performed and compared to a database of age-matched healthy controls. For individual power spectra analysis, the largest significant deviation from each electrode were chosen (Sigvaldesen, 2019).

Standardized low-resolution brain electromagnetic tomography (sLORETA) algorithm was applied to localize potential source generations of oscillatory activity (Kropotov, 2016). In cases where sLORETA was able to localize potential source generators, top 3 best matches were reported (see table 9-14).

Data analysis

Power spectra and source analysis. Relative power spectra (%) was calculated and computed by Mitsar WinEEG 2.129.100 to identify significant qEEG deviations between patients and a healthy age-matched database. This was obtained through an internal t-test within Mitsar WinEEG software. Source analysis was conducted through sLORETA. For clinical data and brain frequency amplitude, statistical analysis was performed in SPSS (version 26.0.0.0)

Assumption of normality and linearity. Due to the small sample size, the assumption of normality was carefully investigated with various techniques. The small sample size makes normality of great importance in the usage of parametric tests, as the central limit theorem is not applicable. Also, a small sample size can also lack enough power to detect any violations of the assumptions needed for parametric tests (Field, 2013). Therefore, checking the assumption of normality was based on both Shapiro Wilk, skewness, and kurtosis, in addition to P-P and Q-Q plots. Shapiro Wilk is an appropriate test for sample sizes beneath 50 participants, also it has more power to detect deviations from normality compared to Kolmogorov-Smirnoff test (Field, 2013).

Shapiro-Wilk, in addition to skewness and kurtosis, was checked for all variables to look for variables that significantly deviated from a normal distribution. A visual inspection of histograms and Q-Q plots was also conducted to fully check for the assumption of normality. Some of the variables fulfilled criteria of normality, but most of them did not. Since several variables did not fulfilled the assumptions of normality, in addition to a small sample size, non-parametric tests were conducted to avoid Type 1 error. Parametric tests are generally preferred and considered the most robust type of statistical analysis. However, this is only true when the assumptions are met. In larger sample sizes the assumption of normality is not as important, as the sampling data often distributes normally around the population

mean. For correlational analysis, Kendall's Tau and Spearman's Rho was conducted. For pre- and post-test comparisons a Wilcoxon Signed-Rank Test was conducted.

Mann-Whitney U. For all variables, the mean, standard deviation, and range were reported in appendix E. Since the two groups were recruited at different time points, a Mann-Whitney U was conducted to identify significant differences in key variables, which could influence the statistical output. These variables include age and psychometrics (VAS, FIQ and ACR) pre-treatment. Since some of the variables did not fulfil the criteria of normality, this non-parametric test was preferred over the student t-test (Field, 2013).

Correlation analysis. Statistical nonparametric tests were applied to look for correlation between clinical and EEG data. Correlational analysis between variables were calculated by computing Spearman's correlation and Kendall's tau (τ). Kendall's tau is suggested to display superior generalizability on small sample sizes with small variations in score ranks compared to Spearman's rho (r_s) (Field, 2013). However, since Kendall's tau does not provide insight into the strength of the relationship or intervariable variance, therefore Spearman's rho was included when reporting Kendall's tau and used as a measurement of effect size (Field, 2013).

Wilcoxon Signed-Rank Test. Pre- and post-test comparisons of qEEG parameters and clinical data were conducted with the nonparametric analysis Wilcoxon Signed-Rank test. The alpha-level of significance were set at 0.05. To calculate the effect size of the significant pre- and post-differences as identified by Wilcoxon Signed-Rank test, by converting the test-statistics to z-scores and calculating Pearson's *r*. Whereas $r = .10$ indicates a small effect, $r = .30$ indicates a medium effect and $r > .50$ indicates a large effect (Field, 2013). As a lack of data due to COVID-19 and subject recruiting at different time points, efforts to replicate separate Wilcoxon Signed-Rank Tests were conducted for group 1. This was to fully ensure that the groups were homogeneous regarding potential treatment effects. Hence, some analysis is reported twice.

Results

Mean and standard deviation for pre-treatment variables including age, ACR-, FIQ- and VAS- scores are summarized in table 5. A total of 23 women met the inclusion criteria for data processing in the preliminary analysis of potential qEEG markers of fibromyalgia. Pre- and post-treatment comparisons of qEEG data were only available for 13 patients, whilst pre- and post-treatment comparisons of psychometric and behavioural scores were available for 20 patients. 12 patients completed 15 sessions of ILF-NFT, 2 completed 14 sessions, 3

completed 13 sessions, 4 completed 12 sessions and the last 2 participants completed 10 and 9 sessions each.

The groups were compared in age and psychometrics. A Mann-Whitney U test indicate that there are no significant differences between the two patient-groups who were recruited at different time points in neither age, pain-levels, fatigue, fibro-fog, ACR nor FIQ (See table 6).

Table 5

Overview of demographics and questionnaire responds pre-treatment (N = 23)

Variable	*M*	*SD*
Age	46.43	10.17
ACR	20.09	5.49
FIQ	63.03	13.41
VAS pain	64.11	13.41
VAS fatigue	67.04	12.72
VAS fibro-fog	59.96	22.90

Note. *M*=mean, *SD*= standard deviation, ACR= American College of Rheumatology, FIQ=fibromyalgia impact questionnaire

Table 6

Mann-Whitney U output for between group comparisons of age and psychometrics

	Group 1 (*N*=13)		Group 2 (*N*=10)				
	M (*SD*)	*Mdn*	*M* (*SD*)	*Mdn*	*U*	*Z*	*p*
Demographics							
Age	46.77 (11.73)	48.00	46.00 (8.31)	47.00	119.00	-.06	.976
Psychometrics							
VAS Pain	62.00 (12.96)	64.00	66.85 (12.20)	69.75	134.00	.87	.410
VAS Fatigue	65.92 (13.99)	70.00	68.50 (11.42)	66.50	125.00	.31	.784
VAS Fibro-fog	58.65 (26.95)	62.50	61.65 (17.54)	56.50	125.00	.31	.784

ACR	20.00 (4.54)	19.00	20.20 (6.80)	19.00	125.00	.31	.784.
FIQ	65.89 (13.49)	69.68	59.33 (13.05)	63.37	102.00	-1.12	.284

Note. *M* = mean, *SD* = standard deviation, *Mdn* = median, VAS = visual analogue scale, ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire

Preliminary findings

Grand average power spectra analysis. To identify group differences from healthy controls, power spectra from patients were superimposed. Grand average power spectra were conducted for all patients before treatment (*N*=23), group 1 (*N*=13) before and after treatment, and group 2 (*N*=10) before treatment in all conditions. No significant deviations were identified for the patient group on average before treatment.

Power spectra for individual patients. Individual power spectra were compared to a normative age-matched database. This found that all patients deviate in one or more frequency band per condition (EO, EC, VCPT). A table viewing all deviations pre-treatment from norm in relative power (%) can be viewed in table 9-14. Where position estimates were obtained (BA), these are reported in the tables. However, some of the significant deviations were not identified by sLORETA (Sigvaldsen, 2019).

Table 7

Percentage of patients with significant deviations before treatment, all patients (N=23)

		EO	EC	VCPT
Theta	Temporal	13.04%	4.35%	13.04%
	Frontal	30.43%	30.43%	30.43%
	Central	4.35%	13.04%	4.35%
	Parietal	13.04%	0%	0%
Alpha	Temporal	0%	13.04%	17.39%
	Frontal	13.04%	0%	4.35%
	Central	4.35%	4.35%	13.04%
	Parietal	43.47%	4.35%	30.43%

Beta	Temporal	8.70%	26.08%	4.35%
	Frontal	47.82%	21.73%	52.17%
	Central	39.13%	60.86%	34.78%
	Parietal	21.73%	56.52%	26.08%

Note. EO = Eyes opened, EC = Eyes closed, VCPT = Visual Continuous Scale

Table 8

Number of patients (%) presenting with significant deviances in relative power spectra for all conditions, pre-treatment (N=23)

Frequency band	Cortical area	Pre-treatment
Theta	Total	78.26%
	Temporal	26.08%
	Frontal	60.86%
	Central	21.73%
	Parietal	13.04%
Alpha	Total	78.26%
	Temporal	17.39%
	Frontal	13.04%
	Central	17.39%
	Parietal	47.82%
Beta	Total	91.30%
	Temporal	30.43%
	Frontal	60.86%
	Central	73.91%
	Parietal	65.21%

All patients (*N*=23) across conditions, 91.30% deviated in the beta frequency, 78.26% patients deviated in the alpha frequency, 78.26% % presented with deviations in the theta band. When examining each frequency band, most patients deviated from healthy controls in frontal theta (60.86%), frontal beta (60.86%, central beta (73.91%) and parietal beta (65.21%). When analysing each condition, frequency band and cortical region, individual power spectra show that most patients displayed deviations in eyes open frontal beta

(47.82%), central beta (39.13%) and parietal alpha (43.47%). In addition to eyes closed central beta (60.86%) and parietal beta (56.52%). For the VCPT, about 52% of patients presented with a frontal beta deviation (see table 7).

For group 1 (*N*=13), almost all patients (92.30%) presented with one or more deviation in the beta frequency across all conditions. Most patients also presented with deviations in the alpha frequency (84.62%) and theta frequency (76.92%) before treatment, across all conditions. Most prominent findings from individual power spectra calculations are that most patients had abnormalities in the parietal alpha band (69.23%), frontal theta (53.85%), in addition to parietal (46.15%) and frontal beta (53.85%) (see table 11).

Table 9

Group 1 (N=13). Significant individual deviations in relative power spectra EEG, compared to normative database. Eyes opened (EO) condition, pre treatment

Frequency band	Cortical site	FIB0034	FIB0035	FIB0036	FIB0037	FIB0039	FIB0040	FIB0041	FIB0042	FIB0044	FIB0046	FIB0047	FIB0048	FIB0049
Theta	Temporal				1.759* BA 22-40-39									
	Frontal		1.659*** Missing								2.96** Missing			-1.26** Missing
	Central											-0.76* Missing		
	Parietal						-0.88* Missing	1.26* Missing						
Alpha	Temporal													
	Frontal									-1.51* missing				
	Central			3.125** BA: 6-32-24										
	Parietal	-3.001* Missing	7.671* BA: 39-22-19			-2.130* Missing	16.92** BA: 19-7-18	-1.36* Missing			-1.26* Missing		8.18** BA: 17-18-19	-2.33* Missing
Beta	Temporal				0.959* Missing									
	Frontal	1.274* BA: 10-11-32	1.197** 47-11-10	1.173*** BA: 10-46-11					0.90* BA: 10-46-47					1.09** Missing
	Central									0.81** Missing		0.53* BA: 11-10-32	1.29** BA: 2-1-5	1.15** Missing
	Parietal			1.484*** BA: 19-7-39		0.907* Missing								1.32* BA:7-40-5

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table 10

Group 1 (N=13). Significant individual deviations in frequency bands compared to normative database. Eyes closed (EC) condition, pre treatment

Frequency band	Cortical site	FIB0034	FIB0035	FIB0036	FIB0037	FIB0039	FIB0040	FIB0041	FIB0042	FIB0044	FIB0046	FIB0047	FIB0048	FIB0049
Theta	Temporal													
	Frontal			-1.459* Missing				2.24* Missing	-1.58* Missing			-1.11* Missing		-1.05* Missing
	Central			-1.459* Missing				4.73** BA: 10-46-32						
	Parietal													
Alpha	Temporal		13.050* 18-19-17						20.43* BA: 39-22-19					
	Frontal													
	Central					1.299* BA: 40-39-7								
	Parietal												14.89* BA: 19-18-17	
Beta	Temporal		0.407* Missing		1.614** Missing				-0.04** Missing	1.44** BA:21-20-22	0.76** Missing			
	Frontal			1.320*** BA: 10-46-11		0.316** Missing				1.34*** BA: 10-46-47				0.88*** Missing
	Central	0.248* Missing	0.437* BA 7-19-31		0.295* Missing			0.46* Missing		0.79*** BA: 8-6-9	0.16* Missing	0.71*** BA: 6-24-31	1.04*** BA: 4-3-6	0.71* BA: 10-11-32
	Parietal	0.455* Missing		1.326* Missing				0.46* Missing				1.55* Missing		

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table 11

Group 1 (N=13). Significant individual deviations in frequency bands compared to normative database. Relative power VCPT condition, pre treatment

Frequency band	Cortical site	FIB0034	FIB0035	FIB0036	FIB0037	FIB0039	FIB0040	FIB0041	FIB0042	FIB0044	FIB0046	FIB0047	FIB0048	FIB0049
Theta	Temporal							1.41* Missing						
	Frontal			-1.659*** Missing								-1.12* Missing		-1.35** Missing
	Central												-0.77* Missing	
	Parietal													
Alpha	Temporal							2.25* BA: 37-19-39						2.39* BA: 37-19-39
	Frontal													
	Central			1.564* BA: 11-10-32										
	Parietal	-2.997* Missing	8.420* BA: 40-39-7			-1.301** Missing	5.05* BA 7-19-31			4.35* BA: 4-3-2			7.50** BA: 19-7-39	
Beta	Temporal									0.99* BA: 21-20-22				
	Frontal	1.188* BA:10-9-46	0.680* Missing	0.404* Missing		2.120*** BA: 11-10-47				1.78** BA: 46-10-45				1.49** Missing
	Central							0.49* Missing				0.46* Missing	1.33*** BA: 6-4-8	0.77* Missing
	Parietal			1.387** BA. 40-7-39								1.25* BA: 40-7-39		

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table 12

Group 2 (N=10). Significant individual deviations in relative power spectra EEG compared to normative database. Eyes opened (EO) condition, pre treatment

Frequency band	Cortical site	FIB0051	FIB0052	FIB0053	FIB0054	FIB0055	FIB0056	FIB0057	FIB0058	FIB0059	FIB0060
Theta	Temporal	8.04*** Missing		1.31* Missing							
	Frontal		-1.67*** Missing			-1.13* BA 38-21-47	-1.10* missing				-0.69* Missing
	Central										
	Parietal	3.00* Missing									
Alpha	Temporal										
	Frontal		10.53*** Missing						-0.69* Missing		
	Central										
	Parietal			-2.33* Missing		5.07* Missing					
Beta	Temporal							0.85* BA 37-19-39			
	Frontal			0.87* Missing	0.75** BA 47-11-10	0.80** Missing		1.25** Missing	0.82** Missing	0.48* Missing	
	Central		1.99*** BA 2-40-1				0.67* Missing		1.04* Missing	0.78** BA 6-4-5	1.93*** BA 22-21-42
	Parietal			3.01** Missing			1.12** Missing				

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table 13

Group 2 (N=10). Significant individual deviations in relative power spectra EEG compared to normative database. Eyes closed (EC) condition, pre treatment

Frequency band	Cortical site	FIB0051	FIB0052	FIB0053	FIB0054	FIB0055	FIB0056	FIB0057	FIB0058	FIB0059	FIB0060
Theta	Temporal					13.96*** Missing					
	Frontal			1.99* BA 6-4-31						-1.06* Missing	
	Central	2.11* BA 21-22-20									
	Parietal										
Alpha	Temporal						1.81* BA 18-17-19				
	Frontal										
	Central										
	Parietal										
Beta	Temporal										5.74*** BA 19-39-18
	Frontal					0.40* Missing			1.01*** Missing		
	Central		1.24*** Missing	0.65*** Missing			0.82** Missing	0.48*** Missing			1.71*** BA 3-1-4
	Parietal	0.14* Missing	0.78** BA 6-4-3	5.11*** BA 6-4-31	0.70* Missing		1.44*** BA 19-18-39	0.68** BA 19-18-7	1.00* Missing	1.47*** Missing	1.93*** Missing

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table 14

Group 2 (N=10). Significant individual deviations in relative power spectra EEG compared to normative database. Visual continuous task (VCPT) condition, pre treatment

Frequency band	Cortical site	FIB0051	FIB0052	FIB0053	FIB0054	FIB0055	FIB0056	FIB0057	FIB0058	FIB0059	FIB0060
Theta	Temporal	2.37*** BA 19-18-37								1.27* Missing	
	Frontal			1.34* Missing	-0.76* Missing		-1.01* Missing				-0.86* Missing
	Central										
	Parietal										
Alpha	Temporal					4.13*** BA 22-40-39					1.53* Missing
	Frontal		9.44*** Missing								
	Central							1.23* Missing	2.38** BA 6-4-3		
	Parietal					5.80* BA 5-2-3					
Beta	Temporal										
	Frontal		1.17** Missing	1.04** BA 11-10-32	0.95* Missing	0.64* BA 11-10-32		1.19** BA 47-11-10	0.77** Missing		
	Central		1.07** BA 6-4-3				0.44* Missing			0.42* Missing	1.54*** BA 2-40-3
	Parietal			3.45*** BA 4-3-5			1.00** Missing	0.76* BA 7-5-40			

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Source analysis. In accordance with a previous study, source analysis found all subjects to deviate in all relevant DPC Brodmann areas except for BA 27 and BA 33 (Sigvaldsen, 2019). sLORETA and source location found over 50% of the FM patients to

reveal significant deviances in BA 10. Approximately 50% of the FM patients deviated significantly from healthy controls in Brodmann 39, which includes cortical regions such as the inferior parietal lobule, angular gyrus, and Wernicke's area.

Table 10

Power spectra deviations associated with Brodmann areas in the DMN, pre-treatment (N=23)

Brodmann area	% of deviations, best match
9	17.39 %
10	52.17 %
13	4.35 %
21	30.43 %
23	8.70 %
24	13.04 %
27	0 %
32	32.78 %
33	0 %
39	52.17%
44	4.35%
45	13.04 %
46	26.09%
47	26.09 %

Correlation analysis. Kendall's tau (τ) and Spearman's rho (r_s) were applied to investigate a statistical relationship between brain frequencies and psychometrics before patients received ILF-NFT. A total of five statistically significant relationships were identified. The correlation matrix can be viewed in appendix C. Correlation analysis between ACR scores and brain frequencies identified that ACR scores was negatively associated with theta temporally before treatment ($\tau(23) = -.335$, $p = .028$; $r_s(23) = -.471$, $p = .023$). Additionally, ACR scores revealed a negative relationship with the beta band in temporal areas of the FM patient group ($\tau(23) = -.327$, $p = .032$; $r_s(23) = -.464$, $p = .026$). Before treatment, pain-scores was negatively associated with theta frontally ($\tau(23) = -.323$, $p = .032$; $r_s(23) = -.466$, $p = .025$) and beta temporally ($\tau(23) = -.323$, $p = .032$; $r_s(23) = -.451$, $p =$

.031). Fatigue scores was negatively correlated with theta centrally (τ(23) = -.302, p = .045; r_s(23) = .461, p = .027). Reports of fibro-fog did not reveal any significant correlation between neither brain frequencies.

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Grand average spectra. Calculation of the grand average spectra of group 1 (N=13) found subjects to present with a deviation in the theta frequency localized at the frontocentral (Fz, Cz) electrodes (5.62 Hz, p=.0001), see figure 3.

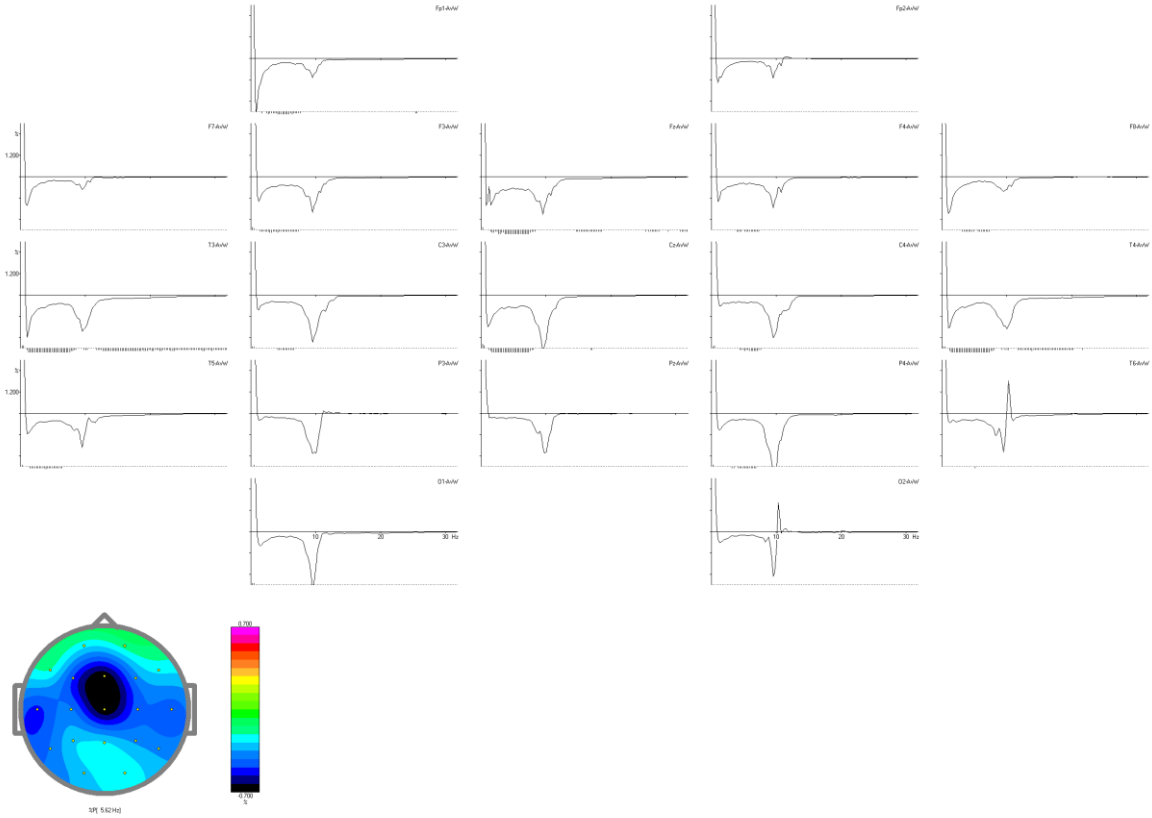


Figure 3. Grand average spectra of patients in group 1 (N=13) compared to a normative age-matched controll database, calculated for the relative power (%), EC condition, post treatment

Brain frequencies Patients in group 1 displayed significantlly less frontal beta amplitude from pre-treatment (*mdn* = 2.01) to post-treatment (*mdn* = 1.54), z = -2.55, p = .011, N = 13, r = -0.50). In addition, patients presentets with a significant increase in parietal alpha when comparing EEG amplitude pre-treatment (*mdn* = 1.75) to post-treatment (*mdn* = 6.43), z = 3.18, p = .001, N = 13, r = 0.62. This was also true for parietal theta amplitude

when comparing pre-treatment (*mdn* = 0.85) to post-treatment (*mdn* = 2.69), *z* = 3.18, *p* = .001, *N* = 13, *r* = 0.62, likewise for parietal beta amplitude pre-treatment (*mdn* = 1.51) compared to post-treatment (*mdn* =5.55), *z* = 3.18, *p* = .001, *N* = 13, *r* = 0.62 There was no significant changes in brain frequencies in other frequency bands or other cortical areas.

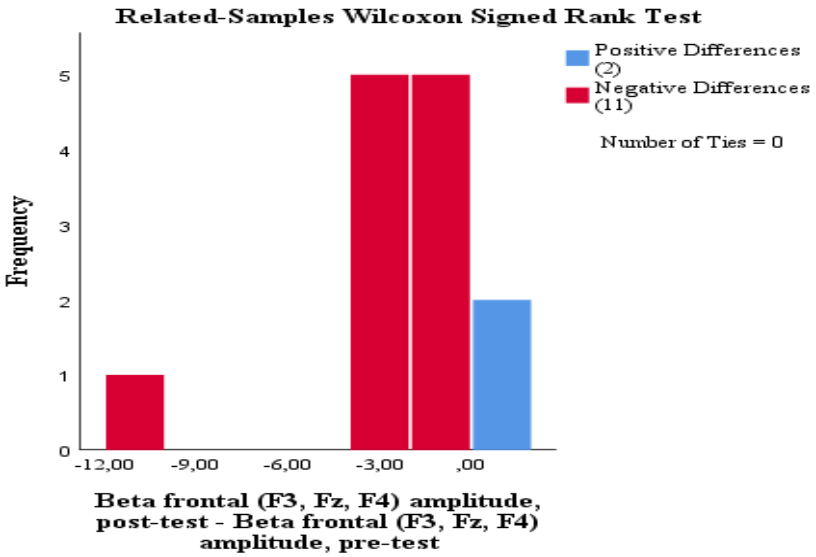


Figure 4. Histogram of output from Wilcoxon Signed-Rank Test for frontal beta amplitude, pre- versus post-test (*N*=13). The negative different in scores imply that patients presented with significant lower frontal beta amplitude after ILF-NFT. While 11 patients reported a decline in frontal beta, 2 patients displayed an increase.

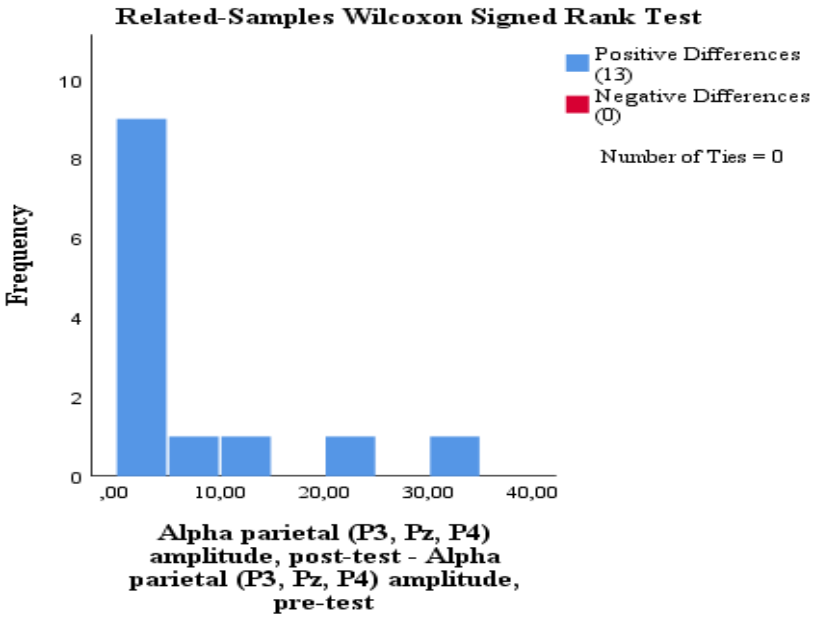


Figure 5. Histogram of output from Wilcoxon Signed-Rank Test for parietal alpha amplitude, pre- versus post-test (*N*=13). The positive different in scores imply that patients presented with significant increase of parietal alpha after ILF-NFT.

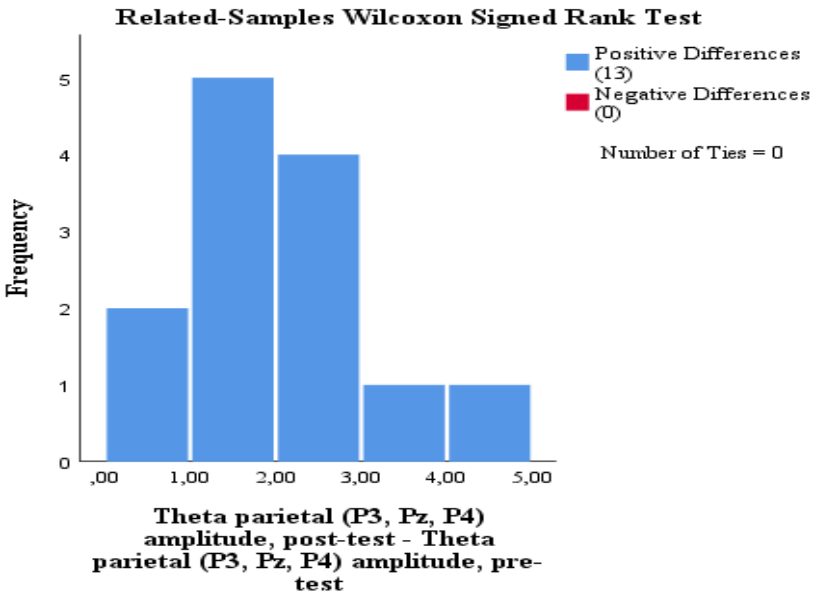


Figure 6. Histogram of output from Wilcoxon Signed-Rank Test for parietal theta amplitude, pre- versus post-test (*N*=13). The positive different in scores imply that all patients presented with significant increase of parietal theta amplitude after ILF-NFT.

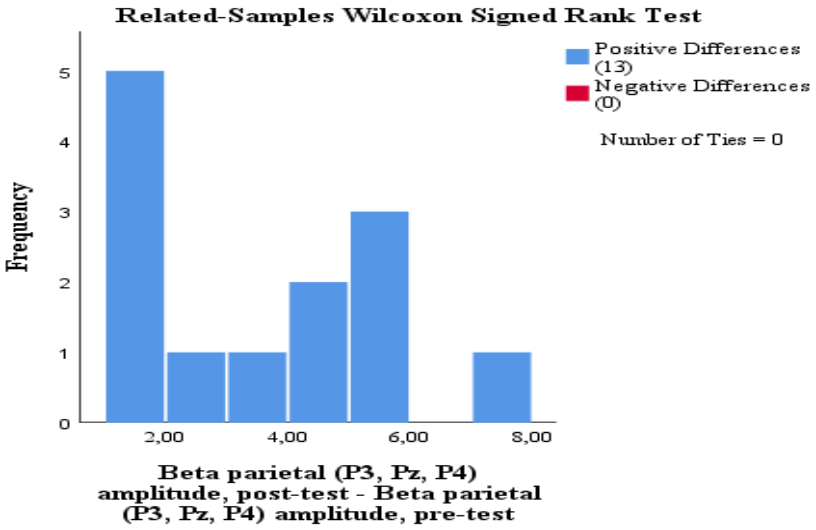


Figure 7. Histogram of output from Wilcoxon Signed-Rank Test for parietal beta amplitude, pre- versus post-test (*N*=13). The negative different in scores imply that patients presented with significant increase of parietal beta amplitude after ILF-NFT.

***Symptom measurements, all patients*.** There was a reduction in all symptoms associated with fibromyalgia for all 20 patients that completed the self-report questionnaire following treatment. Patients displayed a significant decrease in ACR scores from pre-treatment (*mdn* =19.00) to post-treatment (14.50), *z* = -3.56 , *p* = .000, *N*= 20, *r*= -.56) and FIQ-scores pre-treatment (*mdn* = 65.10) compared to post-treatment (mdn = 44.12), *z* = -3.85, *p* = .000, *N* = 20, r =-0.61. Patients report a significant reduction in pain when comparing pain levels pre-treatment (*mdn* = 66.00) to post-treatment (*mdn* = 40.00), *z* = -3.78, *p* =.000, *N* = 20, r =-0.60. Additionally, fatigue-levels pre-treatment (*mdn* = 67.00) versus post-treatment (*mdn* = 45.25), *z* = -3.10, *p* = .002, *N* = 20, *r* = -0.49 and fibro-fog scores pre-treatment (*mdn* = 59.00) versus post-treatment (*mdn* = 40.50) was reduced, *z* = -3.18, *p* = .002, *N* = 20, r = -0.50.

***Symptom measurements, group 1*.** In group 1, patients presented with significant more ACR-scores before treatment (*mdn* = 19.00) compared to after treatment (*mdn* =14.00), *z* = -2.87, *p* =.004, N = 13, r =-.56. FIQ scores before treatment (*mdn* = 69.68) had a significant decline following treatment (mdn = 45.92), *z* = -3.11, *p* =.002, N = 13, r =-.61. Pain-scores after treatment (*mdn* = 40.00) were significantly reduced compared to before treatment (*mdn* = 64.00), *z* =-3.06, *p* = .002, N = 13, r = -.60. The same was true for fatigue, with higher fatigue levels before (*mdn* = 70.00) compared to after treatment (*mdn* = 37.00), *z* = -3.01, *p* =.003, N = 13, r = -.59, and fibro-fog scores before (*mdn* = 62.50) and after (*mdn* = 32.00) treatment, *z* = -2.97, *p* = .003, N = 13, r = -.58. Reaction -time before treatment (*mdn* = 332.00) was significantly slower compared to after ILF-NFT treatment (*mdn* =319.00), *z* = -3.12, *p* = .002, N = 13, *r* =-.61, with less variability after (*mdn* = 6.20) compared to before (*mdn* = 7.00) treatment, *z* = -2.71, *p* = .007, N = 13, *r* =-.53.

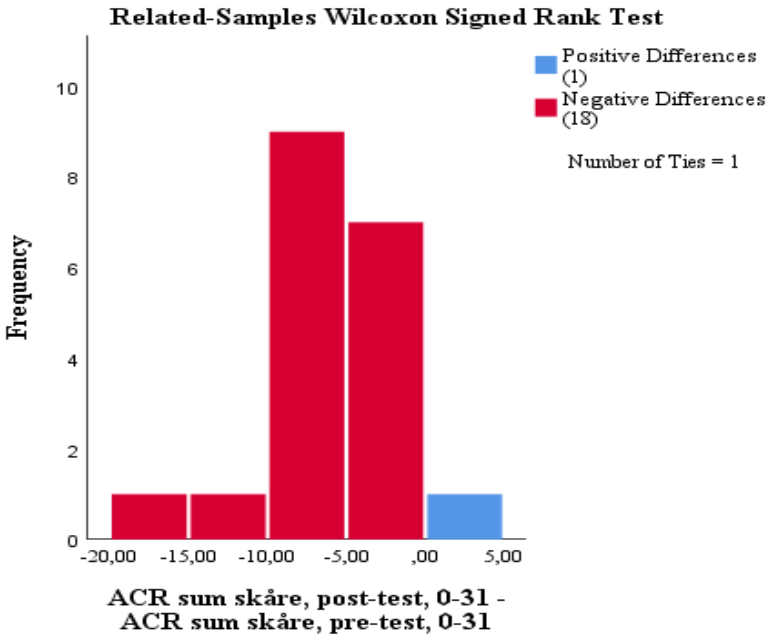


Figure 8. Histogram of output from Wilcoxon Signed-Rank Test for ACR-scores pre- versus post-test (*N*=20). The negative different in scores imply that patients presented with significant lower ACR scores following ILF-NFT. While 18 patients had a decrease in ACR scores, 1 patient had an increase in score, whilst 1 patient had the same score both before and after treatment.

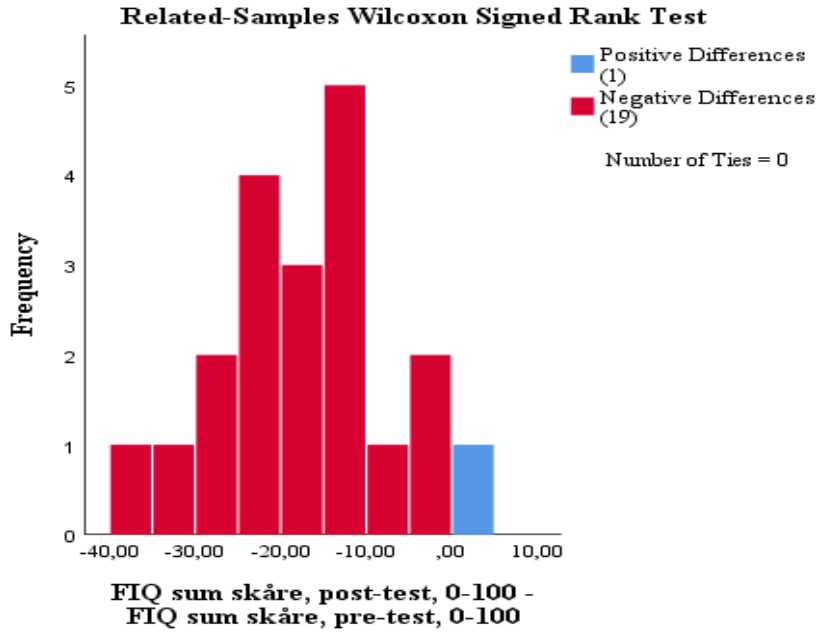


Figure 9. Histogram of output from Wilcoxon Signed-Rank Test for FIQ-scores pre- versus post-test (*N*=20). The negative different in scores imply that patients presented with significant lower FIQ-scores following ILF-NFT. While 19 patients had a decrease in ACR scores, 1 patient had an increase in score compared to before treatment.

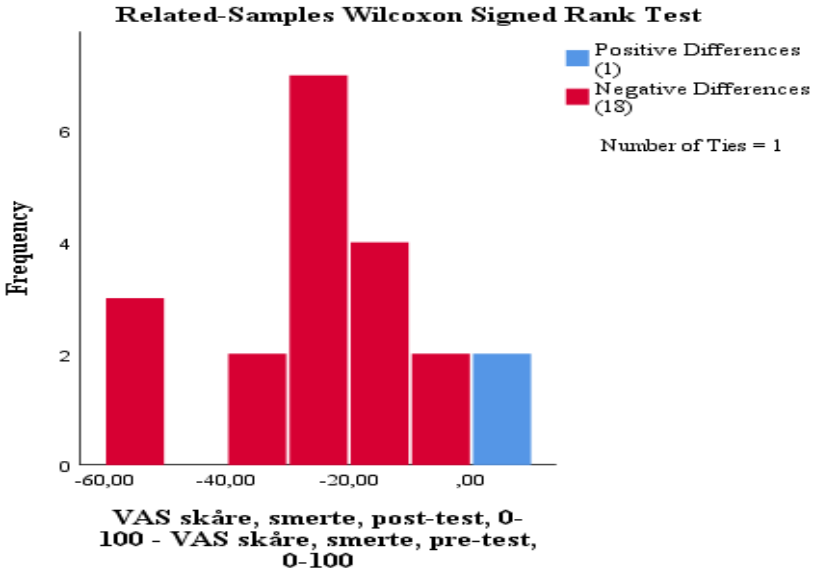


Figure 10. Histogram of output from Wilcoxon Signed-Rank Test for pain-scores pre- versus post-test (*N*=20). The negative different in scores imply that patients presented with significant lower pain following ILF-NFT. While 18 patients had a decrease in pain-scores, 1 patient had an increase in pain, whilst 1 patient had the same score both before and after treatment.

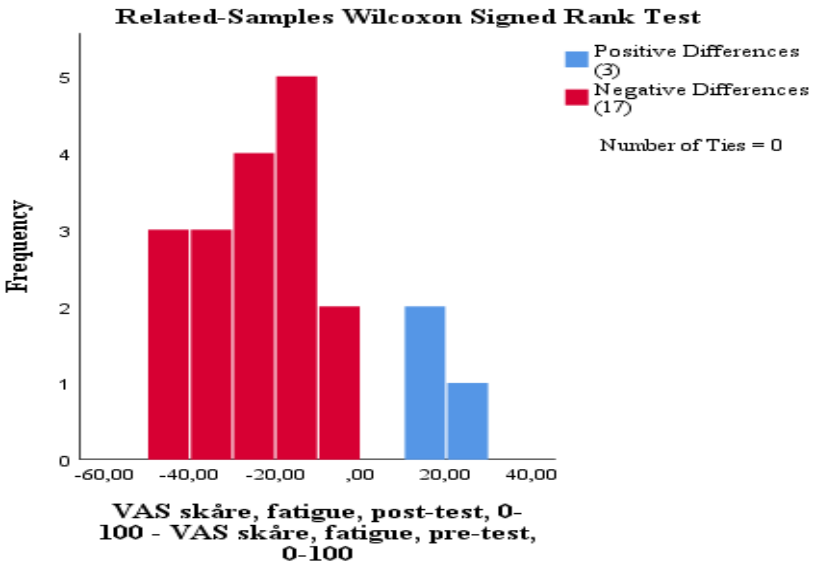


Figure 11. Histogram of output from Wilcoxon Signed-Rank Test for fatigue-scores pre- versus post-test (*N*=20). The negative different in scores imply that patients presented with significant lower fatigue following ILF-NFT. While 17 patients had a decrease in fatigue-scores, 3 patients had an increase in fatigue.

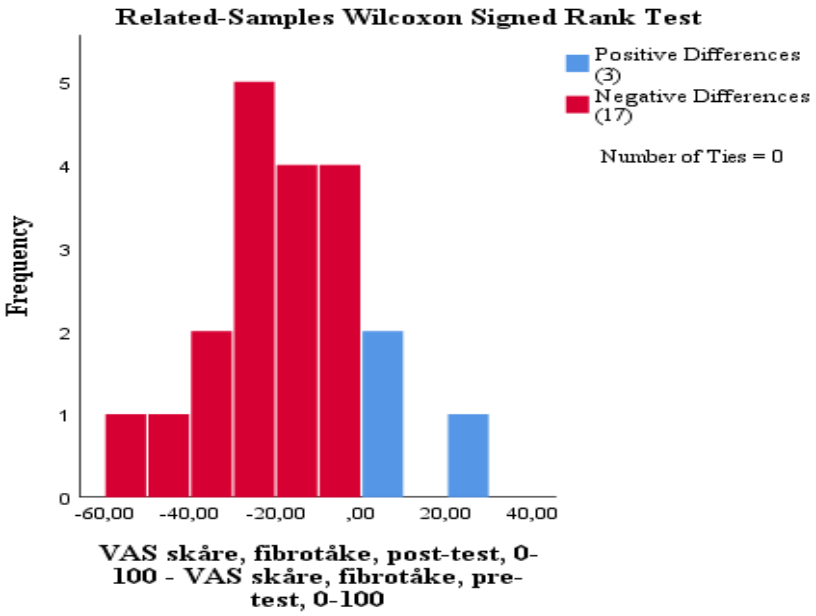


Figure 12. Histogram of output from Wilcoxon Signed-Rank Test for fibro-fog-scores pre- versus post-test (*N*=20). The negative different in scores imply that patients presented with significant lower fibro-fog following ILF-NFT. While 17 patients had a decrease in fibro-fog-scores, 3 patients had an increase in fibro-fog.

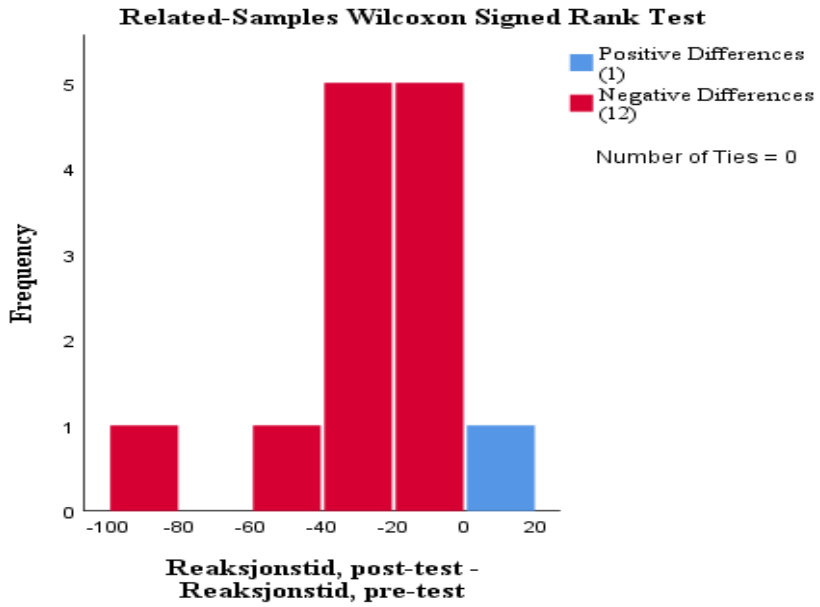


Figure 13. Histogram of output from Wilcoxon Signed-Rank Test for reaction-time pre- versus post-test (*N*=13). The negative different in scores imply that patients presented with significant lower reaction-time following ILF-NFT. While 12 patients had a decrease in reaction-time, 1 patient had an increase in reaction-time.

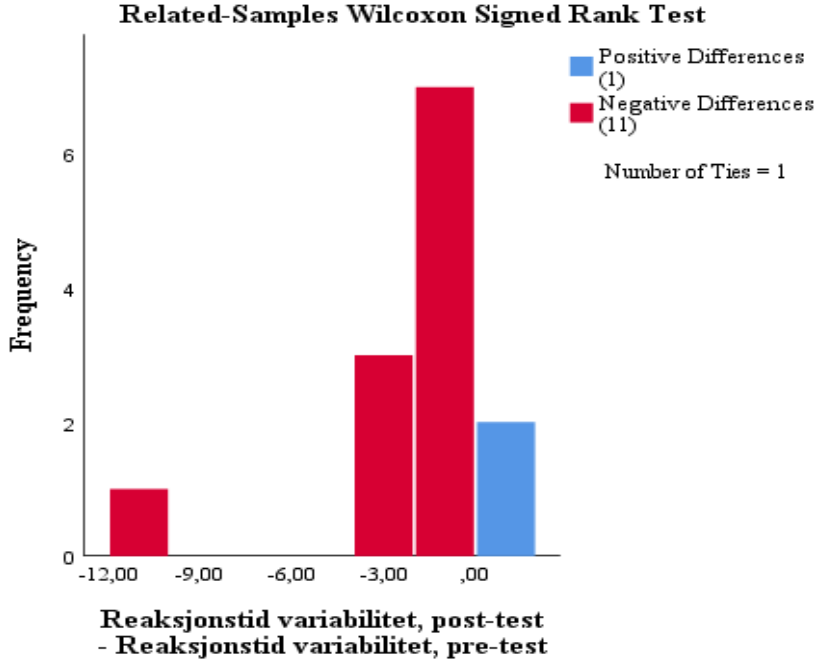


Figure 14. Histogram of output from Wilcoxon Signed-Rank Test for reaction-time variability pre- versus post-test (*N*=13). The negative different in scores imply that patients presented with significant lower reaction-time variability following ILF-NFT. While 12 patients had a decrease in reaction-time, 2 patients had an increase in reaction-time.

Follow-up. A total of 7 patients participated in the 3-month follow-up questionnaire, whereby 6 patient reports are missing. The only measurement to reach statistical significance was the continued improvement in amount of ACR scores before treatment (*mdn* = 19.00) compared to after treatment (*mdn*= 17.00), *z* = -2.05, *p* =.041, *N* = 7, *r* = -.55

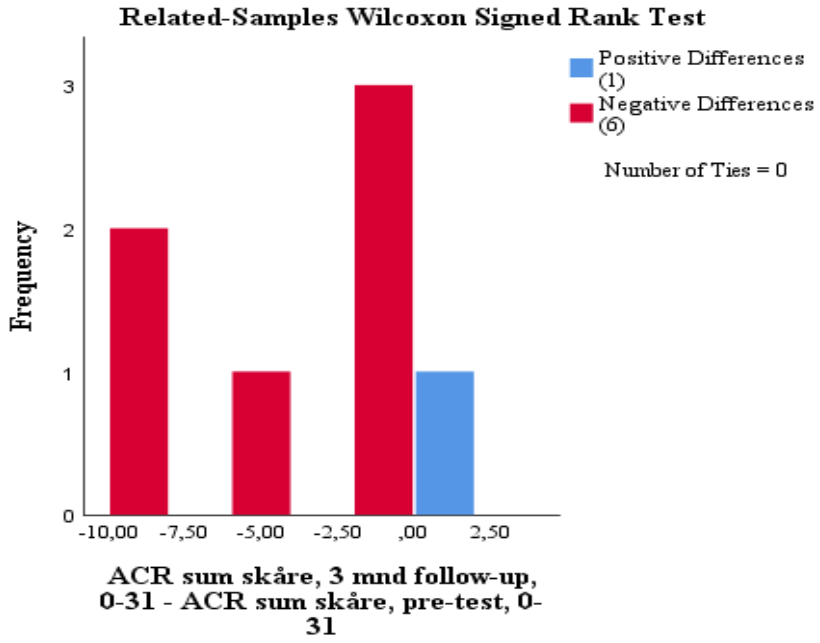


Figure 15. Histogram of output from Wilcoxon Signed-Rank Test for ACR-scores pre-treatment versus 3-month follow-up (*N*=7). The negative different in scores imply that patients presented with significant lower ACR scores 3 months following ILF-NFT. While 6 patients had a decrease in ACR scores, 1 patient had an increase in score.

Pre- and post-treatment comparisons of power spectra. A total of 13 patients were included in pre- and post-treatment comparisons. Pre- and post-treatment comparison of subject deviation from all conditions, revealed that most of the frequency bands and cortical regions increased their deviations following treatment of 13 patients. Hence, compared to a

healthy control database, more deviations were found on average after treatment with neurofeedback.

Table 11

Number of patients (%) presenting with significant deviances in relative power spectra analysis for all conditions, pre- versus post-treatment (N=13).

Frequency band	Cortical area	Pre-treatment	Post-treatment
Theta	Total	76.92%	84.61%
	Temporal	15.38%	23.07%
	Frontal	53.85%	69.23%
	Central	30.77%	30.77%
	Parietal	15.38%	7.69%
Alpha	Total	84.62%	92.23%
	Temporal	30.77%	38.46%
	Frontal	7.69%	7.69%
	Central	15.38%	7.69%
	Parietal	69.23%	69.23%
Beta	Total	92.30%	100%
	Temporal	38.46%	53.85%
	Frontal	53.85%	53.85%
	Central	53.84%	69.23%
	Parietal	46.15%	53.85%

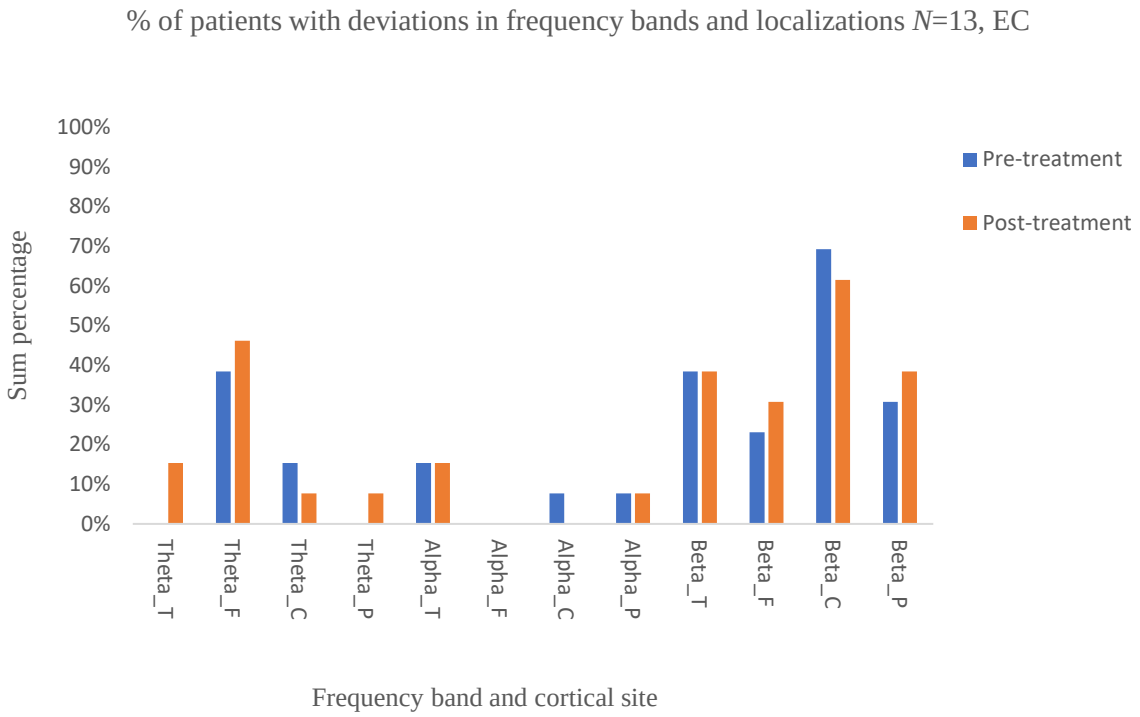


Figure 16. Bar-chart of the amount of deviations during eyes open, with pre- and post-test comparisons. _T = Temporal, _F = Frontal, _C = Central, _P = Parietal , *N* = 13

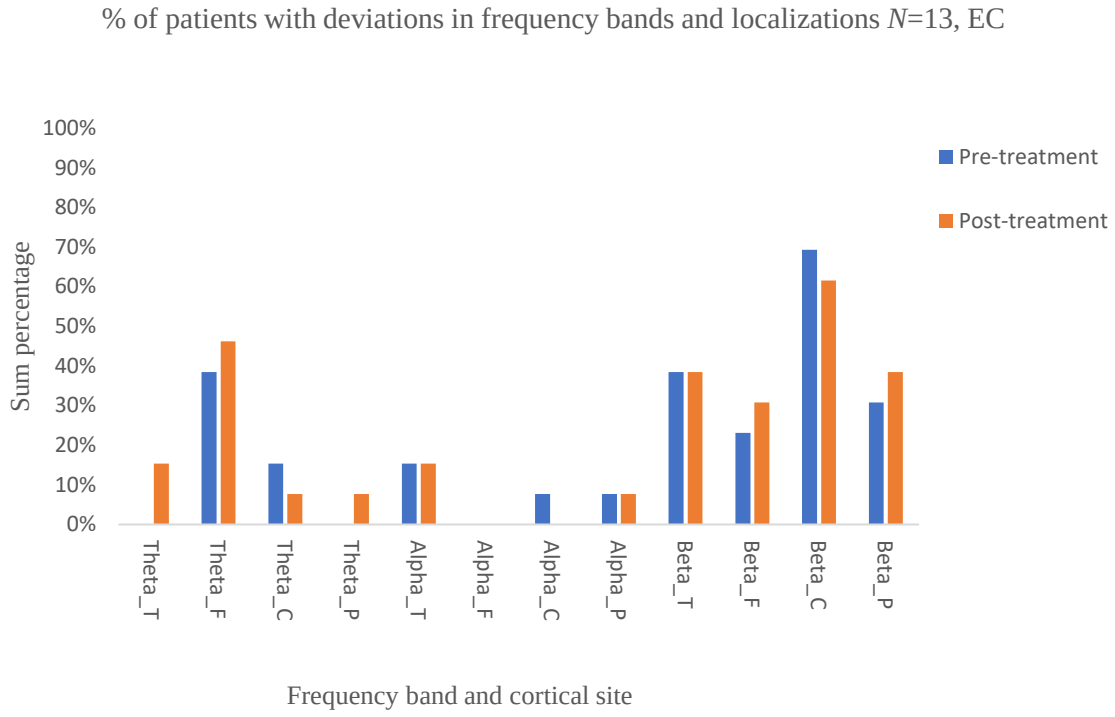


Figure 17. Bar-chart of the amount of deviations during eyes closed, with pre- and post-test comparisons. _T = Temporal, _F = Frontal, _C = Central, _P = Parietal, *N* = 13

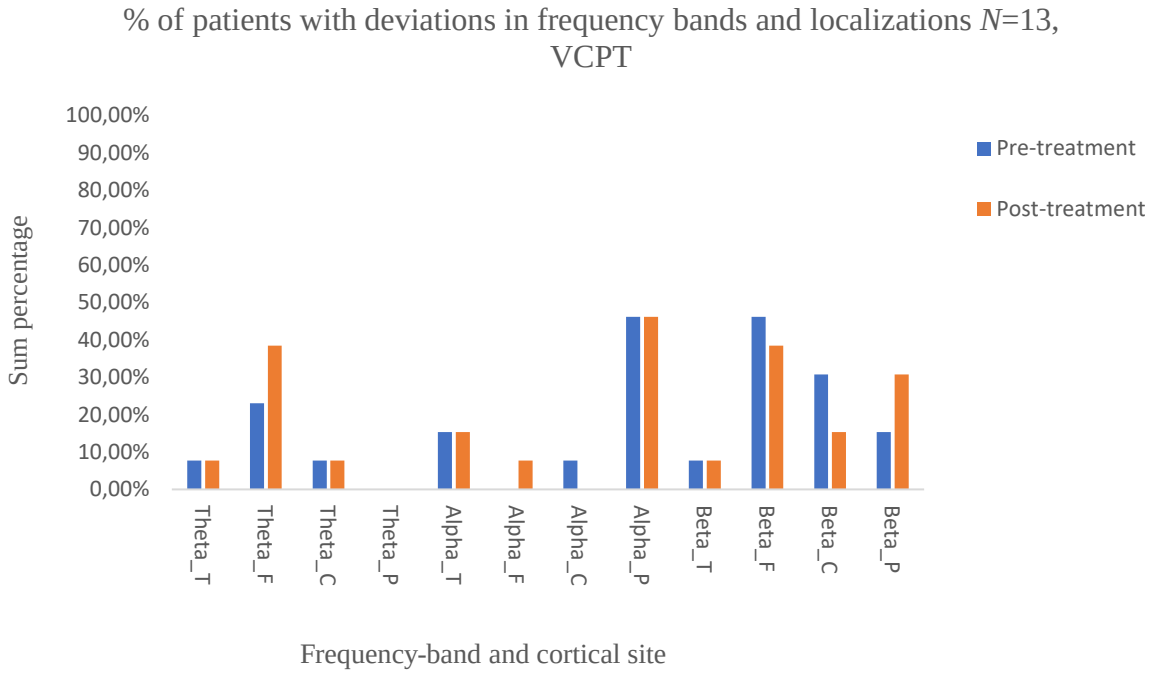


Figure 18. Bar-chart of the amount of deviations during VCPT, with pre- and post-test comparisons, *N*=13.

Discussion

Main findings

This study set out to investigate mainly two objectives. Firstly, this project aimed to explore potential biomarkers of fibromyalgia, as measured by deviances from a healthy control within cortical regions implicated in the dynamic pain connectome. This included both abnormal temporal dynamics as measured by power spectra analysis, in addition to source localization. Furthermore, the second aim was to investigate the clinical benefits of infralow-frequency neurofeedback treatment (ILF-NFT) on fibromyalgia symptoms. This includes pain, fatigue, cognitive difficulties, and the overall impact of the disease, as measured by self-reports and qEEG parameters (Sigvaldsen, 2019). 23 patients conducted a pre-test EEG, whilst a total of 13 patients completed their post-test EEG. 20 patients completed the self-report questionnaire at the end of ILF-NFT, and a total of 7 patients

partook in the 3-month follow-up questionnaire.

***Preliminary results*.** Grand average spectra were analysed for all patients and all conditions. A surprising finding was that pre-test EEG of all subject's pre-treatment did not reveal any significant deviations from a healthy control on average. This was true for all cortical regions (frontal, central, temporal, and parietal) and frequency bands (theta, alpha and beta) in both resting state (eyes open, eyes closed) and active state (VCPT).

Significant deviations in individual power spectra analysis, pre-treatment, is plotted in table 9-14 All patients deviated significantly from healthy age-matched database in one or more frequency band (see table 9-14). Specifically, most patients (91.30%) revealed deviations in the beta band. A total of 78.26% of subjects had abnormalities in the alpha band, while 78.26% had significant changes in theta. Approximately 52% of all patients presented with abnormal findings in the active state, with enhancements in frontal beta. The most prominent findings were that most patients displayed a frontal deviation in both the theta (60.86%) and beta band (60.86%). For centroparietal electrodes, patients deviated the most in beta frequency (73.91%), in additions to parietal beta (65.21%).

60% of all patients deviated significantly from healthy controls presenting with a higher central beta during the EC condition. Additionally, 43% of all patients exhibited anomalies in the parietal alpha, and 47.82% in frontal beta during EO. For the active state condition, frontal beta was the most prominent deviation, with a total of 52% displaying irregularities.

Compared to a study conducted by Sigrid (2019), individual power spectra analysis found a more heterogeneous outcome of either enhanced or decreased relative power in the different frequency bands. This study found that all pre-treatment beta deviations had a positive denotation, indicating an excess amount of beta waves compared to healthy controls. For theta and alpha waves, the deviations were strikingly different. 30.43% of subjects presented with enhanced theta, compared to 43.47% that displayed a significant lower theta in relative power analysis. For the alpha band, 43.47% of patients displayed a significant increase in power, compared to the 34,78% that showed a reduction.

Equivalent to a study conducted by Sigrid (2019), FM patients diverged from healthy controls in all DMN-associated BA-areas, except BA 27 and 33. Furthermore, sLORETA source analysis found patients to deviate the most in BA 10 and BA 39 (52.17%), BA 32 (32.78%), BA 21 (30.43%) and BA 46 and BA 47 (26.09%).

***The effect of ILF-NFT on FM symptoms*.** A Wilcoxon Signed-Rank Test identified a total of 11 significant changes in both brain frequencies and behavioural scores when

comparing pre- and post-treatment reports. For frequency amplitude, patients presented with less frontal beta (p <.05, r= -.50) with a moderate effect. Parietal alpha amplitude (p <.01, r= .62), parietal theta amplitude (p< .01, r= .62) and parietal beta amplitude (p< .01, r= .62) had a significant increase following treatment, with medium effects as well. For behavioural data, patients reported a decline in pain-scores (p <.00, r= -.60), fatigue levels (p <.01, r= -.49) and fibro-fog (p<.01, r= -.50), all with medium effects. Following treatment, patients had a reduction in ACR- (p <.00, r= -.56) and FIQ- (p <.00, r= -.61) scores with a medium effect. For group 1, subjects presented with a faster reaction-time (p<.01, r=-.61) and with less variability (p< .01, r= -.53) with medium effects in both variables.

Visually inspection of individual power spectra (N=13) in all conditions, pre- and post-treatment, found patients to display more deviations in total theta, total beta, and alpha deviations. There was an increase in the number of deviations in all frequency bands and cortical areas, except parietal theta, central theta, frontal alpha, central alpha, parietal alpha, and frontal beta. For EO, a decrease of deviations can be localized in temporal and parietal theta, parietal alpha, and frontal beta. For EC, a decline can be identified in the central theta and central beta. For the active VCPT condition, a reduction of deviations can be found in central beta (see appendix F). It should be stressed that these changes purely rely on the summation of significant power spectra deviation per subject. Differences in the rate of deviations have not been subject to separate significant testing (Sigvaldsen, 2019).

Interpretation of Preliminary Results

Power spectra deviances. As expected, all patients presented with one or more deviation from healthy age-matched controls in the individual relative power spectra analysis (Sigvaldesen, 2019). Contrary to expectations, grand average spectra found no group difference between fibromyalgia patients and a normative database before treatment. Most patients deviated in frontal theta and central, parietal, and frontal beta, before treatment during resting state (See table 7). However, patients are mixed in whether they present with an increase or decrease in theta and alpha waves. These findings suggest that enhanced beta is the most prominent and consistent deviation amongst fibromyalgia patients, whilst theta and alpha deviations are more mixed between patients. This indicates a heterogeneous population, with functional reorganization at the level of the individual.

In this study, approximately 60% of patients presented with excess beta in the frontal

regions, whilst 73% of patients had enhanced beta in the central regions. Increased frontocentral beta has previously been associated with increased pain intensity (González-Roláand et al., 2016; Hargrove et al., 2010; Lim et al., 2016). Previous EEG- and MEG-studies have identified that FM patients displayed elevated relative beta power over the frontal and central regions during resting state (Hargrove et al., 2010; Lim et al., 2016). Another study found that FM patients presented with enhanced beta power over the precentral gyrus, superior frontal gyrus, midcingulate cortex, and the middle frontal gyrus (González-Roláand et al., 2016). Higher frontal beta power, particularly over areas like the dlPFC, has previously been linked to the affective dimension of pain and attention directed towards pain. This suggests a disruption in the salience network, which consequently affects pain perception (Lim et al., 2016). According to findings, anxiety- and depression-scores were negatively correlated with beta in the frontal regions, especially the frontal medial gyrus (González-Roláand et al., 2016). Nevertheless, this was only true for beta-3 (23-30 Hz). It is possible that enhanced frontal beta is important in pain-specific affectional and attentional regulation (Lim et al., 2016).

Enhancement of beta power over the central electrodes are also indications of cortical hyperexcitability, namely increased spontaneous excitatory processes. One can therefore interpret the increased beta power over somatosensory and motor regions during rest as of importance in the constant experience of pain in FM patients (González-Roláand et al., 2016; Lim et al., 2016). This is further supported by an EEG study on FM patients which found that beta amplitude in the central regions following brush strokes correlated with tenderness scores (Fallon et al., 2013). This indicated that central beta is related to allodynia and altered pain perception in FM patients. Nevertheless, these findings contrast with a MEG-study, where clinically induced pain caused beta-power suppression localized in the sensorimotor cortices (Lim et al., 2016; Ploner et al., 2006). Hence, the functional meaning of central beta is still not fully understood.

Many patients presented with deviations in frontocentral theta. Augmented theta over the frontal-central electrodes have previously been source located to crucial DPC-nodes; including the mPFC, dlPFC and ACC (Fallon et al, 2018; Lim et al., 2016). These prefrontal structures are critical in pain perception and regulation, including inhibition of pain signals and attention to pain (Sarnthein et al., 2006; Stern et al., 2006). Enhanced frontocentral theta has been linked to increased tenderness, pain, and tiredness. Correlation analysis found that there was a negative relationship between frontal theta and pain-reports, in addition to central theta and fatigue-levels (Fallon et al., 2018). This further confirms the association between

frontocentral theta and FM-symptoms.

However, there is only some patients that presented with excess theta in frontocentral regions. The theory of TCD suggests that chronic pain derives from abnormalities in the thalamocortical loop, which eventually causes excess theta in the cortex. Frontal deviances might be caused by the relay projections from the thalamus, ultimately giving rise to a frontal anomaly (Lim et al., 2016; Stern et al., 2006; Sigvaldsen, 2019). Even though only a subpart of patients presented with increased theta-frequency deviation during pre-test EEG, it is intriguing that increased theta and increase beta is one of the main findings. In accordance with TCD, higher pain-reports were associated with higher frontal theta amplitude (Sarnthein et al., 2006; Llinas et al., 1999).

Taken together, the power spectra analysis found fibromyalgia patients to significantly deviate from the norm. Pain and fatigue are found to be linked to frontal and central theta, respectively. The results find it plausible that DMN- and SN-structures are implicated in various degree amongst FM patients. Implications in the temporal dynamics of the brain suggest enhanced adaptability, flexibility, and efficiency. When analysing these results, it is reasonable to ask whether this adaptability has become maladaptive and has a cascade of effects which affects its clinical presentation (Kucyi & Davis, 2015).

Interpretation of the Effect of ILF NFT on FM symptoms

Grand average power spectra. Following treatment, group 1 (N=13) only deviated in the frontocentral area, peaking at both Cz and Fz in the theta-band, with a significant decrease in power. It is hypothesised that theta in the frontal midline is associated with the metabolic activity in the ACC (Gevins et al., 1997; Kropotov, 2016), which is a part of the salience network. Specifically, enhanced theta and beta has been associated with neurogenic pain (Santhein et al., 2006). The reduction of theta in frontocentral regions are consistent with the subjective reports of declination in pain reports. Not only is frontocentral theta involved in pain perception, it is also involved in attentional processes (Gonzalez-Villar et al., 2017).

If persistent pain causes continuous demands upon attentional mechanisms, functional reorganization can occur due to learning mechanisms (Apkarian et al., 2011). Consequently, this affects the salient pathways. The lowered frontocentral theta following treatment suggests that a possible alteration has been made in the salient network by the ILF-NFT, potentially redirecting attention away from pain. This could have a cascade of effects upon the various FM symptoms. Freeing attentional resources to be allocated more appropriately could be an

explanatory mechanism behind the decrease in fibro-fog and fatigue scores. Frontocentral theta has previously been linked to tiredness-scores (Fallon et al., 2018). Nevertheless, changes in pain can have direct implications on cognitive complaints. As pain is salient, it is plausible to assume that continuous pain distorts brain processing in general (Apkarian et al., 2011). Elevation of pain can consequently affect both fatigue and fibro-fog.

Ideally, a frontocentral theta deviation should be identified pre-treatment when arguing for a renormalization of cortical activity. However, a combination of unknown parameters in the norm database and small sample size, this could affect the statistical power of the analysis conducted in the WinEEG software program. This is further discussed in the limitation section.

***Brain frequencies*.** As seen in appendix F, patients (N=13) had a decrease of significant deviations in parietal theta, parietal alpha, and frontal beta after treatment in the EO condition. Conversely, patients (N=13) presented with an increase in the amount of deviations in frontal and central beta, in addition to temporal alpha, temporal beta and parietal beta. However, some of the deviations in EO frontal beta have shifted to a negative deviation. The same pattern can be seen in the EC condition (see appendix D). The most striking finding of the EC condition was the decline of significant deviations in central beta deviations. The same trend was seen in the VCPT condition. Following treatment, an increase in frontal theta deviations can be seen in the EO-condition. Notably, the deviations had shifted to significantly lower theta in the frontal areas.

Correlation analysis found temporal beta and theta, frontal theta and central theta correlated with the measurements of symptoms, however. A statistically significant relationship was identified between ACR scores and both temporal theta and beta. Furthermore, frontal theta and temporal beta amplitude correlated significantly with pain treatment. For fatigue, theta centrally was of importance. Additionally, correlation analysis found no frequency band to correlate with fibro-fog scores.

A Wilcoxon Signed-Rank Test indicate that patients had significantly lower frontal beta amplitude (p<.05, r=-.50), increased parietal theta amplitude (p<.01, r=.62), parietal beta (p<.01, r=.62) and parietal alpha (p<.01, r=.62) following ILF-NFT. These findings could plausibly indicate a renormalization of a pain-specific oscillatory deviation in these patient groups. Most of these cannot be source located and can therefore not be attributed to the DPC. Changes in beta frontally are specifically relevant for chronic pain patients, as frontal beta is associated with pain intensity, the affective dimension of pain and attention to pain (Hargrove et al., 2010; Lim et al., 2016; Nickel et al., 2017). The importance of frontal beta in pain-

scores is not found in the correlation analysis. Thus, the implication for frontal beta is non-conclusive.

Typically, parietal alpha increases with increased task load and should therefore be more prominent during active task conditions like the VCPT (Kropotov, 2008). One could imply that increased parietal alpha is seen in FM patients during both EO and VCPT is because of disruptions and compensatory mechanisms (Kropotov, 2016). Pain catastrophizing is associated with power in the alpha band, hence changes in parietal alpha could be a consequence of changes in pain catastrophizing following treatment (Albu & Meagher, 2016). The literature is vaguer upon the functional meaning of parietal theta and parietal beta in chronic pain conditions. Correlation analysis found, however, no relationship between parietal alpha, beta and theta and symptom measures. Hence, these pre- and post-treatment effects may be due to noise, coincidence, or an unknown compensatory mechanism.

***Symptom score measures*.** There was an overall improvement in all clinical measures. All but one patient (N=20) reported a significant decline in ACR scores following ILF-NFT. The same was true for FIQ-scores. For pain, 18 patients reported a significant decline in pain measures following treatment, 17 patients reported declines in fatigue and 17 reported decline in fibro-fog measures. The changes seen in all three VAS scores could be the consequence of a cascade of effects. As pain severity diminishes, cognitive resources can be allocated to executive tasks and ease on both fatigue and fibro-fog. As attention is redirected away from pain, attentional mechanism can be redirected in a more beneficial way (Apkarian et al., 2011).

A more objective measurement of decreased fatigue and fibro-fog is reflected in superior reaction time after ILF-NFT. Participants displayed lowered reaction-time following treatment. Reaction-time, being a measurement of fast performance in stimulus-responds-tasks, is associated with metabolic activity in the frontal regions of the brain. Compared to a study conducted by Sigrid (2019), this study identified changes in all VAS subscales: pains, fibro-fog, and fatigue. Cognitive augmentations are further supported by superior reaction time with lowered reaction time variability. It is unclear whether ILF-NFT targets the underlying mechanisms of pain, fatigue, or fibro-fog. As previously mentioned, affection one of the variables may cause a downstream effect upon the entire clinical picture.

There was an overall increase in parietal alpha, parietal theta, parietal beta and decrease in frontal beta amplitude after ILF-NFT. However, these variables did not correlate symptom score measures before treatment. This challenges any association between frontal beta and symptoms seen in fibromyalgia, as correlation analysis indicate that these variable-

changes did not partake in the reduction of symptom severity.

Positive treatment outcomes may be a consequence of the belief in treatment efficacy or reduction of pain catastrophizing. As fibromyalgia is an illness with low prestige, patients frequently report not being taken seriously by the healthcare system. It is plausible to assume that participating in a study aimed specifically for fibromyalgia can affect treatment-outcome, as patients potentially feel legitimized and optimism. This can plausibly change the pre-existing brain-states, consequently decreasing the anxiety of pain and pain catastrophizing tendencies. Ultimately, giving the impression of symptom relief. Therefore, placebo response can be a result of lowered symptom impact. Studies upon this topic have found that pain can decrease due to belief of symptom relief (Price et al., 2008; Albu & Maegher, 2016). Though patients were informed that this was a placebo-controlled study, placebo effects are expected to be minimized (Price et al., 2008).

Changes in symptom severity might also occur because of natural history and not the administration of any treatment. In pain conditions, such as FM, symptom severity will vary with time (Clauw, 2014). Sudden onset of symptom relief can, therefore, be a result of regression to the mean, rather than causality. (Price et al., 2008). Nevertheless, if FM patients have functional disruptions in pain, affective and cognitive regions of the brain, degree of placebo-responsiveness might also be affected. A consequence of this can be that chronic pain patients have another pain-modulation system compared to healthy controls, which is yet to be discovered (Bushnell et al., 2013). These compensatory mechanisms could present as deviations uncovered by relative power spectra analysis, without the functional meaning being known

In general, researchers suggest that decrease in low frequencies and increases in the high-frequency oscillatory bands is suggestive of a thalamocortical dysrhythmia and a plausible marker of cortical hyperexcitability (Vanneste et al., 2018; Llinás et al., 1999). Reduced pain and fatigue rating accompanied by a decrease in frontocentral theta is in accordance with TCD, suggesting that these low frequencies generated by thalamocortical loops can be a potential source of fibromyalgia symptoms (Lim et al.,2016). The excessive theta is hypothesised to derive from calcium spikes due to abnormalities in the thalamus Downstream this leads to increase of theta activity in frontal areas of the brain, as this area receives projections from the thalamus. Subsequently, a frontocentral deviation can occur of excessive theta (Llinàs & Jahnsen, 1992; Sarnthein & Jeanmonod, 2008; Sarnthein et al., 2006). Increase in beta power in the frontal regions has been linked to heightened anxiety and depression scores (González-Roldán, 2016; Lim et al., 2016). Whether an increase in frontal

beta pre-treatment indicates higher anxiety and depression scores, or if this supports the theory of TCD is unclear.

The association between reduced pain and lower frontal theta following treatment suggest that ILF-NFT can positively affect fibromyalgia symptoms through the modulation of thalamic activity by uptraining of infra-low frequencies. However, it is difficult to justify that these decreased symptom severities are attributable frequency changes, due to several limitations discussed in part 4.5.

***Potential neuromarkers of Fibromyalgia*.** Several nodes within the dynamic pain connectome were found to consistently deviate amongst FM patients before treatment. sLORETA found BA 10 and 39 to deviate amongst this patient group most notably. Equivalent to a study conducted by Sigrid (2019), FM patients diverged from healthy controls in all DMN-associated BA-areas except BA 27 and 33. This included nodes from the DMN, including the dorsal medial prefrontal cortex (BA, 9, 10, 32), the ventral medial prefrontal cortex (BA 10, 32), the inferior parietal lobule (39, 40) and anterior cingulate cortex (BA 24, 32, 33). From the salience network, areas affected included the anterior right insula (BA 13), the temporal parietal junction (TPJ), dorsolateral prefrontal cortex (46) and mid-cingulate cortex (23, 24, 32).

The most prominent deviation was localized in BA 10 and 39. sLORETA source analysis computed that over 50% of patients deviated from a healthy database in BA 39, which includes cortical regions such as the angular gyrus, which is situated in the inferior parietal lobule and the temporoparietal junction. This area has been suggested to play a role in memory retrieval, sustained attention, and social cognition (Seghier, 2013).

Subjects also deviated in BA 10, which is situated in the medial frontal gyrus and is a part of the superior frontal cortex and the prefrontal network (Peng et al., 2018). Associated functions of BA 10 include memory encoding, working and spatial memory. BA 10 forms both intrinsic connections with nearby cortical regions, but also project long pathway fibres. The intricate connections are viewed in figure 19. Amongst these links are the bilateral inferior parietal cortex (Brodmann 39) and the posterior cingulate cortex (PCC) (Peng et al., 2018).

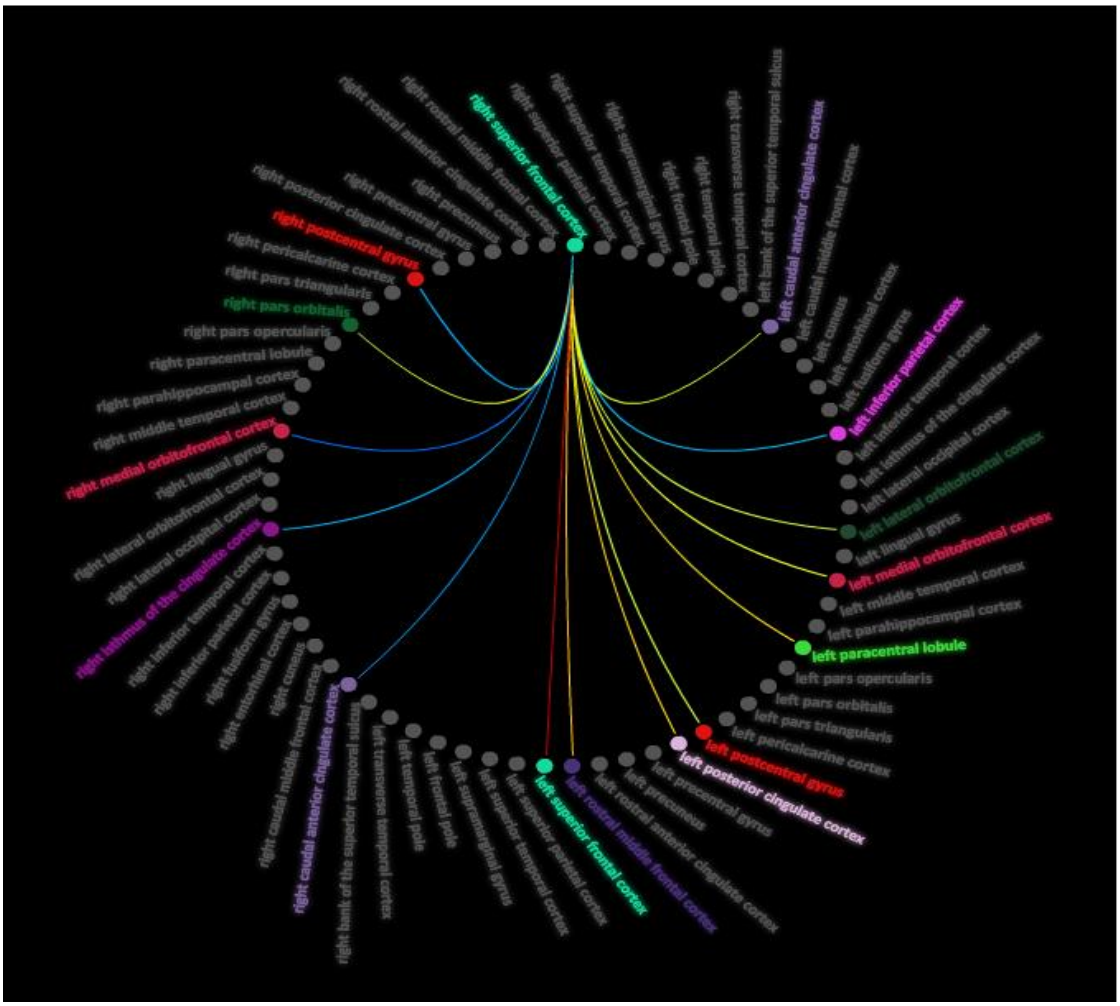


Figure 19. The human connectome, displaying the connections between cortical structures. Warmer colours = stronger connection, cooler colours = weaker connections, by the human connectome project, *http://www.humanconnectomeproject.org/informatics/relationship-viewer/*

It is reasonable to argue that memory and pain are interconnected, as pain serves as a survival mechanism which prompts organisms to avoid harmful stimuli in the future. Hence, pain is a stimulus that generates salient memories as this is key to our survival (Mansour et al., 2014). Pain-templates can derive from learning mechanisms which eventually distorts the pain perception, ultimately leading up to chronification of pain. The continuous background pain can be caused by a continuous state of associative learning. Hence, a consequence of long-term memory formation and continuous reinforced and reconsolidated by learning mechanisms (Apkarian et al., 2011). This can explain maladaptive anticipatory mechanisms of pain, which furthermore causes a disproportionate pain catastrophizing (Apkarian et al., 2011). BA 10 forms connections with pain areas like the dlPFC, orbitofrontal cortex and the

anterior cingulate cortex (Peng et al., 2018), these findings suggest disruptions within the salience network which may stem from abnormal affective evaluative processes (Bushnell et al., 2013; Davis & Moayedi, 2013).

In summary, these findings suggest that FM patients have a variety of disruptions within the DMN and SN, potentially contributing to symptom severity. More research upon this topic is still needed, as the intricate dynamics of the brain is still not fully understood. The usage of neuromarkers in psychiatry and medicine aids healthcare-providers in diagnosing a patient. This requires reliability, sensitivity, and specificity (Kropotov, 2016). There are several issues regarding this, which concerns methodological issues and the ability to promote causality claims in the field.

Limitations of the study

This study suffers from multiple limitations. Some of which were out of the researchers' control. A minimum of 12 participants has been suggested as an acceptable sample size for pilot studies. Due to the SARS-COVID-2 pandemic which affected the amount of available EEG-data, consequently affecting statistical analysis by limiting the sample size for pre- and post-treatment comparisons. Even though there are 23 patients in this study for pre-test analysis, there should have been more participants available for pre- and post-treatment comparisons as this increase statistical power by minimizing sampling error (Julious, 2005; Field, 70). Another issue is related to design. The study was originally intended to be a randomized, placebo-controlled, and double-blinded version of Sigvaldsen (2019). A syntax error led all patients to receive active treatment. We assume this did not affect the result in any other way than potentially lowered placebo-effects, due to modulations in expectations. However, randomized placebo-controlled, double-blinded studies are superior in attributing cause and effect, as placebo responses are minimized, and treatment efficacy is more readily interpreted (Field, 2013).

Subjects and measurements. FM is a complex and multifaceted disorder, hence there is a lot of potential factors that could influence the result in this study. A psychometric scale which measured individual proneness to pain catastrophizing was not included in this study. Pain catastrophizing can offer insight in interindividual variability in emotional pain processing, and therefore provide indications of individual attention to pain. This is important as pain catastrophizing is correlated with pain reports (Gracely et al., 2014). Also, the hallmark of the DPC is how attention and pain are naturally linked. It is reasonable to assume

that there is a connection between pain hypervigilance, abnormal salience processing and pain catastrophizing (Kucyi et al., 2014; Meeus &Nijs, 2007; Sullivan et al., 2005). Furthermore, pain catastrophizing is linked with changes in the alpha band which might explain some of the changes seen in this group of individuals. Including a psychometric scale of this psychological variable could potentially provide a broader understanding of the behavioural link between the DMN, the SN, placebo, and chronic pain.

Another limitation regarding data collection is that pain during EEG acquisition was not controlled for. A recent study found that disruptions in DMN connectivity in chronic pain patients have been associated with pain during scans. Interestingly, FM patients who were pain-free during scans showed no difference in DMN connectivity compared to healthy controls (Ceko et al., 2020). These findings are suggestive of a state-like disruption, compared to specific changes in the DMN attributed chronic pain. Hence, pain at the time of scans increases the likelihood of identifying abnormalities in the brain and should therefore be corrected for. Patient discomfort during scans was also not controlled for. Findings indication a positive effect from ILF-NFT might therefore be false positives, due to coincidences regarding pain levels at the specific day the EEG was obtained, as EEGs are sensitive to an individual's state (Kropotov, 2016). This is further supported by the fact that ACR scores were the only psychometrics that had sustained effects after 3 months. However, few patients participated in the follow-up and is therefore non-conclusive.

***The influence of pharmacology*.** Patients were not instructed to withdraw their current medical usage prescribed by their healthcare provider. An extensive list of patients' pharmaceuticals can be found in table 4. Thus, this study did not comply with a pharmacological-free protocol due to ethical considerations. Almost all patients (91%) consumed one or more drugs around the time of the EEG recordings. It is fair to question the effect of these medications on qEEG parameters discussed in this paper. Some of the patients administered drugs in accordance with their needs and fluctuating symptom severity, so a continuous dosage of any drug is difficult to quantify. This is a potential confounding factor, as several centrally acting medicines are known to influence the EEG recordings Examples of such being antidepressants (e.g. Sarotex), known for increasing theta and decreasing beta. Selective serotonin-reuptake inhibitors (SSRI) are known for inducing increases in frontocentral beta, while decreasing anterior alpha. Methylphenidate typically decreases both delta and theta, with an additional increase in posterior alpha and beta. Medicine usage is therefore expected to alter the EEG data to a certain degree (Blume, 2006; Kropotov, 2008, 2016, Niedermeyer & Lopes de Silva, 2005). Therefore, abnormalities in the beta band might

not be representative of fibromyalgia symptoms, merely a psychopharmacological consequence.

Software and WinEEG. In this study, comparisons of relative power spectra to a healthy control database was conducted through a WinEEG t-test. The analysis found several participants to present with sharp peaks and clear deviations from healthy controls, without the discrepancy being significant. Based on the peak amplitude, one would expect several of these abnormalities to be statistically significant. This database of healthy controls has unspecified parameters, including the standard deviation (*SD*). Knowing the *SD* is important as it indicates how data is distributed within a group (Field, 2015). The unknown distribution will thereby weaken the conclusions drawn from the statistical analysis, as this affects the p-value obtained through WinEEG. Hence, one was not able to control on which fundaments the alpha-level was calculated and why these peaks did not reach a satisfactory significance level. For instance, a large distribution around the mean might explain why this was the case (Field, 2013). Optimally, a large database of healthy controls should have been obtained by the researcher, so no parameter was unknown. Differences in the databases used amongst researchers, there may be other factors contributing to what is identified to be abnormal amongst FM patients (Hargrove et al., 2010). Due to time constraints of the project, this was not possible.

Issues with EEG. Deploying research techniques such as EEG and qEEG is beneficial due to their non-invasive, low-cost, and safe nature. One of the limitations with EEG is poor spatial resolution, as the strength is its the temporal resolution, especially when comparing to fMRI (Evans & Abarbanel, 1999; Jackson & Bolger, 2014; Pinheiro et al., 2016). Compared to MEG, EEG provides a more complex signal deriving from both tangential and radial sources in the brain, given that the signals are strong enough. However, the issues with spatial resolution are related to source location and signals originating from deep structures. Due to the signal-to-noise ratio from deep structures and their typically small size, EEG signals may be too weak to be detected. Activity from the cortex can overpower the small currents deriving from these deep structures, with further distortions caused by volume conduction, skull thickness etc. (Puce & Hämäläinen, 2017). Overall, source location by estimation techniques such as sLORETA can be utilized in EEG research if one is aware of the potential inaccurate estimations (Kropotov, 2016). In this study, many of the individual deviations were not able to be localized. Hence, giving a non-representable presentation of the deviations amongst FM-patients.

Noncerebral activity generates voltage changes in the EEG, which is eliminated during

artifact correction with ICA. Non-adequate artifact correction can generate false deflections from norm data. Consequently, giving rise to type 1 error in the individual deviation estimation viewed in table 9-14. An example being that not adequately removed ocular artifacts, can falsely generate a peak in the frontal electrodes, often in beta frequency (Urigüen & Garcia-Zapirain, 2015). As a large percentage of patients displayed frontal beta deviations, it is reasonable to question whether these are true deviations or artifacts.

Lastly, this study applied tin (Sn) electrodes during data acquisition. DC-EEG are more appropriate for measuring infra-low oscillations and delta waves, which were not included in this study due to the unavailability of the equipment. DC-EEG electrodes comprise of silver chloride (AgCl), which can measure low frequencies as they are non-polarizable electrodes (Kropotov, 2008). To draw conclusion upon the effects of ILF-NFT directly on infra-low oscillations, is therefore not possible in this study, which is a large limitation.

***Statistics*.** Due to the Covid-19 pandemic, statistical analysis was compromised due to missing data. For the Wilcoxon Signed-Rank Test for symptoms, 20 subjects were included in the analysis, as some patients did not fill out the last questionnaire following treatment. For post-test EEG data, entire group 2 comprising of 10 participants are missing. Drawing conclusions on the link between brain frequency changes and treatment effects based on 20 participants, with no more than 13 participants available for pre- and post-test EEG comparisons is challenging.

Even though non-parametric tests allow for statistical analysis in the absence of parametric assumptions, it generally lacks power compared to the parametric alternatives (Whitley & Ball, 2002), hence increasing the risk of conducting a type 2 error. When one is ranking data, a lot of information is lost. An example is the magnitude of difference, consequently affecting power. However, there are high risks of conduction type 1 error when deploying parametric tests when variables do not meet the assumptions as bias is introduced. Therefore, the fact that a parametric test is superior in power-statistics is only valid if all parametric assumptions are fulfilled (Field, 2013). Nevertheless, non-parametric tests are limited as they cannot control for interaction effects. Optimally, controlling for medicine usage and mood-disorders could enhance the strength of this paper. Additionally, repeated measures ANOVA (RANOVA) would be superior in pre- and post-test comparisons, as it is more appropriate for experimental conditions. This could not be done due to factors including sample size and time restrictions (Field, 2013; Sigrid, 2019).

Chronic pain research. Interindividual differences in EEG patterns can cause non-

reliable deviations from healthy controls, which does not necessarily indicate pathology. Some individuals present with a higher alpha amplitude during eyes open condition, without it being dysfunctional. These interindividual variations are due to factors like genetics, anatomical and physical variations. Reported in this study are relative qEEG power spectra, which is meant to counteract some of the influences these factors have on individual qEEG spectra (Kropotov, 2016). Fibromyalgia itself is a heterogeneous illness, often with fluctuating symptoms and the co-occurrence of other neuropsychiatric disorders. An average, this patient group is often more anxious and depressed that a normal population (Baliki et al., 2006; Pinherio et al., 2016).

Identifying correlations between disrupted brain dynamics and symptoms does not readily answer questions about causation. Deviations can indeed be a marker of a symptom, and it can merely be a pre-existing and predisposing factor for a chronic pain disease (Caspi et al., 2014; Kucyi & Davis, 2017). It is therefore difficult to identify potential biomarkers that are distinctive to FM, as the cohort is heterogeneous by itself, and may have a variety of endophenotypes (Kropotov, 2016). It is reasonable to ask whether individual uniqueness and different endophenotypes can explain why some patients diverge with either enhanced or decreased power in the various frequency-bands (Fallon et al., 2018; Kropotov, 2016). This introduces a large possibility of the influence of confounding and third variables.

The difficulty of addressing interindividual differences originates from the lack of knowledge upon individual distinctiveness. Individual uniqueness can still reach statistical significance compared to healthy controls even in the absence of any pathology. Deviations from norm can be a result of compensatory mechanisms, hence a biproduct of cortical abnormalities and a secondary effect of the illness at hand (Kropotov, 2016). Still unknown are which mechanisms that contribute to the transition from acute to chronification of pain. Whilst EEG bypasses the verbification of subjective experiences, pain perception is still affected by environmental and contextual factors (Mouraux & Iannetti, 2018). Focusing on non-phase locked EEG oscillations, like resting-state recordings, does provide a greater window into the brain's spontaneous activity. As spontaneous activity is of importance in cognitive- and affective processing and the understanding of how pre-existing brain states affect pain (Fallon et al., 2016: 2018; Apkarian et al., 2011).

In general, the search for an aetiology of chronic pain presents as a scientific challenge (Pinheiro et al.). Classifying psychosomatic illnesses into distinct categorize have been criticized for many years, as researchers has suggested the existence of more parsimonious structures underlying psychopathology (Caspi et al., 2014). It is possible that chronic pain

sufferers have similar underlying features or risk factors, which make the populations more similar than previously assumed. There has been controversy in the field whether FM should be treated as a discrete entity or a part of the chronic widespread pain-spectrum (Cohen, 2017). The research fundament of FM can therefore be skewed, as cut-off points for of symptoms and diagnostic criteria often are arbitrary (Caspi et al., 2014). The fact that FM can coexist with other overlapping illnesses poses an additional challenge, as boundaries between diseases are unclear. When researching chronic pain conditions, it is challenging to identify relevant fMRI, MRI, and EEG markers of pain from other possible confounds (Apkarian et al., 2011).

The absence of longitudinal research upon fibromyalgia generates a lack of knowledge, chronic pain is known for changing its manifestation over the course of both years and months (Baliki et al., 2006). Life-long research provides enhanced ecological validity compared to studies conducted at one specific time (Field, 2013). As we known, factors such as early life stress can affect the inclination to develop disorders like fibromyalgia and chronic pain (Zeev et al., 2019). It is also plausible that pain duration can affect the degree of functional reorganization, which can further explain why findings are so varying (Baliki et al., 2014). What we know, is that chronic pain is related to a disruption of a cortical equilibrium (Cifre et al., 2012)

Conclusion

The aim of this study was to research the effect of infra-low frequency neurofeedback training (ILF-NFT) upon symptoms of fibromyalgia (FM), which includes pain, fatigue, and fibro-fog. Furthermore, it was of interest to investigate how FM patients deviate from healthy controls in cortical structures which make up the dynamic pain connectome (DPC), and whether a potential neuromarker could be uncovered.

Patients displayed several deviations from healthy controls, for instance in frontal beta-, central beta, frontal theta, and central theta activity. Many of these deviations were source located to key nodes in both the default mode network (DMN) and the salience network (SN). It is possible that these findings point towards an initial maladaptive affective pain processing, related to reinforced pain templates. Following treatment, there were more deviations amongst patients in individual power spectra analysis. Whether this is the consequence of a beneficial reorganization and compensatory mechanisms, is unclear. The theory of thalamocortical dysrhythmia is hypothesised to explain the underlying

pathophysiology of chronic pain. Some of the findings point in that direction, however not in a consistent manner. Furthermore, patients had a significant decline in all symptom measures. This indicates that ILF-NFT may be beneficial in reducing symptom severity amongst FM patients. Whether these changes are related to treatment effects is unclear, as a decrease in key symptoms did not have long-lasting effects. Limitations of this study have also been addressed.

Pain research have come a long way in recent years. It has now become apparent that pain and chronic pain is a result of a complex spatial-temporal-spectral pattern of cortical activity, embedded in the total brain dynamics (Ploner & May, 2018). Today, chronic pain is managed by the healthcare system with a symptom-based approach. This does not consider the underlying mechanisms that maintain the constant pain (Mansour, Farmer, Baliki & Apkarian, 2014). Our understanding of a psychosomatic phenomenon as pain rests on the frontier of consciousness research as pain is inherently subjective (Mouraux & Ianetti, 2018). As of now, the association between physiological processes and the experience of pain is purely correlational (Apkarian et al.2011).

Not identifying how fibromyalgia patients coherently deviate from healthy controls may simply be due to a variety of endophenotypes (Kropotov, 2016). Further development of effective treatment for fibromyalgia requires a more comprehensive understanding of chronic pain (Kucyi & Davis, 2017). When discussing deviation from healthy controls, it is still unknown what is considered normal in the human brain. Rather than a set value of brain frequency amplitude, there might be an unknown equilibrium we have yet to identify and define. Further research should aim to use cross-modality research methods, with both MEG, EEG, and fMRI to increase the ability to source localize and utilize the strength of each method (Puce & Hämaläinen, 2017). Future EEG studies should also focus on using DC-EEG together with ILF-NFT, to identify the specific changes this treatment has on the infra-low fluctuations. Extensive longitudinal studies upon the developmental changes, effects of age and larger sample sizes are also encouraged.

References

Albu, S., & Meagher, M. W. (2016). Expectation of nocebo hyperalgesia affects EEG alpha-activity. *International Journal of Psychophysiology, 109*, 147-152. doi:10.1016/j.ijpsycho.2016.08.009

Album, D., Johannessen, L. E. F., & Rasmussen, E. B. (2017). Stability and change in disease prestige: A comparative analysis of three surveys spanning a quarter of a century. *Social Science & Medicine, 180*, 45-51. doi:10.1016/j.socscimed.2017.03.020

Alshelh, Z., Marciszewski, K. K., Akhter, R., Di Pietro, F., Mills, E. P., Vickers, E. R., . . . Henderson, L. A. (2018). Disruption of default mode network dynamics in acute and chronic pain states. *Neuroimage-Clinical, 17*, 222-231. doi:10.1016/j.nicl.2017.10.019

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *Journal of Neuroscience, 19*(1), 484-494.

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9*(4), 463-484. doi:10.1016/j.ejpain.2004.11.001

Apkarian, A. V., Hashmi, J. A., & Baliki, M. N. (2011). Pain and the brain: Specificity and plasticity of the brain in clinical chronic pain. *Pain, 152*(3), S49-S64. doi:10.1016/j.pain.2010.11.010

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., & Gitelman, D. R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *Journal of Neuroscience, 24*(46), 10410-10415. doi:10.1523/Jneurosci.2541-04.2004

Arnstein, P., Broglio, K., Wuhrman, E., & Kean, M. B. (2011). Use of Placebos in Pain Management. *Pain Management Nursing, 12*(4), 225-229. doi:10.1016/j.pmn.2010.10.033

Baliki, M. N., & Apkarian, A. V. (2015). Nociception, Pain, Negative Moods, and Behavior Selection. *Neuron, 87*(3), 474-491. doi:10.1016/j.neuron.2015.06.005

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., & Apkarian, A. V. (2006). Chronic pain and the emotional brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *Journal of Neuroscience, 26*(47), 12165-12173. doi:10.1523/Jneurosci.3576-06.2006

Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond feeling: Chronic pain hurts the brain, disrupting the default-mode network dynamics. *Journal*

of Neuroscience, 28(6), 1398-1403. doi:10.1523/Jneurosci.4123-07.2008

Baliki, M. N., Mansour, A. R., Baria, A. T., & Apkarian, A. V. (2014). Functional Reorganization of the Default Mode Network across Chronic Pain Conditions. *Plos One, 9*(9). doi:ARTN e10613310.1371/journal.pone.0106133

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and Molecular Mechanisms of Pain. *Cell, 139*(2), 267-284. doi:10.1016/j.cell.2009.09.028

Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., & Zubieta, J. K. (2005). Neurobiological mechanisms of the placebo effect. *Journal of Neuroscience, 25*(45), 10390-10402. doi:10.1523/Jneurosci.3458-05.2005

Bennett, R. (2005). The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. *Clinical and Experimental Rheumatology, 23*(5 Suppl 39), S154-162.

Bingel, U., Wanigasekera, V., Wiech, K., Mhuircheartaigh, R. N., Lee, M. C., Ploner, M., & Tracey, I. (2011). The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil. *Science Translational Medicine, 3*(70). doi:ARTN 70ra1410.1126/scitranslmed.3001244

Blume, W. T. (2006). Drug effects on EEG. *Journal of Clinical Neurophysiology, 23*(4), 306-311. doi:DOI 10.1097/01.wnp.0000229137.94384.fa

Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., . . . Laureys, S. (2007). Baseline brain activity fluctuations predict somatosensory perception in humans. *Proceedings of the National Academy of Sciences of the United States of America, 104*(29), 12187-12192. doi:10.1073/pnas.0611404104

Branco, J. C., Bannwarth, B., Failde, I., Carbonell, J. A., Blotman, F., Spaeth, M., . . . Matucci-Cerinic, M. (2010). Prevalence of Fibromyalgia: A Survey in Five European Countries. *Seminars in Arthritis and Rheumatism, 39*(6), 448-453. doi:10.1016/j.semarthrit.2008.12.003

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain, 10*(4), 287-333. doi:10.1016/j.ejpain.2005.06.009

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience & Biobehavioral Reviews, 33*(3), 279-296. doi:10.1016/j.neubiorev.2008.09.002

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network:

anatomy, function, and relevance to disease. *Annals of the New York Academy of Science, 1124*, 1-38. doi:10.1196/annals.1440.011

Burke, N. N., Finn, D. P., McGuire, B. E., & Roche, M. (2017). Psychological stress in early life as a predisposing factor for the development of chronic pain: Clinical and preclinical evidence and neurobiological mechanisms. *Journal of Neuroscience Research, 95*(6), 1257-1270. doi:10.1002/jnr.23802

Bushnell, M. C., Ceko, M., & Low, L. A. (2013). Cognitive and emotional control of pain and its disruption in chronic pain. *Nature Reviews Neuroscience, 14*(7), 502-511. doi:10.1038/nrn3516

Buzsaki, G. (2002). Theta oscillations in the hippocampus. *Neuron, 33*(3), 325-340. doi:Doi 10.1016/S0896-6273(02)00586-X

Buzsáki, G. (2006). *Rhythms of the Brain*. New York: Oxford University Press.

Buzsaki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents - EEG, ECoG, LFP and spikes. *Nature Reviews Neuroscience, 13*(6), 407-420. doi:10.1038/nrn3241

Buzsaki, G., Logothetis, N., & Singer, W. (2013). Scaling Brain Size, Keeping Timing: Evolutionary Preservation of Brain Rhythms. *Neuron, 80*(3), 751-764. doi:10.1016/j.neuron.2013.10.002

Buzsaki, G., & Wang, X. J. (2012). Mechanisms of Gamma Oscillations. *Annual Review of Neuroscience, Vol 35, 35*, 203-225. doi:10.1146/annurev-neuro-062111-150444

Cagnie, B., Coppieters, I., Denecker, S., Six, J., Danneels, L., & Meeus, M. (2014). Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Seminars in Arthritis and Rheumatism, 44*(1), 68-75. doi:10.1016/j.semarthrit.2014.01.001

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., . . . Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychological Science, 2*(2), 119-137. doi:10.1177/2167702613497473

Ceko, M., Bushnell, M. C., & Gracely, R. H. (2012). Neurobiology underlying fibromyalgia symptoms. *Pain research and treatment, 2012*, 585419. doi:10.1155/2012/585419

Ceko, M., Frangos, E., Gracely, J., Richards, E., Wang, B. Q., Schweinhardt, P., & Bushnell, M. C. (2020). Default mode network changes in fibromyalgia patients are largely dependent on current clinical pain. *Neuroimage, 216*. doi:ARTN 116877 10.1016/j.neuroimage.2020.116877

Choy, E., Perrot, S., Leon, T., Kaplan, J., Petersel, D., Ginovker, A., & Kramer, E. (2010). A patient survey of the impact of fibromyalgia and the journey to diagnosis. *BMC Health Services Research, 10*, 102. doi:10.1186/1472-6963-10-102

Cifre, I., Sitges, C., Fraiman, D., Munoz, M. A., Balenzuela, P., Gonzalez-Roldan, A., . . . Montoya, P. (2012). Disrupted functional connectivity of the pain network in fibromyalgia. *Psychosomatic Medicine, 74*(1), 55-62. doi:10.1097/PSY.0b013e3182408f04

Clauw, D. J. (2014). Fibromyalgia: a clinical review. *JAMA, 311*(15), 1547-1555. doi:10.1001/jama.2014.3266

Cohen, H. (2017). Controversies and challenges in fibromyalgia: a review and a proposal. *Therapeutic Advances in Musculoskeletal Diseases, 9*(5), 115-127. doi:10.1177/1759720X17699199

Craig, A. D. (2009). How do you feel - now? The anterior insula and human awareness. *Nature Reviews Neuroscience, 10*(1), 59-70. doi:10.1038/nrn2555

Crofford, L. J., Rowbotham, M. C., Mease, P. J., Russell, I. J., Dworkin, R. H., Corbin, A. E., . . . Grp, P.-S. (2005). Pregabalin for the treatment of fibromyalgia syndrome - Results of a randomized, double-blind, placebo-controlled trial. *Arthritis and Rheumatism, 52*(4), 1264-1273. doi:10.1002/art.20983

Darnall, B. D., & Colloca, L. (2018). Optimizing Placebo and Minimizing Nocebo to Reduce Pain, Catastrophizing, and Opioid Use: A Review of the Science and an Evidence-Informed Clinical Toolkit. *Neurobiology of the Placebo Effect, Pt Ii, 139*, 129-157. doi:10.1016/bs.irn.2018.07.022

Davis, K. D., & Moayedi, M. (2013). Central Mechanisms of Pain Revealed Through Functional and Structural MRI. *Journal of Neuroimmune Pharmacology, 8*(3), 518-534. doi:10.1007/s11481-012-9386-8

den Boer, C., Dries, L., Terluin, B., van der Wouden, J. C., Blankenstein, A. H., van Wilgen, C. P., . . . van der Horst, H. E. (2019). Central sensitization in chronic pain and medically unexplained symptom research: A systematic review of definitions, operationalizations and measurement instruments. *Journal of Psychosomatic Research, 117*, 32-40. doi:10.1016/j.jpsychores.2018.12.010

Dobrushina, O. R., Vlasova, R. M., Rumshiskaya, A. D., Litvinova, L. D., Mershina, E. A., Sinitsyn, V. E., & Pechenkova, E. V. (2020). Modulation of Intrinsic Brain Connectivity by Implicit Electroencephalographic Neurofeedback. *Frontiers in Human Neuroscience, 14*. doi:ARTN 19210.3389/fnhum.2020.00192

Dressler, O., Schneider, G., Stockmanns, G., & Kochs, E. F. (2004). Awareness and the EEG power spectrum: analysis of frequencies. *British Journal of Anaesthesia 93*(6), 806-809. doi:10.1093/bja/aeh270

Dubin, A. E., & Patapoutian, A. (2010). Nociceptors: the sensors of the pain pathway. *Journal of Clinical Investigation, 120*(11), 3760-3772. doi:10.1172/Jci42843

Evans, J. R., & Abarbanel, A. (Eds.). (1999). *Introduction to quantitative EEG and neurofeedback.* Academic Press.

Fallon, N., Chiu, Y., Nurmikko, T., & Stancak, A. (2016). Functional Connectivity with the Default Mode Network Is Altered in Fibromyalgia Patients. *Plos One, 11*(7). doi:ARTN e015919810.1371/journal.pone.0159198

Fallon, N., Chiu, Y., Nurmikko, T., & Stancak, A. (2018). Altered theta oscillations in resting EEG of fibromyalgia syndrome patients. *European Journal of Pain, 22*(1), 49-57. doi:10.1002/ejp.1076

Fallon, N., Chiu, Y. H., Li, X., Nurmikko, T. J., & Stancak, A. (2013). Ipsilateral cortical activation in fibromyalgia patients during brushing correlates with symptom severity. *Clinical Neurophysiology, 124*(1), 154-163. doi:10.1016/j.clinph.2012.06.014

Farmer, M. A., Baliki, M. N., & Apkarian, A. V. (2012). A dynamic network perspective of chronic pain. *Neuroscience Letters, 520*(2), 197-203. doi:10.1016/j.neulet.2012.05.001

Field, A. (2013) Discovering statistics using Ibm Spss Statistics. SAGE Publications Limited.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8*(9), 700-711. doi:10.1038/nrn2201

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America, 102*(27), 9673-9678. doi:10.1073/pnas.0504136102

Fröhlich, F. (2016). Network neuroscience. San Diego: Academic Press

Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: Effects of task difficulty, type of processing, and practice. *Cerebral Cortex, 7*(4), 374-385. doi:DOI 10.1093/cercor/7.4.374

Gonzalez-Roldan, A. M., Cifre, I., Sitges, C., & Montoya, P. (2016). Altered Dynamic of EEG Oscillations in Fibromyalgia Patients at Rest. *Pain Medicine, 17*(6), 1058-1068. doi:10.1093/pm/pnw023

Gonzalez-Villar, A. J., Pidal-Miranda, M., Arias, M., Rodriguez-Salgado, D., & Carrillo-de-la-Pena, M. T. (2017). Electroencephalographic Evidence of Altered Top-Down Attentional Modulation in Fibromyalgia Patients During a Working Memory Task. *Brain Topography, 30*(4), 539-547. doi:10.1007/s10548-017-0561-3

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B., . . . Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry, 72*(4), 305-315. doi:10.1001/jamapsychiatry.2014.2206

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A. B., Petzke, F., Williams, D. A., & Clauw, D. J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain, 127*, 835-843. doi:10.1093/brain/awh098

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America, 100*(1), 253-258. doi:10.1073/pnas.0135058100

Grin-Yatsenko, V. A., Othmer, S., Ponomarev, V. A., Evdokimov, S. A., Konoplev, Y. Y., & Kropotov, J. D. (2018). Infra-low frequency neurofeedback in depression: Three case studies. *NeuroRegulation, 5*(1), 30-42.

Gunkelman, J. D., & Johnstone, J. (2005). Neurofeedback and the brain. *Journal of Adult Development, 12*(2-3), 93-98. doi:10.1007/s10804-005-7024-x

Hargrove, J. B., Bennett, R. M., Simons, D. G., Smith, S. J., Nagpal, S., & Deering, D. E. (2010). Quantitative Electroencephalographic Abnormalities in Fibromyalgia Patients. *Clinical EEG and Neuroscience, 41*(3), 132-139. doi:Doi 10.1177/155005941004100305

Hari, R., & Salmelin, R. (1997). Human cortical oscillations: A neuromagnetic view through the skull. *Trends in Neurosciences, 20*(1), 44-49. doi:Doi 10.1016/S0166-2236(96)10065-5

Harte, S. E., Harris, R. E., & Clauw, D. J. (2018). The neurobiology of central sensitization. *Journal of Applied Biobehavioral Research, 23*(2). doi:ARTN e1213710.1111/jabr.12137

Hauser, W., Sarzi-Puttini, P., & Fitzcharles, M. A. (2019). Fibromyalgia syndrome: under-, over- and misdiagnosis. *Clinical and Experimental Rheumatology, 37*(1), S90-S97.

Hemington, K. S., Wu, Q., Kucyi, A., Inman, R. D., & Davis, K. D. (2015). Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms. *Brain Structure and Function, 221*(8), 4203-4219. doi:10.1007/s00429-

015-1161-1

Hiltunen, T., Kantola, J., Abou Elseoud, A., Lepola, P., Suominen, K., Starck, T., . . . Palva, J. M. (2014). Infra-Slow EEG Fluctuations Are Correlated with Resting-State Network Dynamics in fMRI. *Journal of Neuroscience, 34*(2), 356-362. doi:10.1523/Jneurosci.0276-13.2014

Hsiao, F. J., Wang, S. J., Lin, Y. Y., Fuh, J. L., Ko, Y. C., Wang, P. N., & Chen, W. T. (2017). Altered insula-default mode network connectivity in fibromyalgia: a resting-state magnetoencephalographic study. *The Journal of Headache and Pain, 18*(1), 89. doi:10.1186/s10194-017-0799-x

Hudson, J. I., & Pope, H. G. (1994). The concept of affective spectrum disorder: relationship to fibromyalgia and other syndromes of chronic fatigue and chronic muscle pain. *Baillière's Clinical Rheumatology, 8*(4), 839-856. doi:10.1016/s0950-3579(05)80051-2

Human connectome project (2010). *The human connectome.* Retrieved from: http://www.humanconnectomeproject.org/informatics/relationship-viewer/

Ioannides, A. A. (2018). Neurofeedback and the Neural Representation of Self: Lessons From Awake State and Sleep. *Frontiers in Human Neuroscience, 12*. doi:ARTN 14210.3389/fnhum.2018.00142

IASP (2020, 16. july). IASP Announces Revised Definition of Pain. *Iasp-pain.* https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=10475

Jackson, A. F., & Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: a review for the rest of us. *Psychophysiology, 51*(11), 1061-1071. doi:10.1111/psyp.12283

Jensen, K. B., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., . . . Ingvar, M. (2009). Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain, 144*(1-2), 95-100. doi:10.1016/j.pain.2009.03.018

Jensen, O., Kaiser, J., & Lachaux, J. P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences, 30*(7), 317-324. doi:10.1016/j.tins.2007.05.001

Julius, D., & Basbaum, A. I. (2001). Molecular mechanisms of nociception. *Nature, 413*(6852), 203-210. doi:Doi 10.1038/35093019

Kayiran, S., Dursun, E., Dursun, N., Ermutlu, N., & Karamursel, S. (2010). Neurofeedback Intervention in Fibromyalgia Syndrome; a Randomized, Controlled, Rater Blind Clinical Trial. *Applied Psychophysiology and Biofeedback, 35*(4), 293-302.

doi:10.1007/s10484.010.9135.9

Kety, S. S., & Schmidt, C. F. (1948). The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men. *Journal of Clinical Investigation, 27*(4), 484-492. doi:10.1172/JCI101995

Kravitz, H. M., & Katz, R. S. (2015). Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. *Rheumatology International, 35*(7), 1115-1125. doi:10.1007/s00296-014-3208-7

Kropotov, J., (2008). *Quantitative EEG, Event-Related Potentials and Neurotherapy.* San Diego: Academic Press.

Kropotov, J., (2016). *Functional Neuromarkers for Psychiatry: Application for diagnosis and treatment.* Elsevier Academic Press

Kucyi, A., & Davis, K. D. (2015). The dynamic pain connectome. *Trends Neurosci, 38*(2), 86-95. doi:10.1016/j.tins.2014.11.006

Kucyi, A., & Davis, K. D. (2017). The Neural Code for Pain: From Single-Cell Electrophysiology to the Dynamic Pain Connectome. *Neuroscientist, 23*(4), 397-414. doi:10.1177/1073858416667716

Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced Medial Prefrontal-Default Mode Network Functional Connectivity in Chronic Pain and Its Association with Pain Rumination. *Journal of Neuroscience, 34*(11), 3969-3975. doi:10.1523/Jneurosci.5055-13.2014

Kucyi, A., Salomons, T. V., & Davis, K. D. (2013). Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. *Proceedings of the National Academy of Sciences of the United States of America, 110*(46), 18692-18697. doi:10.1073/pnas.1312902110

Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. *Journal of Pain, 10*(9), 895-926. doi:10.1016/j.jpain.2009.06.012

Legrain, V., Van Damme, S., Eccleston, C., Davis, K. D., Seminowicz, D. A., & Crombez, G. (2009). A neurocognitive model of attention to pain: Behavioral and neuroimaging evidence. *Pain, 144*(3), 230-232. doi:10.1016/j.pain.2009.03.020

Lim, M., Kim, J. S., Kim, D. J., & Chung, C. K. (2016). Increased Low- and High-Frequency Oscillatory Activity in the Prefrontal Cortex of Fibromyalgia Patients. *Frontiers in Human Neuroscience, 10*. doi:ARTN 11110.3389/fnhum.2016.00111

Lin, C., Lee, S. H., & Weng, H. H. (2016). Gray Matter Atrophy within the Default Mode Network of Fibromyalgia: A Meta-Analysis of Voxel-Based Morphometry Studies. *Biomed Research International, 2016*. doi:Artn 729612510.1155/2016/7296125

Llinas, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *PNAS, 96*(26), 15222-15227. doi:10.1073/pnas.96.26.15222

Malik, A. S. & Amin, H.U. (2017). Designing an EEG experiment. In Malik, A.S & Amin, H.U (Eds). *Designing EEG experiments for studying the brain* (1st edition, p. 1-30). Academic Press.

Mansour, A. R., Farmer, M. A., Baliki, M. N., & Apkarian, A. V. (2014). Chronic pain: The role of learning and brain plasticity. *Restorative Neurology and Neuroscience, 32*(1), 129-139. doi:10.3233/Rnn-139003

Meeus, M., & Nijs, J. (2007). Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clinical Rheumatology, 26*(4), 465-473. doi:10.1007/s10067-006-0433-9

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences, 15*(10), 483-506. doi:10.1016/j.tics.2011.08.003

Menon V. (2015) *Salience Network. In: Arthur W. Toga, editor. Brain Mapping: An Encyclopedic Reference,* vol. 2, pp. 597-611. Academic Press: Elsevier.

Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology, 66*(6), 355-474. doi:Pii S0301-0082(02)00009-6 Doi 10.1016/S0301-0082(02)00009-6

Morgan, M. M., Whittier, K. L., Hegarty, D. M., & Aicher, S. A. (2008). Periaqueductal gray neurons project to spinally projecting GABAergic neurons in the rostral ventromedial medulla. *Pain, 140*(2), 376-386. doi:10.1016/j.pain.2008.09.009

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology, 93*(3), 385-404. doi:10.1016/j.pneurobio.2011.01.002

Mork, P. J., & Nilsen, T. I. L. (2012). Sleep problems and risk of fibromyalgia-untenable conclusions: comment on the article by Mork et al Reply. *Arthritis and Rheumatism, 64*(5), 1693-1694. doi:10.1002/art.34446

Mork, P. J., Vasseljen, O., & Nilsen, T. I. L. (2010). Association Between Physical Exercise, Body Mass Index, and Risk of Fibromyalgia: Longitudinal Data From the Norwegian

Nord-Trondelag Health Study. *Arthritis Care & Research, 62*(5), 611-617. doi:10.1002/acr.20118

Mouraux, A., & Iannetti, G. D. (2018). The search for pain biomarkers in the human brain. *Brain, 141*, 3290-3307. doi:10.1093/brain/awy281

Napadow, V., Kim, J., Clauw, D. J., & Harris, R. E. (2012). Brief report: decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. *Arthritis & Rheumatology, 64*(7), 2398-2403.

Napadow, V., Lacount, L., Park, K., As-Sanie, S., Clauw, D. J., & Harris, R. E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis & Rheumatism, 62*(8), 2545-2555. doi:10.1002/art.27497

Nickel, M. M., May, E. S., Tiemann, L., Schmidt, P., Postorino, M., Dinh, S. T., . . . Ploner, M. (2017). Brain oscillations differentially encode noxious stimulus intensity and pain intensity. *Neuroimage, 148*, 141-147. doi:10.1016/j.neuroimage.2017.01.011

Niedermeyer, E., & Lopes da Silva, F. H. (2005). *Electroencephalography: basic principles, clinical applications, and related fields (*5th ed. ed.). Philadelphia: Lippincott Williams & Wilkins

Niv, S. (2013). Clinical efficacy and potential mechanisms of neurofeedback. *Personality and Individual Differences, 54*(6), 676-686. doi:10.1016/j.paid.2012.11.037

Nunez, P. L., & Srinivasan, R. (2006*). Electric fields of the brain: The neurophysics of EEG*. Oxford: Oxford University Press.

Ohnhaus, E. E., & Adler, R. (1975). Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain, 1*(4), 379–384. https://doi.org/10.1016/0304-3959(75)90075-5

Othmer, S., & Othmer, S. F. (2016). Infra-Low-Frequency Neurofeedback for Optimum Performance. *Biofeedback, 44*(2), 81-89.

Othmer, S., & Othmer, S. F. (2017). Toward a Frequency-based Theory of Neurofeedback. In J. R. Evans & R. A. Turner (Eds.), *Rhythmic Stimulation Procedures in Neuromodulation* (pp. 225-278). London: Elsevier.

Othmer, S., Othmer, S. F., Kaiser, D. A., & Putman, J. (2013). Endogenous neuromodulation at infralow frequencies. *Seminars in Pediatric Neurology, 20*(4), 246-257.

Othmer, S. F. (2005). Interhemispheric EEG training. Journal of Neurotherapy, 9(2), 87-96.

Peng, K., Steele, S. C., Becerra, L., & Borsook, D. (2018). Brodmann area 10: Collating, integrating and high-level processing of nociception and pain. *Progress in Neurobiology, 161*, 1-22. doi:10.1016/j.pneurobio.2017.11.004

Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. *Frontiers in Systems Neuroscience, 10*, 104. doi:10.3389/fnsys.2016.00104

Pevzner, A., Izadi, A., Lee, D. J., Shahlaie, K., & Gurkoff, G. G. (2016). Making Waves in the Brain: What Are Oscillations, and Why Modulating Them Makes Sense for Brain Injury. *Frontiers in Systems Neuroscience, 10*, 30. doi:10.3389/fnsys.2016.00030

Pinheiro, E. S. D., de Queiros, F. C., Montoya, P., Santos, C. L., do Nascimento, M. A., Ito, C. H., . . . Baptista, A. F. (2016). Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature. *Plos One, 11*(2). doi:ARTN e014908510.1371/journal.pone.0149085

Ploner, M., & May, E. S. (2018). Electroencephalography and magnetoencephalography in pain research-current state and future perspectives. *Pain, 159*(2), 206-211. doi:10.1097/j.pain.0000000000001087

Ploner, M., Gross, J., Timmermann, L., Pollok, B., & Schnitzler, A. (2006). Pain suppresses spontaneous brain rhythms. *Cerebral Cortex, 16*(4), 537-540. doi:10.1093/cercor/bhj001

Ploner, M., Sorg, C., & Gross, J. (2017). Brain Rhythms of Pain. *Trends in Cognitive Sciences, 21*(2), 100-110. doi:10.1016/j.tics.2016.12.001

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: recent advances and current thought. *Annual Review of Psychology, 59*, 565-590. doi:10.1146/annurev.psych.59.113006.095941

Puce, A., & Hamalainen, M. S. (2017). A Review of Issues Related to Data Acquisition and Analysis in EEG/MEG Studies. *Brain Sciences, 7*(6). doi:ARTN 5810.3390/brainsci7060058

Rahman, A., Underwood, M., & Carnes, D. (2014). Fibromyalgia. *BMJ, 348*, g1224. doi:10.1136/bmj.g1224

Raichle, M. E. (2015a). The restless brain: how intrinsic activity organizes brain function. *Philosophical Transactions of the Royal Society B-Biological Sciences, 370*(1668), 82-92. doi:ARTN 2014017210.1098/rstb.2014.0172

Raichle, M. E. (2015b). The Brain's Default Mode Network. *Annual Review of Neuroscience*, Vol 38, 38, 433-447. doi:10.1146/annurev-neuro-071013-014030

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*(2), 676-682. doi:DOI

10.1073/pnas.98.2.676

Sarnthein, J., Stern, J., Aufenberg, C., Rousson, V., & Jeanmonod, D. (2006). Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain, 129*(Pt 1), 55-64. doi:10.1093/brain/awh631

Schulz, E., Tiemann, L., Witkovsky, V., Schmidt, P., & Ploner, M. (2012). Gamma oscillations are involved in the sensorimotor transformation of pain. *Journal of Neurophysiology, 108*(4), 1025-1031. doi:10.1152/jn.00186.2012

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349-2356. doi:10.1523/Jneurosci.5587-06.2007

Seghier, M. L. (2013). The Angular Gyrus: Multiple Functions and Multiple Subdivisions. *Neuroscientist, 19*(1), 43-61. doi:10.1177/1073858412440596

Shulman, G. L., Corbetta, M., Buckner, R. L., Fiez, J. A., Miezin, F. M., Raichle, M. E., & Petersen, S. E. (1997). Common blood flow changes across visual tasks .1. Increases in subcortical structures and cerebellum but not in nonvisual cortex. *Journal of Cognitive Neuroscience, 9*(5), 624-647. doi:DOI 10.1162/jocn.1997.9.5.624

Sigvaldsen, S. (2019). *QEEG and Infra-Low Frequency Neurofeedback Training in Fibromyalgia: A Pilot Study*, (Master thesis). NTNU, Trondheim

Sitaram, R., Ros, T., Stoeckel, L., Haller, S., Scharnowski, F., Lewis-Peacock, J., . . . Sulzer, J. (2017). Closed-loop brain training: the science of neurofeedback. *Nature Reviews Neuroscience, 18*(2), 86-100. doi:10.1038/nrn.2016.164

Sluka, K. A., & Clauw, D. J. (2016). Neurobiology of Fibromyalgia and Chronic Widespread Pain. *Neuroscience, 338*, 114-129. doi:10.1016/j.neuroscience.2016.06.006

Staud, R. (2006). Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome. *Arthritis Research & Therapy, 8*(3), 208. doi:10.1186/ar1950

Staud, R., & Rodriguez, M. E. (2006). Mechanisms of disease: pain in fibromyalgia syndrome. *Nature Clinical Practice Rheumatology, 2*(2), 90-98. doi:10.1038/ncprheum0091

Stern, J., Jeanmonod, D., & Sarnthein, J. (2006). Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *Neuroimage, 31*(2), 721-731. doi:10.1016/j.neuroimage.2005.12.042

Sullivan, M. J., Lynch, M. E., & Clark, A. J. (2005). Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain

conditions. *Pain, 113*(3), 310-315. doi:10.1016/j.pain.2004.11.003

Tallon-Baudry, C., Kreiter, A., & Bertrand, O. (1999). Sustained and transient oscillatory responses in the gamma and beta bands in a visual short-term memory task in humans. *Visual Neuroscience, 16*(3), 449-459. doi:Doi 10.1017/S0952523899163065

Tetreault, P., Mansour, A., Vachon-Presseau, E., Schnitzer, T. J., Apkarian, A. V., & Baliki, M. N. (2016). Brain Connectivity Predicts Placebo Response across Chronic Pain Clinical Trials. *Plos Biology, 14*(10). doi:ARTN e1002570 10.1371/journal.pbio.1002570

Timofeev, I. & Bazhenov, M. (2005). Mechanisms and biological role of thalamocortical oscillations. In Columbus, F. (ed.) *Trends in Chronobiology Research* (pp. 1-47). Nova Science Publisher Inc.

Urigüen, J. A., & Garcia-Zapirain, B. (2015). EEG artifact removal-state-of-the-art and guidelines. *Journal of Neural Engineering, 12*(3), 031001. doi:10.1088/1741-2560/12/3/031001

van Deursen, J. A., Vuurman, E. F. P. M., Verhey, F. R. J., van Kranen-Mastenbroek, V. H. J. M., & Riedel, W. J. (2008). Increased EEG gamma band activity in Alzheimer's disease and mild cognitive impairment. *Journal of Neural Transmission, 115*(9), 1301-1311. doi:10.1007/s00702-008-0083-y

Vanhatalo, S., Palva, J. M., Holmes, M. D., Miller, J. W., Voipio, J., & Kaila, K. (2004). Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *PNAS, 101*(14), 5053-5057. doi:10.1073/pnas.0305375101

Vanneste, S., Song, J. J., & De Ridder, D. (2018). Thalamocortical dysrhythmia detected by machine learning. *Nature Communications, 9*. doi:ARTN 110310.1038/s41467-018-02820-0

Verbunt, J. A., Pernot, D. H. F. M., & Smeets, R. J. E. M. (2008). Disability and quality of life in patients with fibromyalgia. *Health and Quality of Life Outcomes, 6*. doi:Artn 810.1186/1477-7525-6-8

Wiech, K., Lin, C. S., Brodersen, K. H., Bingel, U., Ploner, M., & Tracey, I. (2010). Anterior Insula Integrates Information about Salience into Perceptual Decisions about Pain. *Journal of Neuroscience, 30*(48), 16324-16331. doi:10.1523/Jneurosci.2087-10.2010

Wolfe, F. (2011). The Modification of the American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia Should Be Supplemented and Revised reply. *Journal of Rheumatology, 38*(9), 2075-2076. doi:10.3899/jrheum.110545

Wolfe, F., Brahler, E., Hinz, A., & Hauser, W. (2013). Fibromyalgia Prevalence, Somatic

Symptom Reporting, and the Dimensionality of Polysymptomatic Distress: Results From a Survey of the General Population. *Arthritis Care & Research, 65*(5), 777-785. doi:10.1002/acr.21931

Wolfe, F., Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., . . . Yunus, M. B. (2010). The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care & Research, 62*(5), 600-610. doi:10.1002/acr.20140

Wolfe, F., Schmukler, J., Jamal, S., Castrejon, I., Gibson, K. A., Srinivasan, S., . . . Pincus, T. (2019). Diagnosis of Fibromyalgia: Disagreement Between Fibromyalgia Criteria and Clinician-Based Fibromyalgia Diagnosis in a University Clinic. *Arthritis Care & Research, 71*(3), 343-351. doi:10.1002/acr.23731

Yamamotova, A. (2019). Endogenous Antinociceptive System and Potential Ways to Influence It. *Physiological Research, 68*, S195-S205. doi:10.33549/physiolres.934351

Zeev-Wolf, M., Levy, J., Goldstein, A., Zagoory-Sharon, O., & Feldman, R. (2019). Chronic Early Stress Impairs Default Mode Network Connectivity in Preadolescents and Their Mothers. *Biological Psychiatry-Cognitive Neuroscience and Neuroimaging, 4*(1), 72-80. doi:10.1016/j.bpsc.2018.09.009

Appendix

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

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

C. Table for Kendall's tau correlation matrix, pre-treatment

D. Table for individual power spectra analysis, all conditions post-treatment

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

F. Table viewing percentage of deviations in all conditions

G. Informed consent schema

H. VAS questionnaire for pain, fatigue, and fibro-fog (Norwegian version)

I. ACR questionnaire (Norwegian version)

J. FIQ questionnaire (Norwegian version)

Appendix A

Table A1

Shapiro-Wilk of normality for brain frequencies and clinical measurements, pre-treatment N=23

Variable	*W*	*df*	*p*-level
Age	.96	22	.381
ACR	.98	22	.825
FIQ	.93	22	.102
VAS pain	.90	22	.020
VAS fatigue	.95	22	.267
VAS fibrofog	.97	22	.727
RT	.90	22	.036
RT_Var	.75	22	.000
Theta_F	.92	22	.079
Theta_C	.84	22	.002
Theta_T	.90	22	.031
Theta_P	.70	22	.000
Alpha_F	.93	22	.106
Alpha_C	.90	22	.027
Alpha_T	.94	22	.081
Alpha_P	.78	22	.000
Beta_F	.68	22	.000
Beta_C	.83	22	.001
Beta_T	.96	22	.504
Beta_P	.90	22	.031

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale, RT = reaction time, RT_Var = reaction time variability, y _F = frontal, _C = central, _T = temporal, _P = parietal

Table A2

Shapiro-Wilk of normality for brain frequencies and clinical measurements, group 1 pre-treatment N=13

Variable	*W*	*df*	*p*-level
ACR	.93	12	.374
FIQ	.91	12	.201
VAS pain	.90	12	.152
VAS fatigue	.89	12	.088
VAS fibrofog	.94	12	.474
RT	.91	12	.172
RT_Var	.79	12	.005
Theta_F	.92	12	.257
Theta_C	.87	12	.045
Theta_T	.91	12	.160
Theta_P	.74	12	.001
Alpha_F	.95	12	.588
Alpha_C	.94	12	.430
Alpha_T	.92	12	.235
Alpha_P	.81	12	.009
Beta_F	.71	12	.001
Beta_C	.84	12	.19
Beta_T	.96	12	.727
Beta_P	.89	12	.093

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale, RT = reaction time, RT_Var = reaction time variability, y _F = frontal, _C = central, _T = temporal, _P = parietal

Table A3

Shapiro-Wilk of normality for clinical measurements, post-treatment N=20

Variable	*W*	*df*	*p*-level
ACR	0.98	19	.856
FIQ	0.98	19	.917
VAS pain	0.95	19	.306
VAS fatigue	0.94	19	.200
VAS fibrofog	0.96	19	.538

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale,

Table A4

Shapiro-Wilk of normality for brain frequencies and clinical measurements, group 1, post-treatment, N=13

Variable	*W*	*df*	*p*-level
ACR	0.91	12	.159
FIQ	0.96	12	.780
VAS pain	0.86	12	.044
VAS fatigue	0.90	12	.123
VAS fibrofog	0.96	12	.731
RT	0.90	12	.115
RT_Var	0.91	12	.177
Theta_F	0.81	12	.009
Theta_C	0.66	12	.000
Theta_T	0.76	12	.003
Theta_P	0.86	12	.044
Alpha_F	0.91	12	.164
Alpha_C	0.86	12	.037
Alpha_T	0.92	12	.264
Alpha_P	0.68	12	.000
Beta_F	0.81	12	.009
Beta_C	0.84	12	.024
Beta_T	0.82	12	.011

Beta_P	0.91	12	.202

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale, RT = reaction time, RT_Var = reaction time variability, y _F = frontal, _C = central, _T = temporal, _P = parietal

Appendix B

Table B1

Skewness & Kurtosis pre-treatment for brain frequencies and clinical measurements, pre-treatment (N=23)

Variable	Skewness	Kurtosis
ACR	0.04	-0.61
FIQ	-0.85	0.26
VAS Pain	-1.10	0.75
VAS Fatigue	-0.52	-0.56
VAS Fibrofog	-0.09	-0.32
RT	1.07	0.97
RT Var	1.67	1.78
Theta_F	1.02	0.84
Theta_C	1.61	2.69
Theta_T	1.29	3.14
Theta_P	2.65	8.20
Alpha_F	1.04	1.38
Alpha_C	0.89	0.03
Alpha_T	1.08	1.07
Alpha_P	1.82	3.06
Beta_F	2.82	9.78
Beta_C	1.30	0.74
Beta_T	0.24	-0.89
Beta_P	1.19	1.63

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale, RT = reaction time, RT_Var = reaction time variability, y _F = frontal, _C = central, _T = temporal, _P = parietal

Table B2

Skewness & Kurtosis pre-treatment for brain frequencies and clinical measurements pre-treatment Group 1 (N=13)

Variable	Skewness	Kurtosis
ACR	0.46	-0.92
FIQ	-1.15	1.56
VAS Pain	-1.07	0.76
VAS Fatigue	-0.71	-0.79
VAS Fibrofog	-0.25	-0.98
RT	1.06	0.76
RT Var	1.87	3.48
Theta_F	0.64	0.09
Theta_C	1.63	3.39
Theta_T	-0.13	-1.64
Theta_P	2.36	6.41
Alpha_F	0.05	-0.99
Alpha_C	0.45	-0.59
Alpha_T	1.15	2.30
Alpha_P	1.42	1.12
Beta_F	2.46	6.93
Beta_C	1.27	0.66
Beta_T	-0.15	-1.18
Beta_P	1.38	2.74

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale, RT = reaction time, RT_Var = reaction time variability, y _F = frontal, _C = central, _T = temporal, _P = parietal

Table B3

Skewness & Kurtosis pre-treatment for brain frequencies and clinical measurements post-treatment *(N=20)*

Variable	Skewness	Kurtosis
ACR	0.28	-0.52
FIQ	0.36	-0.14
VAS Pain	0.71	1.34
VAS Fatigue	0.47	-0.83
VAS Fibrofog	0.41	-0.58

Table B4

Skewness & Kurtosis pre-treatment for brain frequencies and clinical measurements, post-treatment group 1 (N=13)

Variable	Skewness	Kurtosis
ACR	1.23	2.42
FIQ	0.55	0.21
VAS Pain	-1.22	0.89
VAS Fatigue	0.71	-0.71
VAS Fibrofog	0.54	-0.27
RT	1.08	1.77
RT Var	1.08	1.34
Theta_F	2.03	5.35
Theta_C	2.75	8.53
Theta_T	1.48	0.98
Theta_P	1.30	1.33
Alpha_F	1.12	1.09
Alpha_C	1.23	0.79
Alpha_T	-0.28	-1.41
Alpha_P	1.95	2.86
Beta_F	1.18	0.01
Beta_C	0.92	-0.40
Beta_T	1.22	0.20
Beta_P	0.35	-1.19

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia impact questionnaire, VAS = Visual analogue scale, RT = reaction time, RT_Var = reaction time variability, y _F = frontal, _C = central, _T = temporal, _P = parietal

Table C1

Kendall's tau (t) correlation matrix of variables, pre-treatment (N=23)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1.ACR	-	.335*	.183	.268	.362*	.040	.097	-.279	-.230	-.335*	-.141	.016	.012	-.117	.077	-.069	.008	-.327*	.052
2.FIQ		-	.108	.429**	.442**	-.048	.040	-.107	-.099	-.051	.051	.055	-.004	.107	.123	-.123	-.111	-.075	-.028
3.Pain			-	.124	.141	.152	.000	-323*	-.243	-.291	-.267	-.136	-.084	-.131	-.068	-.251	-.248	-.323	-.195
4.Fatigue				-	.281	-.100	.028	-.207	-.302*	.008	-.183	.124	-.024	.207	.103	-.016	.108	-.008	.175
5.Fibrofog					-	.248	.287	-.139	-.036	-.076	.116	-.016	-.028	-.020	.076	-.147	.024	-.028	.092
6.RT						-	.552**	-.150	-.103	-.008	-.079	-.282	-.127	.000	-.174	-.143	-.083	.048	-.111
7.RT_Var							-	-.024	-.174	.000	-.071	.020	-.071	.024	-.040	.000	.028	.063	.016
8.Theta_F								-	.581**	.502**	.652**	.349*	.375	.217	.312*	.130	.230	.289	.257
9.Theta_C									-	.352*	.723**	.214	.415**	.130	.257	.107	.261	.265	.281
10.Theta_T										-	.455**	.119	.130	.399**	.146	.028	.182	.407**	.186
11.Theta_P											-	.253	.391**	.170	.360*	-.012	.285	.194	.320*
12.Alpha_F												-	.610**	.436**	.705**	.317*	.536**	.222	.562**
13.Alpha_C													-	.415**	.700**	.202	.531**	.138	.565**
14.Alpha_T														-	.462**	-.004	.420**	.439**	.455**
15.Alpha_P															-	.091	.483**	.091	.534**
16.Beta_F																-	.277	.304*	.209
17.Beta_C																	-	.356*	.887**
18.Beta_T																		-	.320*
19.Beta_P																			-

Note. ACR = American Center of Rheumatology, FIQ = Fibromyalgia Impact Questionnaire, VAS = Visual Analogue Scale, _F= frontally, blab la, RT = Reaction Time, RT Var = reaction time variability; * <.05, ** <.01, *** <.001

Table D1

Group 1 (N=13). Significant individual deviations in relative power spectra EEG compared to normative database. Eyes opened (EO) condition, post-treatment

Frequency band	Cortical site	FIB0034	FIB0035	FIB0036	FIB0037	FIB0039	FIB0040	FIB0041	FIB0042	FIB0044	FIB0046	FIB0047	FIB0048	FIB0049
Theta	Temporal													
	Frontal		-1.41** Missing	-1.70** Missing				-1.22* BA 10-9-46		-1.46* BA 10-9-32			-1.18* Missing	-1.13* Missing
	Central							1.95* BA 6-24-31				-1.42* Missing	1.41* Missing	
	Parietal													
Alpha	Temporal							2.92* Missing	3.02* Missing	4.44** BA 21-20-22				
	Frontal													
	Central			2.15* BA 3-1-4										
	Parietal	-2.99* Missing	8.91** BA 7-40-19			-1.47*	21.36*** BA 7-5-31				-1.30* Missing		12.52*** BA 7-31-5	
Beta	Temporal	1.45* Missing				1.00* BA 18-19-17			0.50* BA 37-19-21	1.16** Missing			-0.44* Missing	
	Frontal							1.71*** Missing		1.45** Missing	0.95* Missing			
	Central		0.41* Missing							0.50'* Missing		0.40* Missing		1.63*** BA 6-4-3
	Parietal			1.85*** BA 19-39-37	0.75* Missing	1.13* BA 31-7-39						1.72* BA 7-40-5		1.66*** Missing

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table D2

Group 1 (N=13). Significant individual deviations in relative power spectra EEG compared to normative database. Eyes closed (EC) condition, post-treatment

Frequency band	Cortical site	FIB0034	FIB0035	FIB0036	FIB0037	FIB0039	FIB0040	FIB0041	FIB0042	FIB0044	FIB0046	FIB0047	FIB0048	FIB0049
Theta	Temporal					2.09* BA 21-20-38							-0.71* Missing	
	Frontal		-0.83* Missing				-1.15** Missing		-1.28* Missing	33.80** *BA 8-9-6		-1.32* Missing		-0.76* Missing
	Central	2.35** Missing												
	Parietal							5.23** Missing						
Alpha	Temporal								16.77* Missing				6.63* Missing	
	Frontal													
	Central													
	Parietal							-5.08* Missing						
Beta	Temporal	1.11** Missing	0.54* Missing			1.62** BA 18-19-17			0.32** Missing		0.54* Missing			
	Frontal				0.25* Missing	0.49* Missing				1.67*** BA 47-45-46				0.57* Missing
	Central	0.21* Missing	0.31* Missing	2.29** BA 8-6-9			0.28* Missing	0.22* Missing			0.17* Missing	0.29** Missing		1.09* BA 3-1-4
	Parietal	0.79* Missing			0.75** Missing			0.35* Missing				0.97* BA 19-18-7		0.42* Missing

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Table D3

Group 1 (N=13). Significant individual deviations in relative power spectra EEG compared to normative database. VCPT condition, post-treatment

Frequency band	Cortical site	FIB0034	FIB0035	FIB0036	FIB0037	FIB0039	FIB0040	FIB0041	FIB0042	FIB0044	FIB0046	FIB0047	FIB0048	FIB0049
Theta	Temporal								0.92** Missing					
	Frontal		-1.17** Missing	-1.63*** Missing						-1.28** Missing		-1.01** Missing		-1.44*** Missing
	Central												-1.25* Missing	
	Parietal													
Alpha	Temporal							2.07* Missing				3.14* BA 21-38-47		
	Frontal						6.06*** BA 47-11-10							
	Central													
	Parietal	-3.12* Missing	7.20* BA 3-1-4				8.31** BA 6-5-4		4.07* BA 3-1-4	-1.32* Missing			7.60*** BA 7-5-4	
Beta	Temporal						0.57** Missing							
	Frontal					0.64* Missing				1.67** BA 47-11-10	0.54* Missing		0.50* Missing	1.32** Missing
	Central				0.22* Missing							0.59* BA 44-6-22		
	Parietal			1.67** BA 40-2-3	0.67* BA 7-5-40	0.94* BA 39-19-18								1.22* Missing

Note. Values given in this table refers to relative power (%) deviations compared to a normative age matched control. p<.05 = *, p< .01=**, p<0.001 = ***. The 3 hits of best match of BA (Brodmann Area) position estimates, as localized with sLORETA, are listed. Missing: some positions estimates were non-localizable.

Appendix E

Table E1
Descriptive statistics for all variables, pre and post treatment

	M		*SD*		*Range*	
	Pre (*N*)	Post (*N*)	Pre	Post	Pre	Post
Variables						
Age	46.43 (23)	-	10.17	-	42	-
ACR	20.08 (23)	14.65 (20)	10.17	5.49	21.00	23.00
FIQ	63.04 (23)	46.30 (20)	13.41	13.82	48.03	54.71
VAS Pain	64.11 (23)	39.85 (20)	12.59	16.57	47.00	70.00
VAS Fatigue	67.04 (23)	48.03 (20)	12.72	18.98	44.00	66.00
VAS Fibrofog	59.96 (23)	43.10 (20)	22.90	28.08	90.00	96.60
RT	352.78 (23)	325.62 (13)	69.22	59.67	264.00	219.00
RT var	8.90 (23)	6.66 (13)	5.26	2.97	18.60	10.70
Theta F	1.35 (23)	1.22 (13)	.56	.59	2.26	2.30
Theta C	1.09 (23)	1.13 (13)	.67	.78	2.80	3.06
Theta T	1.32 (23)	1.56 (13)	.74	1.12	3.33	3.40
Theta P	1.06 (23)	3.19 (13)	.76	1.84	3.50	6.16
Alpha F	2.07 (23)	1.97 (13)	1.17	1.13	4.93	3.94
Alpha C	1.97 (23)	2.47 (13)	1.36	1.95	5.13	6.23
Alpha T	2.54 (23)	2.84 (13)	1.62	1.38	6.48	3.90
Alpha P	2.91 (23)	10.76 (13)	2.75	13.02	10.36	41.47
Beta F	3.32 (23)	2.81 (13)	3.41	1.19	16.07	3.58
Beta C	1.79 (23)	1.93 (13)	1.34	1.35	4.46	3.78
Beta T	2.33 (23)	2.61 (13)	1.27	1.98	4.52	5.84
Beta P	1.69 (23)	5.33 (13)	1.12	3.15	4.55	8.82

Note. ACR = American College of Rheumatology, FIQ = Fibromyalgia Impact Questionnaire, VAS = Visual Analogue Scale, RT = Reaction time, RT_Var = Reaction time variability, _F = Frontal, _C = Central, _T = Temporal, _P = Parietal.

Appendix F

Table F1

Percentage of patients with significant deviations in all conditions, group 1 pre-test (N=13)

		EO	EC	VCPT
Theta	Temporal	7,69%	0%	7,69%
	Frontal	23,08%	38.46%	23,07%
	Central	7,69%	15,38%	7,69%
	Parietal	15,38%	0%	0%
Alpha	Temporal	0%	15,38%	15,38%
	Frontal	7,69%	0%	0%
	Central	7,69%	7,69%	7,69%
	Parietal	61,15%	7,69%	46,15%
Beta	Temporal	7,69%	38,46%	7,69%
	Frontal	38.46%	23,08%	46,15%
	Central	30,77%	69,23%	30,77%
	Parietal	23,07%	30,77%	15,38%

Note. EO = Eyes opened, EC = eyes closed, VCPT = Visual continuous performance task

Table F2

Percentage of patients with significant deviations in all conditions, group 1 post-test (N=13)

Frequency band	Cortical area	EO	EC	VCPT
Theta	Temporal	0%	15.38%	7.69%
	Frontal	46.15%	46,15%	38,46%
	Central	23,08%	7,69%	7,69%
	Parietal	0%	7,69%	0%
Alpha	Temporal	23.07%	15,38%	15,38%
	Frontal	0%	0%	7,69%
	Central	7,69%	0%	0%
	Parietal	46,15%	7,69%	46,15%
Beta	Temporal	38.46%	38.46%	7,69%

Frontal	23.07%	30.76%	38.46%
Central	30,77%	61.53%	15,38%
Parietal	38,46%	38.46%	30.76%

Note. EO = Eyes opened, EC = eyes closed, VCPT = Visual continuous performance task

Appendix G

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

qEEG og Nevrofeedback på Fibromyalgipasienter

Dette er en forespørsel til deg om å delta i et forskningsprosjekt for å undersøke hjerneaktivitet hos fibromyalgipasienter, samt å utprøve intervensjonsmetoden Nevrofeedback (treningsmetode) og vurdere dens effektivitet. Prosjektet utføres i forbindelse med en masteroppgave ved Psykologisk Institutt (NTNU, Dragvoll), i samarbeid med vitenskapelig assistent Sigrid Hegna Ingvaldsen, førsteamanuensis Stig Hollup og psykiater Egil Fors.

HVA INNEBÆRER PROSJEKTET?

Prosjektet innebærer å teste intervensjonsmetoden infra-low frekvens nevrofeedback trening (ILF NFT) som behandling for fibromyalgi, samt å undersøke hjerneaktiviteten hos fibromyalgipasienter for å tilegne oss mer kunnskap om diagnosen.

Først vil du gjennomføre en pre-test undersøkelse som består av å måle hjerneaktivitet med EEG (ElektroEncefalografi) i tillegg til å fylle ut 5 ulike spørreskjemaer som omhandler livskvalitet og grad av symptomer. Pre-test undersøkelsen er beregnet og ta ca. 1,5 timer. Deretter vil du gjennomføre 15 treninger med ILF NFT. Hver trening er beregnet å ta ca. 1 time. Etter treningene er fullført vil du gjennomføre en post-test undersøkelse som består av et nytt EEG-opptak og utfylling av de samme spørreskjemaene som i pre-test undersøkelsen. Post-test undersøkelsen er beregnet og ta ca. 1, 5 timer. Deltagerne kan bli forespurt om å delta i en oppfølgingsundersøkelse for å måle langtidseffekter. Da vil deltakerne få samme spørreskjemaer sendt per post som de skal fylle ut og sende i retur.

For å måle hjerneaktiviteten din, vil vi bruke en målemetode kalt ElektroEncefalografi (EEG). Denne teknikken måler hjernebølger i ulike områder av hjernen, og vi får mulighet til å se om noen hjerneområder skiller seg ut i forhold til høy eller lav hjerneaktivitet.

Videre vil deltagere bli tilfeldig fordelt på to grupper. Den ene gruppen vil motta aktiv Nevrofeedback-behandling, den andre gruppen vil fungere som kontrollgruppe og vil ikke motta aktiv Nevrofeedback-behandling.

Nevrofeedback er en treningsmetode som krever minimalt med fysisk innsats, hvor deltakerne skal sitte foran en dataskjerm med 3 elektroder på hodet i ca. 20-25 minutter. Elektrodene blir plassert på relevante hjerneområder relatert til fibromyalgi-symptomer. Deltagerne skal etter instrukser konsentrere seg om animasjonen på skjermen som er tilbakemelding på egen hjerneaktivitet. Metoden går ut på at hjernen skal trene seg selv opp til ønsket hjerneaktivitet ut ifra resultatene vi får på EEG-målingen som er utført i forkant av nevrofeedback- treningen. Denne treningsmetoden er uten særlig ubehag og bivirkninger. I dette prosjektet vil det være 15 treninger per deltaker. Det er ingen begrensning på hvor ofte man kan utføre treninger, og hvor raskt vi blir ferdig med alle treningene 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.

MULIGE FORDELER OG ULEMPER

Per dags dato finnes det ingen behandling for fibromyalgi. Fordelen med å delta i dette prosjektet er at man får prøve en intervensjon som krever minimalt med fysisk aktivitet. Intervensjonen har lav risiko og ubehag. Et mulig ubehag ved treningen kan være trøtthet/slitenhet etter treningen.

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@ntnu.no) eller Jasmin Stølevik Eide (tlf: 988 83 549, e-post: jasmin.eide@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. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

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.

Opplysningene om deg vil bli anonymisert eller slettet fem år etter prosjektslutt.

OPPFØLGINGSPROSJEKT

Deltakere kan bli kontaktet vedrørende deltagelse i oppfølgingsprosjekter knyttet til qEEG og fibromyalgi.

ØKONOMI

Alle deltagere som gjennomfører prosjektet vil motta et Midtby-gavekort på 1000 NOK som kompensasjon for deltagelse. I tillegg skal prosjektet dekke reiseutgifter så langt det lar seg gjøre i forhold til forskningsprosjektets budsjett.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning (2015/1745).

Etter ny personopplysningslov har behandlingsansvarlig (Psykologisk Institutt, NTNU Dragvoll) og prosjektleder (Stig Arvid Hollup) et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med Sigrid Hegna Ingvaldsen (tlf: 915 13 022, e-post: sigrihi@ntnu.no) eller Jasmin Stølevik Eide (tlf: 988 83 549, e-post: jasmin.eide@ntnu.no).

Personvernombud ved institusjonen er thomas.helgesen@ntnu.no.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

Sted og dato | **Deltakers signatur**

Deltakers navn med trykte bokstaver

Appendix H

Appendix H

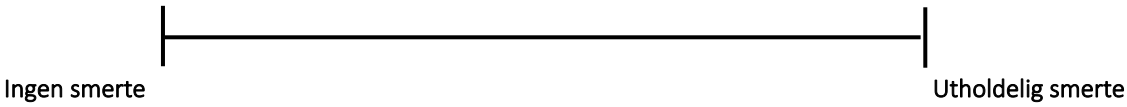
Appendix H

VISUELL ANALOG SKALA (VAS)

I løpet av den siste uken:

Smerte

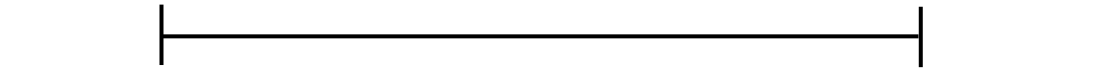
Hvor kraftig er smerten din? Sett et kryss på linjen.



Ingen smerte — Utholdelig smerte

Fatigue/trøtthet

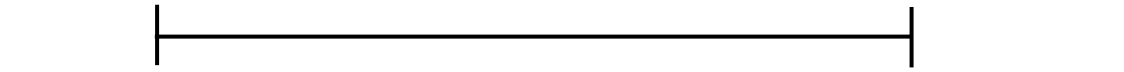
Hvor kraftig er din fatigue/trøtthet? Sett et kryss på linjen.



Ingen fatigue — Kraftig fatigue

Fibrotåke

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



Ingen fibrotåke — Kraftig fibrotåke

Appendix I

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 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

Jasmin Stølevik Eide

Infra-low frequency neurofeedback and fibromyalgia

NTNU
Norwegian University of
Science and Technology