Graduate thesis

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

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Towards an Understanding of the Hidden Pain: a qEEG Study of Fibromyalgia

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Preface and acknowledgements

This project has been both exciting and demanding. Due to the covid-19 pandemic, we had to change our original plan of providing neurofeedback treatment to fibromyalgia patients in a double blinded study. Nevertheless, we are happy with the direction we chose, and the following results of the study. We have learned a lot throughout the process, both about fibromyalgia, EEG and the brain in general.

From the day we first heard about fibromyalgia, we have grown an increasing interest in the field of unexplainable disorders. Because fibromyalgia is a severe public health issue leading to great subjective suffering, we found it to be a particularly important subject of research. Especially since it is a group with no established cure or successful treatment option. Being a part of the NTNU EEG lab as scientific assistants opened a great opportunity to pursue this interest. We hope that our project can contribute to a better understanding of the disorder, and hopefully aid in the development of new diagnostic- and treatment procedures.

There are several important contributors who made this project possible. First, we would like to thank the fibromyalgia patients, for giving us the opportunity to research such an important topic. Next, we want to thank our fellow lab assistants, who helped gathering information we could use in the study. In the process of conducting statistical analyses, Martin Rasmussen Skogstad has taken the time to discuss methodological issues and procedures, which we are thankful for. Lastly, we would like to give a special thanks to our supervisor Stig Arvid Hollup. Not only on this project, but also throughout our studies, your door has always been open. Through your lectures, you have spiked our interest in the neuroscientific field, and encouraged us to be curious. As a supervisor, you have shared your knowledge and been available for discussions when needed, as well as encouraged us to work and think independently.

Sammendrag

Bakgrunn: Fibromyalgi (FM) er et kronisk smertesyndrom med en verdensomspennende prevalens på 2-3%. Det er en lidelse karakterisert av utbredt smerte uten noen klar årsak, i tillegg til plager som søvnvansker, utmattelse (fatigue) og kognitive vansker. FM-pasientene gjennomgår ofte betydelig smerte og lidelse, og tilstanden har en negativ innvirkning på livskvaliteten. Pasientene risikerer også å bli stigmatisert, både av helsepersonell og av samfunnet for øvrig.

Foreløpig er det ingen kjente objektive mål eller biomarkører for å sette diagnosen, og patofysiologien til FM er fortsatt uklar. Dette gjør både diagnostiseringen og behandlingen av pasientene utfordrende, og de økonomiske og sosiale kostnadene er omfattende. Studier peker på forstyrrelser i smerteprosessering som en mulig forklaring på fibromyalgi. Med utgangspunkt i eksisterende forskning, ønsker vi å fortsette å lete etter elektrofysiologiske biomarkører for FM, med søkelys på Dynamic Pain Connectome (DPC).

Metode: Det ble gjennomført individuelle EEG-spekteranalyser av 63 FM-pasienter, som ble sammenlignet med gjennomsnittlig spekter av en frisk kontrollgruppe. Kildelokalisering ble gjennomført der det ble funnet signifikante avvik ($p < .01$) fra normalen, og de 5 mest sannsynlige Brodmannområdene (BA) ble rapportert. Videre ble det gjennomført analyser for å undersøke frekvensbånd og hvorvidt avvikene er lokalisert i DPC, samt statistiske analyser for å undersøke sammenhengen mellom hjerneaktivitet og subjektivt symptomtrykk.

Resultat: Alle FM-pasienter hadde spekteravvik i hjerneaktivitet sammenlignet med friske kontroller, og økte beta-oscillasjoner var det mest fremtredende (85.7% av pasientene). Dessuten hadde 87.3% av forsøkspersonene avvik lokalisert i DPC. Korrelasjonsanalyse indikerer en assosiasjon mellom antall BA-avvik innenfor DPC og subjektiv smerteopplevelse. I tillegg er avvik i Salience Network (SN) under en oppmerksomhetskrevende oppgave assosiert med sterkere subjektiv smerte.

Tolkning av resultatene indikerer at økt hjerneaktivitet i DPC er en mulig biomarkør for FM. Resultatene indikerer også at et større område av aktivering innenfor DPC er assosiert med mer subjektiv smerte, i tillegg til at oppmerksomhetsprosesser ser ut til spille en viktig rolle i lidelsen. Videre er "predictive coding" eller thalamokortikal dysrytmi plausible forklaringsmodeller for FM-patofysiologi. Implikasjoner fra funnene diskuteres.

Abstract

Background: Fibromyalgia (FM) is a chronic pain syndrome with a worldwide prevalence of 2-3%. It is a disorder characterized by widespread pain without any clear cause, and additional ailments such as unsatisfactory sleep, fatigue, and cognitive difficulties. Moreover, comorbidity is frequent. The FM patients often undergo considerable suffering, and the condition has an adverse impact on quality of life. Also, the patients are at risk of being stigmatized, both by health care professionals and by society in general.

Currently, there are no known objective measure or biomarker to confirm the disorder, and the pathophysiology of FM remains unclear. This makes both the diagnostic process and treatment of the patients challenging, and the financial and social costs are substantial. Studies point towards disturbances in pain processing as a possible explanation for fibromyalgia. Building on existing research, we wish to continue the search for electrophysiological biomarkers for FM, focusing on the dynamic pain connectome (DPC).

Method: There were conducted individual EEG power spectra analyses of 63 FM patients, which were compared to the grand average power spectra of a healthy control group. Source localization was applied for significant deviances ($p < .01$), and the most likely Brodmann areas (BA) were reported. Furthermore, analyses were conducted to investigate specific frequency bands, and if the deviances were located in the DPC. Moreover, statistical analyses were conducted to explore the association between brain activity and subjective symptom pressure.

Results: All the FM patients had power spectra brain activity deviances compared to healthy controls, and increased beta oscillations were the most prominent (85.7%). Also, 87.3 % of the subjects had deviances localized in the DPC. Correlation analysis indicate an association between the number of BA deviances within the DPC and subjective pain perception. Also, deviant activity in Salience Network (SN) during an attention demanding task is associated with more subjective pain.

Interpretation of the results indicate that augmented brain activity in the DPC may be a potential biomarker for FM. Also, a larger scaled activation of the DPC is associated with higher subjective pain intensity, and attentional processes seem to play an important part in the disorder. Moreover, predictive coding or thalamocortical dysrhythmia are plausible explanatory models for FM pathophysiology. Implications of the results are discussed.

Table of contents

Abbreviations

a…….. Animal (in the VCPT-task)
ACC……. Anterior cingulate cortex
ACR……. American College of Rheumatology
aINS……. Anterior insula
amPFC……. Anterior medial prefrontal cortex
BA……... Brodmann Area
BOLD…….. Blood-Oxygen-Level-Dependent
CBT……. Cognitive Behavioral Therapy
CEN……. Central executive network
CFS…….. Chronic Fatigue Syndrome
CNS……. Central nervous system
CS…… Central Sensitization
dACC…….. Dorsal anterior cingulate cortex
dlPFC…….. Dorsolateral prefrontal cortex
DMN……... Default Mode Network
dmPFC…… Dorsomedial prefrontal cortex
DPC……. Dynamic Pain Connectome
DTI…….. Diffusor tensor imaging
Ec……..... Entorhinalcortex
EC……..... Eyes Closed
EEG……. Electroencephalography
EMG……..... Electromyogenic
EO……..... Eyes Opened
EPs……... Evoked potentials
FIQ……..... Fibromyalgia Impact Questionnaire
FM……... Fibromyalgia
fMRI…… Functional magnetic resonance imaging
h……..... Human (in the VCPT-task)
IAP……..... Intrinsic attention to pain
IBS……..... Irritable Bowel Syndrome
ILF-NFT…... Infra-low frequency neurofeedback training
IPL……... Inferior parietal lobule

MCC…… Mid-cingulate cortex

MEG…… Magnetoencephalography

mPFC…….. Medial prefrontal cortex

MRI……..... Magnetic resonance imaging

MTL……..... Medial temporal lobe

NFT……. Neurofeedback Training

p…….... Plant (in the VCPT-task)

PAG……. Periaqueductal gray

PCC……. Posterior cingulate cortex

PET…….. Positron emission tomography

QST…….. Quantitative sensory testing

qEEG…….... Quantitative Electroencephalography

rfMRI…….... Resting state fMRI

RQ……..... Research question

Rsp……..... Retosplenial cortex

RVM……..... Rostral ventral medulla

RVM……..... Rostroventral medulla

SI……. Primary somatosensory cortex

SII…… Secondary somatosensory cortex

sLORETA.... Standarized Low-Resolution Brain Electromagnetic Tomography

SMC……. Sensory Motor Cortex

SMR……. Sensory motor rhythm

SN…… Salience Network

SNR……. Signal-to-noise-ratio

SNRI…… Serotonin Norepinephrine Reuptake Inhibitors

SPSS…… Statistical Package for the Social Sciences

SS……. Symptom Severity scale (ACR)

SSRI……. Selective Serotonin Reuptake Inhibitors

TCA……. Tricyclic antidepressants

TCD……. Thalamocortical Dysrhythmia

tDCS……..... Transcranial Direct Current Stimulation

TPJ…….... Temporoparietal junction

VAS……. Visual Analogue Scale

VCPT…….... Visual Continuous Performance Task

vmPFC……. Ventral medial prefrontal cortex

WPI…….. Widespread Pain Index (ACR)

%P…… Relative spatial power density in percent

μV^2……... Absolute spatial power-density in micro voltage squared

1. Introduction

Fibromyalgia (FM) is a chronic pain disorder that affects many people across the world (Woolf, 2010). Currently, there is no common understanding of the disorder, which makes the diagnostic process and treatment challenging (Sarzi-Puttini et al., 2020). In addition, the economic and social costs are substantial (Bair & Krebs, 2020). The identification of objective biomarkers would aid health care personnel in assessment of the patients, as well as providing proper treatment. This could in turn reduce societal costs and stigma related to the disorder, in addition to a potential sense of relief for each individual FM patient.

The implementation of neuroimaging techniques has contributed to a new understanding of the brain, as well as the neural representation of pain (Davis et al., 2017). In this study, we wish to investigate if this knowledge can be used to develop biomarkers of fibromyalgia, using quantitative electroencephalography (qEEG). qEEG can be used to compare brain activity of fibromyalgia patients with healthy controls. If deviances are detected, this could represent potential biomarkers of the fibromyalgia disorder.

First, we will present recent developments in the neuroscientific field, introducing a dynamic view on neural communication. Secondly, we will introduce the concept of pain and objective ways to assess it. Next, we will present relevant theory and research on pain, focusing the dynamic pain connectome. Lastly, the fibromyalgia disorder and possible explanatory models will be presented. Based on this, we will formulate our research questions and hypotheses.

1.1 Towards a dynamic view on the brain

The way we understand processing in the brain has changed drastically during the last decades (Poeppel et al., 2012). Historically, different brain functions were thought to be localized solely at discrete “modules” (Uddin, 2017). The classical models of the brain derived from relatively rough measures, seen from a neurobiological perspective, e.g. correlations between lesions and deficits in stroke patients, and sporadic intracranial recordings during surgical interventions (Poeppel et al., 2012).

Following the implementation of non-invasive functional brain imaging and electrophysiological methods, new research opportunities arose. Increased temporal and spatial resolution led to a greater understanding of brain function, and enabled the study of network communication (Poeppel et al., 2012). Consequently, classical models of brain

function and processing were gradually replaced with new models, emphasizing the role of network dynamics and connectivity between brain areas (Uddin, 2017).

1.1.1 Structural and functional connectivity. The brain as a whole can be understood as a complex set of both structural and functional networks (Stam et al., 2016). Structural networks consists of "fixed anatomical connections between distributed brain areas" (Stam et al., 2016). Brain regions in a structural network are physically connected to each other through white matter tracts, and these tracts determines the "structural connectivity" of the areas (Uddin, 2013). Following an MRI scan, the connectivity and integrity of the white matter tracts can be studied by analyzing T1 images and diffusion tensor imaging (DTI), respectively (Davis & Moayedi, 2013).

Areas of the brain that display strong structural connectivity also tend to show strong functional connections (Uddin, 2013). However, although brain function naturally depends on the overall anatomic structure of the brain, it has become increasingly evident that the relationship between structure and function in the brain is relatively complex, and not necessarily one-to-one (Damoiseaux & Greicius, 2009). Brain areas that are structurally separated can still be "functionally connected" (Honey et al., 2009).

The term "functional connectivity" derives from the discovery that all neural activity in the central nervous system (CNS) fluctuates spontaneously (Raichle, 2015), and that this activity is synchronized in specific spatiotemporal patterns (Kucyi & Davis, 2017). A common method to study this spontaneous neural activation is the "resting-state paradigm" combined with functional magnetic resonance imaging (fMRI), in which subjects are lying "at rest" in an MRI-scanner (Smith et al., 2013). In this way, the data is collected "in the absence of any overt stimulus or task" (Davis et al., 2017, p. 631). In the analysis of the data, the goal is to discover brain areas with high temporal synchronicity, or functional connectivity, by calculating the correlation of signal fluctuations between neural populations (Kucyi & Davis, 2015). Thus, functional connectivity is defined as "the temporal dependency of neuronal activation patterns of anatomically separated brain regions" (Heuvel & Pol, 2010).

Through accumulating resting state fMRI-data from large populations, e.g. The Human Connectome Project (Smith et al., 2013), it has become evident that brain areas that co-activate during specific tasks also tend to display functional connectivity spontaneously (Kucyi & Davis, 2015). Brain areas with strong functional connectivity are thought to represent large-scale networks, that are relatively stable and can be found across individuals (Uddin, 2017). It has been proposed that these functional networks could be involved in

ongoing, organizational processes in the brain, and that disruption of the network communication can indicate neuropathology (Honey et al., 2009).

1.2 Neural oscillations

The brain consists of billions of neurons (nerve cells), who work together to generate brain activity through neural signals (Buzsáki, 2006). A fundamental characteristic of neural activity is that it facilitates functional connectivity across the brain through "oscillations" (Mostame & Sadaghiani, 2021). Neural oscillations consists of rhythmic electrical activity generated spontaneously or in response to stimuli by the nerve cells (Başar, 2013). They reflect rhythmic alternations in the excitability of populations of neurons, and occur in different temporal and spatial scales (Cohen, 2011). Neural oscillations seem to facilitate important functions in the brain, such as neural plasticity, perceptual binding, and long-distance coordination of distinct brain regions (Canolty et al., 2006). Moreover, oscillations seem to play an important role in perception.

Perception is the process where an individual selects, organizes, identifies, and interprets information to understand the environment, and roughly consists of two processes: 1) Collecting information from our senses too our brain (bottom-up), and 2) Making sense of this information based on previous experience (top-down). Because different people have distinct experiences, we will have diverse interpretations of the stimuli presented (Kenyon & Sen, 2015). The theory of predictive coding is a new and more fruitful approach for explaining perception, which is why we choose to highlight this theory in the following section.

1.2.1. Predictive coding. The theory of predictive coding provides a possible illustration of how the brain operates with bottom-up (feedforward) and top-down (feedback) processing, within a hierarchical structure of the brain. The theory postulates a Bayesian computational model for managing information, where the brain continuously matches existing evidence (encoded by deeper cells) with incoming sensory information (encoded by superficial cells) (Bastos et al., 2012). When existing and incoming information does not match, the brain is surprised, and we get what we call a "prediction error". The organism will always try to minimize this prediction error to maintain homeostasis, which can be done in one of two ways; 1) change predictions (the template) to better match the sensory input, or 2) filter the sensory input to better match existing predictions (Adams et al., 2015). In this way, the brain creates a hierarchical model of how perception occurs. Not only in conjunction with external sensory input, but also with internal/bodily sensations (Edwards et al., 2012).

Both bottom-up and top-down-processes are facilitated through neural oscillations and functional connectivity between areas in the central nervous system (CNS). Most models now suggests that beta (12-30 Hz) rhythms (and in some cases alpha rythms, 8-12 Hz) are more associated with top-down signaling, while gamma is associated with bottom-up sensory inputs (Bastos et al., 2020; Song et al., 2021). In addition to gamma, theta is recently proposed as a potential feedforward (bottom-up) frequency. This makes sense as theta can nest higher frequencies (as gamma) and assist long distance communication in the brain (Bastos et al., 2020), as further explained in section 1.4.4.1. Furthermore, research suggests that perception may also have an influence on pain experience (Tracey & Mantyh, 2007), which may indicate that different oscillations could have an influence on the subjective feeling of pain.

1.3 The concept of pain

From an evolutionary perspective, the ability to experience pain is crucial for survival. The adaptive value of pain has been demonstrated through studies of pain deficiencies, in which people without this capacity gain increasing tissue damage, and fails to respond accurately in potentially threatening situations (Nesse & Schulkin, 2019). Pain has a unique ability to detect and draw attention to threats in the environment, and can thus dramatically affect behavior (Kucyi & Davis, 2015).

Even though pain generally has an adaptive function, this is not the case for all types of pain. In this context, a distinction should be made between at least two different types of pain: acute nociceptive pain and chronic pain (Clauw et al., 2019). As opposed to nociceptive pain, which i.a. contributes to the avoidance of future, potentially painful stimuli (Tracey, 2017), chronic pain generally serves no adaptive purpose (Clauw et al., 2019).

1.3.1 Nociception and pain. Nociception can be defined as "the neurophysiological process of encoding noxious stimuli that produce actual or potential tissue injury" (Gilam et al., 2020). Noxious stimuli can be both thermal, mechanical, chemical and electrical, but the common factor is the potential ability to cause tissue damage (Gilam et al., 2020). Specialized neurons called nociceptors respond to the noxious stimuli (Tracey, 2017), and if the nociceptors are sufficiently depolarized, an ascending nociceptive signal is initiated (Smith, 2018).

The activation of nociceptors create reflexive behavioral responses, and is often accompanied by a following discomfort or pain experience (Elwood, 2019). The pain experience itself occurs in the brain (Tracey, 2017), and can be defined as "an unpleasant subjective experience with a sensory and an emotional component" (Gilam et al., 2020). It is

important to make a clear distinction between the terms nociception and pain; Although a vast amount of the pain literature considers pain to be analogous to nociception (Moseley & Vlaeyen, 2015), there is not necessarily a one-to-one relationship between the two concepts (Gilam et al., 2020). It has been established through numerous of studies that nociception is not sufficient to explain pain, nor is it a prerequisite for the pain experience (Moseley & Vlaeyen, 2015). Nociception can occur without pain, for instance in the reflex of withdrawing a hand in contact with a hot object. In this case, nociception happens in the absence of descending brain control (Tracey, 2017). In the same way, pain can be found in the absence of noxious stimuli, e.g. chronic pain (Apkarian, 2019).

1.3.2 Ascending nociceptive pathways. The process of nociception is initiated when axons from the nociceptors send output to the spinal cord (Tracey, 2017). From here, the information is transferred to the brain through ascending neuronal pathways (Tracey, 2017). Axons of second order neurons cross the midline from the spinal cord, and project to thalamus and various areas in the brain stem (Brodin et al., 2016). Thalamic neurons then send projections to the primary- and secondary somatosensory cortex, that are responsible for sensory-discriminatory aspects of pain, and to limbic cortical areas, involved in mediating emotional components of pain (Brodin et al., 2016).

Earlier, the shared view on pain processing was that nociceptive signals were passively delivered to the brain through nociceptive pathways, where conscious awareness of pain occurred (Woolf, 2011). However, it is now established that pain perception depends on the dynamic balance between nociceptive signals and pain modulation in the central nervous system (Hemington & Coulombe, 2015).

1.3.3 Pain modulation. Pain modulation occurs through various mechanisms, and one of them is the descending pain modulatory system (Hemington & Coulombe, 2015). The periaqueductal gray (PAG) and the rostral ventral medulla (RVM) are considered to be important structures in this system (Hemington & Coulombe, 2015). As illustrated in figure 1, higher brain areas send signals to the periaqueductal gray (PAG), which again synapses with the rostral ventral medulla (RVM) and the locus coeruleus. From the RVM, pain modulatory projections are sent to the dorsal horn in the spinal cord (Hemington & Coulombe, 2015). In the dorsal horn, complex pain modulation occurs through interaction between afferent neurons, interneurons and descending modulatory pathways (Reddi et al., 2014). See figure 1 for an overview of major pathways involved in pain processing.

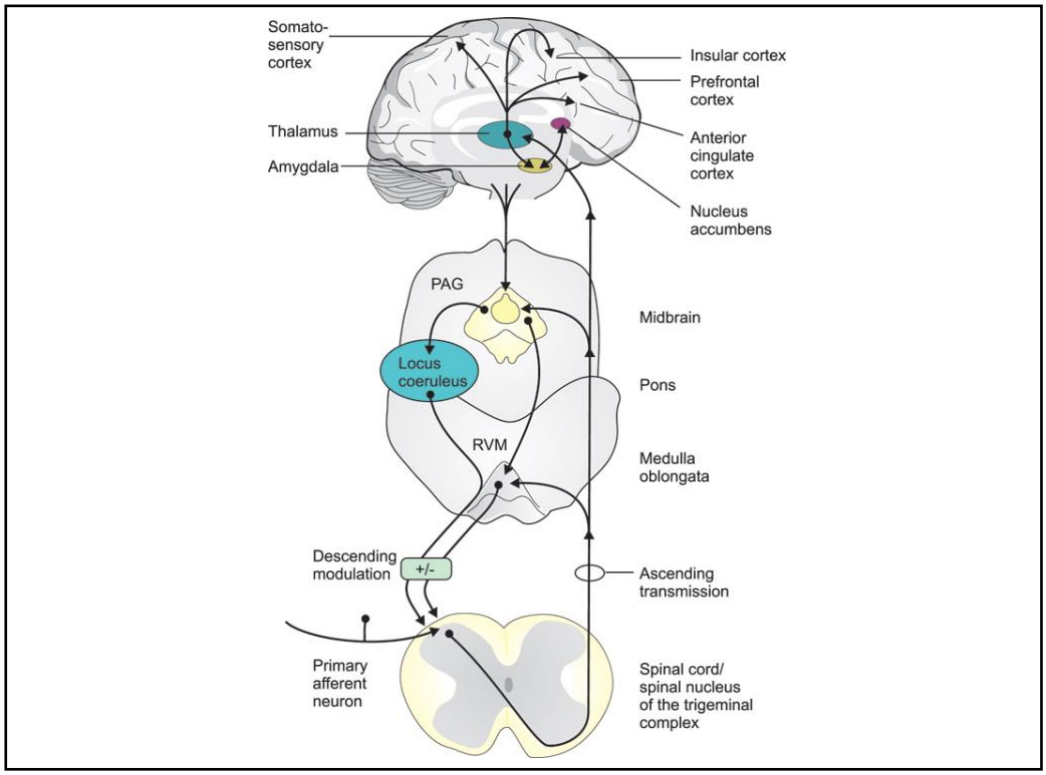
An outdated conception was that the pain modulatory system only had an inhibitory effect. It is now known that descending pain modulation can be both inhibitory and

faciliatory, and can thus both enhance and attenuate pain (Kwon et al., 2014). Monoamines such as serotonin, norepinephrine and dopamine are largely responsible for these modulatory effects (Kwon et al., 2014).

Growing evidence suggests that disruption of the balance of descending pain modulation, specifically increased facilitation and decreased inhibition, plays a part in the promotion and maintenance of chronic pain (Ossipov et al., 2014). The concept of "neural plasticity" is considered to be a precondition for the pathogenesis of pain (Woolf & Salter, 2000). Neural plasticity involved the capability of neuronal and synaptic functions to be molded and shaped, in an manner that influences subsequent perceptual experiences (Melzack, 1999).

Figure 1

An overview of major pathways involved in pain processing.



Note. Retrieved from Brodin et al. (2016).

1.3.4 Chronic pain. The standard definition of chronic pain includes the presence of long lasting pain, typically persisting 3-6 months after healing or due to unknown reasons (Apkarian, 2019). As opposed to acute, nociceptive pain, a behavioral characteristic of chronic pain is that it does not warn us of injury or disease, and thus serves no adaptive purpose (Katz et al., 2015). In addition, chronic pain entails several negative consequences for

the individual, including psychological distress, job loss, social isolation, as well as comorbid anxiety and depression (Katz et al., 2015).

Today, chronic pain is considered to be a disease in itself, and the mechanisms that underly the disease differs from acute pain (Phillips & Clauw, 2011). According to Phillips and Clauw (2011), many researchers believe that neuroplastic changes combined with individual differences in pain sensitivity can contribute to enhanced pain transmission. In contrast to acute pain, chronic pain is not a result of tissue damage or inflammation, but of a dysfunctional nervous system (Woolf, 2010). It can occur because of damage to the nervous system (i.e. neuropathic pain), but damage or inflammation is not necessarily present (i.e. dysfunctional pain) (Woolf, 2010). Chronic pain conditions that can be classified as "dysfunctional pain" include i.a. fibromyalgia, irritable bowel syndrome, tension type headache and other conditions without preceding noxious stimuli or inflammation (Woolf, 2010).

1.4 Objective assessment of pain

In the search for biomarkers, as well as diagnosis, prognosis and prediction of treatment outcome in people with chronic pain, objective brain imaging and electrophysiological methods and are considered to have great potential (Davis et al., 2017). Techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG) and electroencephalography (EEG) enables objective measures of brain activity, and can provide valuable insight into perceptual experiences (Davis et al., 2017). Ultimately, the techniques can be used to develop "pain biomarkers" of different pain-related constructs, such as pain self-report (Reddan & Wager, 2018).

1.4.1 fMRI. The use of functional magnetic resonance imaging (fMRI) has been an essential contributor to the knowledge we have on pain-processing today (Cagnie et al., 2014). fMRI as a technique measures hemodynamic changes after enhanced neural activity, and thus is able to detect networks of interacting brain areas during different activities or tasks (Logothetis, 2008). Consequently, the method has been used to detect multiple cortical and subcortical brain areas that are co-activated, or show functional connectivity, during the pain experience (Xu & Huang, 2020).

Neuronal activity modulates the flow and oxygenation of blood in the brain (Drew et al., 2020). Increased neural activity in specific brain regions leads to a local drop in oxygenated hemoglobin, as well as an increase of local CO_2 and deoxygenated hemoglobin

(Gaillard & Sciacca, 2021). After 2-6 seconds, an increase in blood flow occurs, which increases the amount of oxygenated- relative to deoxygenated hemoglobin (Gaillard & Sciacca, 2021). Due to differences in magnetic properties, oxygenated hemoglobin leads to a stronger MR-signal compared to deoxygenated hemoglobin (Drew et al., 2020). It is this signal, called the "blood-oxygen-level-dependent" (BOLD) signal, that is measured in fMRI. In this way, the fMRI BOLD-signal reflects an indirect measurement of neural activity in the brain.

1.4.1.1 Advantages and disadvantages of fMRI. fMRI is one of the most used methods to study brain function in general (Vu et al., 2017), and there are many advantages of using the technique to study pain mechanisms. Of particular significance is the ability to study ultra-slow oscillations of 0.1 Hz or less, identified through resting state fMRI (rfMRI) as the "resting state signal" (Heuvel & Pol, 2010). The temporal correlation of these fluctuations across brain areas are considered to be "functional connections" (Drew et al., 2020), and thus, rfMRI can be used to identify functional connectivity between both cortical and subcortical areas of the brain (Xu & Huang, 2020). The method has proven useful i.a. in the study of chronic pain states, in which several rfMRI studies have disclosed disrupted functional connectivity within pain-related networks (e.g. Cifre et al., 2012; Davis & Moayedi, 2013; Hemington et al., 2016). Another strength of fMRI as a method is the high spatial resolution of approximately 2-5 mm (Frøkjær et al., 2011), which allows for precise mapping of specific brain areas that could be involved in pain processing. The spatial resolution is highest in the superficial layers, due to pulsation artifacts in deeper areas such as the thalamus (Frøkjær et al., 2011).

Despite the advantages of using fMRI in pain research, some potential weaknesses should be mentioned. First of all, it provides an indirect measurement of neural activity. In this way, the underlying neural mechanisms remain invisible to fMRI, and it is difficult to determine which type of neuronal activity (e.g. intrinsic oscillations, excitatory postsynaptic potentials or inhibitory postsynaptic potentials…) that causes the changes in BOLD-signal (Buzsáki, 2006). The indirect measurement method also puts limitations on the study of temporal aspects of the neural activity. The blood flow and oxygenation responses to neural activity are slow (2-6 seconds), whereas the neural firing itself can occur in the scope of hundreds of milliseconds (Constable, 2006). Furthermore, the temporal resolution is limited by the time it takes for the MR-scanner to acquire one image (Constable, 2006). An fMRI-scan usually has a temporal resolution in the order of seconds (Jamadar et al., 2021), which is significantly lower than that achieved by e.g. EEG and MEG (Morton et al., 2016). In order to

improve the temporal resolution of fMRI, it will come at the expense other factors like the spatial resolution and signal-to-noise-ratio (SNR) (Constable, 2006). Consequently, although fMRI can be used to measure ultra-slow oscillation, the poor temporal resolution makes it difficult to measure rapid brain activities (Xu & Huang, 2020).

1.4.2 PET. Over the last couple of decades, positron emission tomography (PET) has contributed to improve our knowledge of how pain is perceived and modulated (Staud, 2011). The technique involves injecting a radioactive tracer into the individual while they are executing an overt or covert task (Chen, 2001). Then, changes in regional cerebral blood flow, blood volume, oxygen absorption, and glucose metabolism are measured using radionucleotides (Morton et al., 2016). The brain areas involved in functional activation require more oxygen and glucose energy, and the increase in regional cerebral blood flow and metabolism is proportional to neuronal activation (Chen, 2001). Thus, similarly to fMRI, PET provides an indirect measurement of neural activity.

1.4.2.1 Advantages and disadvantages of PET. There are some advantages of using PET compared to fMRI. First, PET is unique in that you have the ability to choose the radioactive tracer (Bunge & Kahn, 2009). Researchers can synthesize radiopharmaceutical compounds that bind to different types of receptors, making it an optimal method for studying different neurotransmitters involved in cognitive processes (Bunge & Kahn, 2009). Thus, PET can directly monitor events within the central opioid and dopaminergic systems, allowing it to analyze the neurochemical components of central pain processing (Morton et al., 2016). Similarly to fMRI, PET has a high spatial resolution in the scope of millimeters, which makes it suitable to accurately locate brain structures involved in pain processing (Morton et al., 2016).

However, despite its unique insight into the experience of pain, PET has some major weaknesses. The most prominent weakness is the exposure to ionizing radiation (Staud, 2011). Beta decay effects can cause serious harm to living tissue, which makes it unsuitable for routine use (Chen, 2001). In addition, it is very costly compared to the other neuroimaging methods, given the requirement of both a PET scanner and a cyclotron to create radioactive tracers (Bunge & Kahn, 2009). Lastly, the method has a temporal resolution in the span of minutes (Morton et al., 2016), which is significantly lower than both fMRI and electrophysiological methods.

1.4.3 MEG. Lastly, two acknowledged, electrophysiological neuroimaging methods are magnetoencephalography (MEG) and electroencephalogram (EEG). These methods utilizes the fact that neurons have intrinsic magnetic and electrical properties, and have the

ability to produce magnetic and electric fields (Mulert & Lemieux, 2009). MEG measures the magnetic fields, whereas EEG measures electrical field potentials (Mulert & Lemieux, 2009).

In MEG, small magnitudes of magnetic fields can be detected through a sensor called SQUID (superconducting quantum interference device) (Buzsáki, 2006). Today, neuromagnetometers consists of helmet shaped sensor arrays, containing hundreds of SQUID-sensors (Hari & Salmelin, 2012). The SQUID-sensors are extremely sensitive to small changes in the magnetic fields, and are positioned above the scalp (Hansen et al., 2010). It allows the detection of the brains magnetic fields without interference from electrical signals (Hari & Salmelin, 2012). For the procedure, the neuromagnetometers must be immersed in liquid helium at the temperature of 4 K (− 269 °C) (Hari & Salmelin, 2012). After the procedure, the results are placed upon an image of the living brain (Baars & Gage, 2013). The sources of brain activity are placed upon MRI-provided anatomical pictures though the process of *magnetic source imaging* (MSI) (Baars & Gage, 2013).

1.4.3.1 Advantages and disadvantages of MEG. MEG is a direct measure of neural activity, and can provide information about real time communication between neurons (Hansen et al., 2010). It also provides millisecond time resolution (Hari & Salmelin, 2012). However, it does not need placement of electrodes on the scalp (Ploner & May, 2018). This is considered to be an advantage, as it eliminates much of the signal distortion caused by the differences in conductivity of the brain, skull and scalp (Hansen et al., 2010). The magnetic fields recorded outside the head is to a large extent the same as it would be on the surface of the brain, which makes it easier to reconstruct the neural activity (Hansen et al., 2010). It also has a higher signal-to-noise-ratio than EEG, and these factors combined leads to a greater spatial resolution and sensitivity (Hall et al., 2014). In contrast to the spatial resolution of approximately 5-9 cm^2 for EEG, MEG has a spatial resolution in the scope of a few millimeters (Baars & Gage, 2013).

Despite the many strengths of MEG, it also comes with weaknesses. It is mostly sensitive to currents close to the skull, and does not provide information about deeper brain structures (Hari & Salmelin, 2012). In addition, some limitations compared to EEG should be mentioned, including the fact that it is "technically more demanding, less accessible and more expensive, rarely available, and stationary" (Ploner & May, 2018).

1.4.4 EEG. Electroencephalography (EEG) is a medical imaging technique that records electrical brain activity directly from the scalp (Teplan, 2002). It was first accepted as a method in the 1920s, when Berger demonstrated its use on the human scalp (Mulert & Lemieux, 2009). Today, it is widely used to study a variety of brain functions, including pain

processing (e.g. Kakigi et al., 2005; Prichep et al., 2018). By placing a number of electrodes on the scalp surface, each electrode can measure local field potentials generated by the activity of populations of neurons, and together create a map of electrical brain activity (Mulert & Lemieux, 2009). Figure 2 shows an example of an EEG recording.

1.4.4.1 Frequency bands. EEG can record oscillations in different frequencies from the scalp (Kamel, 2015). For example, beta oscillations in the EEG recording of a patient are marked in figure 2. The most common frequency bands are delta (0.5-3.5 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz) and gamma (above 30 Hz), and it is broadly accepted that the different frequencies have distinct functions and properties (Buzsáki, 2006; Hammond, 2011).

The delta frequency band is a slow, high-amplitude brainwave, which is mainly present during sleep and "drowsiness" (Hammond, 2011; Louis et al., 2016). Delta waves could also be associated with lesions or metabolic diseases (Nisar & Yeap, 2015).

Activity in the theta frequency band is often seen in young children, but is also observed in adults in a state of drowsiness or arousal, and even in meditation (Nisar & Yeap, 2015). Theta is especially central in the hippocampus, as it is important for spatial and episodic memory processing, as well as contributing to information processing by temporally segmenting information from the environment (Colgin & Moser, 2010). It seems like theta is an associative wave, binding and creating coherence between wide-spread cortical and subcortical structures (Karakaş, 2020). Synchronized theta oscillations are suitable for connecting distinct neuronal networks due to their 100-200 ms period, which can tolerate long conduction delays (Colgin & Moser, 2010).

The alpha frequency band was the first to be discovered by Dr. Hans Berger in 1929 (İnce et al., 2021). It appears during relaxed wakefulness and relative mental inactivity, and is especially prominent in occipital areas when eyes are closed (Kamel, 2015; Niedermeyer, 1999). Normally, the alpha rhythm disappears during mental work, reflecting local suppression of alfa when cortical areas become engaged in sensory or cognitive functions (Drever, 1955; Williamson et al., 1997).

The beta frequency band is of higher frequencies, and is associated with attentiveness and behavioral arousal (Başar & Bullock, 1992). These oscillations tend to correlate with active attention and thinking, including problem solving, and focus on the external world (Nisar & Yeap, 2015). Evidence also suggests that beta oscillations are involved in top-down cortical processing, and provide behavioral context to lower level sensory neurons (Bressler & Richter, 2015).

Just like beta frequency band, gamma oscillations are associated with attention, perception and cognition (Kopell et al., 2000). Gamma has the fastest frequency that is detectable at the scalp, and is thought to temporally link the activity of distributed neuronal populations (Nisar & Yeap, 2015). According to Buzsáki (2006), gamma activity could be modulated by slower theta oscillations in gamma-theta couplings. Theta waves might help combine and segregate cell assemblies that are nested within gamma waves, depending on the synchronization between the gamma- and theta frequencies (Buzsáki, 2006). Gamma is difficult to detect with EEG because of its low amplitude and high frequency, and may be confused with muscular artifacts (Puce & Hämäläinen, 2017; Tandle et al., 2015).

1.4.4.2 EEG in pain research. Roughly speaking, two main approaches have been used when applying EEG in pain research: resting state-EEG and evoked potentials (Ploner & May, 2018). In the resting state, EEG-recordings are taken in the absence of task or instructions (Corchs et al., 2019). Normally, the spontaneous EEG activity during rest is classified into different frequency bands, which are distributed across the scalp in a certain manner, and represent a certain biological significance (Lu & Hu, 2019). As mentioned, alpha waves tend to dominate occipital regions of the cortex in resting state with eyes closed, while being suppressed during eyes open or mental activity (Lu & Hu, 2019). Several studies applying resting state EEG have demonstrated deviances in various frequency bands in chronic pain patients (Pinheiro et al., 2016).

The other main approach investigates "evoked potentials" (EPs), which are elicited from an external stimulus, and are traditionally thought to reflect basic sensory processing of the stimulus (Lu & Hu, 2019). Time-locked, electrophysiological brain responses to either internal or external stimuli are more generally referred to as "event related potentials" (ERPs), and they are considered to reflect higher cognitive processes (Zani, 2013). In connection with nociceptive pain research, the objective has traditionally been to investigate EPs to noxious stimuli, in which a common source of stimuli has been thermal laser (Ploner & May, 2018). Using this approach, a specific pattern of response has been identified, in which the amplitude of the responses is sensitive to damage to nociceptive pathways (Ploner & May, 2018). Thus, in addition to detecting deviances in resting state brain activity, EEG can be useful to detect abnormalities in stimulus processing during pain (Ploner & May, 2018). In general, resting state EEG is typically used to study pathophysiology in chronic pain patients, whereas EPs are applied in studies of nociceptive pain response (Frøkjær et al., 2011).

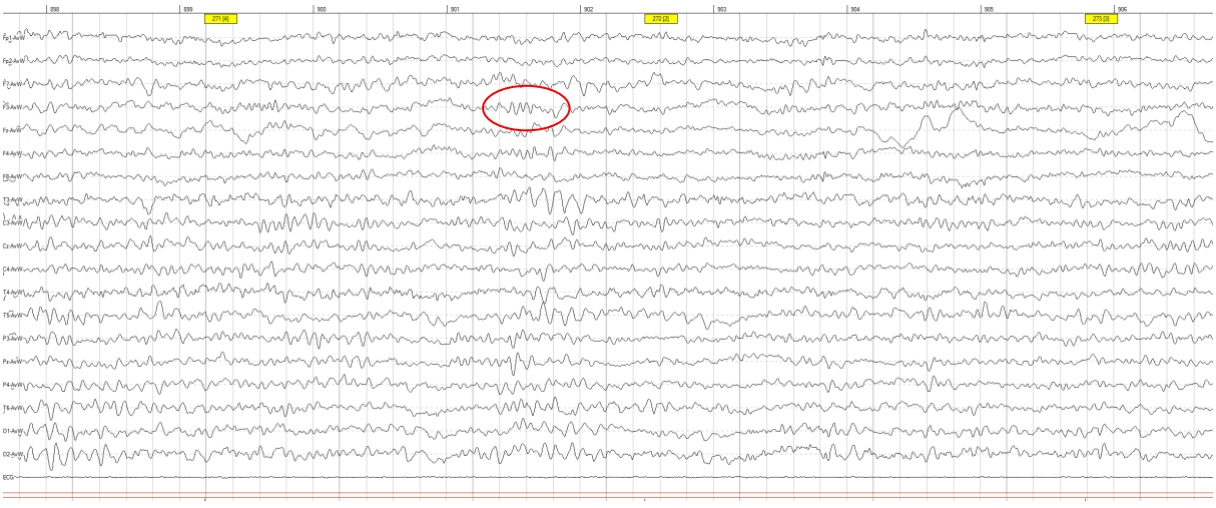
1.4.4.3 Advantages and disadvantages of EEG. There are several advantages of applying EEG in pain research. Generally, one of the greatest strengths of EEG is the good

temporal resolution, as it can detect electric potentials in the scope of milliseconds (Morton et al., 2016). Thus, it is more suitable for studying temporal aspects of the cerebral pain response, for instance the concept of pain *expectation* (Morton et al., 2016). In addition, the EEG-device is very cost-efficient, portable and largely available across many institutions (Morton et al., 2016). Given that neural activity can be measured directly through scalp electrodes, it is also very time-efficient (Teplan, 2002).

Like all other neuroimaging methods, EEG also comes with weaknesses. A recognized issue with EEG is the spatial resolution. One of the main reasons for this is the ’inverse problem’ or ‘source localization problem’, which involves estimating the source of the scalp potential measurements (Jatoi, Kamel, Malik, Faye, et al., 2014). During the EEG-recording, electrical currents must travel through several resistive layers of the brain, including the skull, which creates a blurring effect and results in a distorted view of the brain activity (Burle et al., 2015). Thus, each electrode measures a spatially smoothed version of the local field potentials underneath the scalp (Buzsáki, 2006). As a result, the EEG generally has a spatial resolution of approximately 5-9 cm^2 (Burle et al., 2015), which is poor compared to brain imaging methods like fMRI.

Figure 2

EEG of fibromyalgia patient



Note. An example of excessive beta is shown at lead F3.

1.5 Pain theories

1.5.1 Earlier theories. Several different theories have been proposed to explain pain and the underlying mechanisms. According to Moayedi and Davis (2013), 4 of the historically

most influential theories of pain are 1) the Specificity Theory, 2) the Intensity Theory, 3) the Pattern Theory and 3) the Gate Control Theory. In the Specificity Theory of Pain, pain and touch are considered to be processed through different pathways and by different sense organs. The Intensity Theory of pain discarded the idea of specific pathways and postulated that pain was created by stronger activation of neurons by an intense stimulus, while non-painful sensations were created by a weaker activation. According to the Pattern Theory of Pain, pain perception happens as a result of intense stimulation, that leads to the activation of specific patterns of neural activity. (Moayedi & Davis, 2013).

Common for the three aforementioned theories of pain is that they consider pain signals to be passively delivered to the brain (Woolf, 2011). Melzack's Gate Control Theory of Pain from 1965 was the first theory that included the influence of central control processes in the brain (Melzack & Katz, 2004). The theory emphasized how the brain actively filters, selects and modulates inputs from the environment, and gave account for the role of the dorsal horns in excitation, inhibition and modulation of pain signals (Melzack, 1999).

1.5.2 Neuromatrix. Building on the Gate Control Theory, Melzack launched a new theory in the 90s called the neuromatrix theory of pain (Melzack, 1999). Melzack (1999) introduces a distributed neural network in the brain, called the "neuromatrix", and highlights the importance of synaptic structures within this network. According to the theory, both genetics, sensory influences, and cognitive events such as psychological stress influence the "neurosignature output", which comprises patterns of nerve impulses varying on spatial and temporal scales. Thus, the pain experience was no longer considered to be solely dependent on injury, inflammation or other tissue damage (Melzack, 1999).

1.5.3 Pain matrix. Following the implementation of various brain imaging and electrophysiological methods, pain theories advanced further. Specific brain areas involved in pain processing were identified, using either fMRI, PET, EEG or MEG (Iannetti & Mouraux, 2010). As a result, the term neuromatrix was replaces with "pain matrix", consisting of structures such as the primary (SI) and secondary (SII) somatosensory, insular and anterior cingulate (ACC) areas (Legrain et al., 2011). As opposed to the neuromatrix, the output of the pain matrix is considered to be (at least partially) pain specific (Iannetti & Mouraux, 2010). According to the theory, pain matrix represents a unique neural signature of pain perception, and has therefore been used to study the underlying mechanisms of pain and pain pathology (Iannetti & Mouraux, 2010).

Some evidence has shown support for the pain matrix theory. For example, most experimental studies show activation of pain matrix structures in response to nociceptive

stimuli, and correlation between activation and pain intensity (Iannetti & Mouraux, 2010). However, more recent studies have found evidence that contradicts previous conceptions and findings. For instance, evidence has found that the pain matrix 1) can be dissociated from perception of pain intensity, 2) is influenced by other factors than intensity of nociceptive input, and 3) can be activated by stimuli that is neither nociceptive nor painful (Legrain et al., 2011). Thus, although the pain matrix is linked to pain perception, there seems to be other functions involved. Amongst others, the areas are found to be involved in cognition, emotion, motivation and sensation (Ossipov et al., 2014). According to Ossipov et al (2014), these are functionally connected to each other, and contribute to the pain experience itself (Ossipov et al., 2014).

1.5.4 Dynamic pain connectome. A more recent theory, described by i.a. Kucyi and Davis (2015), introduces the term "dynamic pain connectome" (DPC) that highlights the importance of dynamic network communication in pain perception. Given the relative consensus about the existence of a dynamic pain connectome (see for example Bosma et al., 2018; Kisler et al., 2020; Kucyi & Davis, 2015, 2017), we have chosen to focus on this network in the current study.

1.6 DPC: A dynamic view on pain.

The conceptualization of pain as a dynamic construct differs from earlier models of understanding pain. Historically, pain theories focused mainly on nociceptive processes, leaving out significant interactions with cognitive and attentional processes (Moayedi & Davis, 2013). According to the DPC theory, pain is a dynamic construct in which nociceptive, cognitive and attentional processes mutually influence each other, and combine to shape the pain experience (Moayedi & Davis, 2013).

In line with newer models of brain network communication, the DPC theory postulates that a "whole-brain-wide" network, or a "connectome", contributes to the experience of pain (Kucyi & Davis, 2015). The connectome includes several large-scale networks that are functionally connected to each other and are involved in a variety of different brain functions. Thus, according to the DPC-theory, the pain experience is a result of brain-wide network communication, which is expressed through specific spatiotemporal patterns of neural activation (Kucyi & Davis, 2017).

1.6.1 Attention and pain. Attentional processes in pain have gained a particularly important role in the DPC-theory. Pain signals threat to survival, and is therefore naturally attention-demanding (Kucyi & Davis, 2015). In the same way, attention-demanding tasks,

stimuli or thoughts can change the quality and salience of pain, as well as nociceptive processing (Kucyi & Davis, 2015). According to Kucyi et al. (2013) attention towards and away from pain fluctuates spontaneously.

A way of studying attentional pain fluctuations and its neural correlates is by sporadically questioning subjects about their experience, a method called "experience sampling", while measuring brain activity through fMRI (Kucyi & Davis, 2015). In Kucyi and Davis' (2015) study, healthy individuals received painful stimulation while randomly providing self-report regarding their focus. The subjects were questioned about whether their attention had been on pain or on something else (sensory distractions from the environment, thoughts about the task they were performing, or mind wandering). As a result, three functionally connected brain network were found to be involved in spontaneous fluctuations towards and away from pain, namely the salience network, the default mode network and the antinociceptive system (Kucyi & Davis, 2015). This is further elaborated in section 1.7. Furthermore, individual differences in these processes were discovered.

1.6.2 Individual differences in attention to pain. The degree to which individuals attend to pain varies, and this can be termed "intrinsic attention to pain" (IAP) (Kucyi & Davis, 2015). According to Kucyi et al. (2013), the variation in IAP has to do with functional connectivity between brain areas that are relevant to pain processing. They discovered that people who are more prone to mind wandering away from pain have stronger anatomical links and functional communication between networks within the dynamic pain connectome (DPC), specifically between the antinociceptive system and the default mode network (Kucyi et al., 2013). On the other hand, high IAP is associated with weak structural connectivity, and reduced variability in functional connectivity, between these areas (Kucyi & Davis, 2015). Thus, there could be a link between flexible communication within the DPC and the ability to cope with or redirect focus away from pain (Kucyi & Davis, 2015).

With respect to chronic pain populations, structural and functional abnormalities in the salience network, default mode network and the antinociceptive system have been identified (Kucyi & Davis, 2015). Kucyi and Davis (2015) hypothesizes that variations in IAP over time alters the structural and functional organization within the pain connectome. However, these processes have not been sufficiently investigated.

1.6.3 Electrophysiological correlates of pain-attention-interactions. Studies have shown that people with chronic pain have abnormal EEG activity patterns compared to healthy individuals (M. P. Jensen et al., 2013). For instance, people with chronic pain have more beta, delta and theta activity, but *less* occipital alpha activity than healthy controls (M.

P. Jensen et al., 2013). The reduction in alpha activity have been found primarily in eyes closed-condition (M. P. Jensen et al., 2013). Evidence shows that alpha band-oscillations functions as an attentional mechanism, through mediating selective suppression of distracting information (Foxe & Snyder, 2011). In awake EEG in eyes-closed condition, alpha activity typically dominates across the occipital lobe (M. P. Jensen et al., 2013). If the EEG-abnormalities found in chronic pain populations reflect increased pain, or reduced ability to suppress pain, therapies directed at altering EEG-signals (e.g. TDCS, neurofeedback) could aid in the relief of pain symptoms for this patient group (M. P. Jensen et al., 2013).

1.7 Areas and networks within the dynamic pain connectome

The further study of network dynamics within the DPC in people with fibromyalgia can provide valuable information about individual differences in the pain experience, and eventually discover potential biomarkers. To localize brain activity, research often use Brodmann Areas (BA; Brodmann, 1909), which are predefined regions of the cortex based on cellular architecture (Amunts, 2021).

By using Brodmanns method (morphology), there has been defined 52 distinct Brodmann areas (Strotzer, 2009). This is a universal way of mapping the cortex, and we can localize brain activity in these areas through e.g., EEG and source localization programs (see "Source Localization" in the method section). The Brodmann map is still used as a reference for interpreting results in neuroimaging studies (Amunts, 2021) and electrophysiological studies (Langerlund, 2021). See figure 3 and 4 for an overview of the different Brodmann areas.

Figure 3

Illustration of Brodmann areas from a lateral view, retrieved from Gray and Lewis (2000).

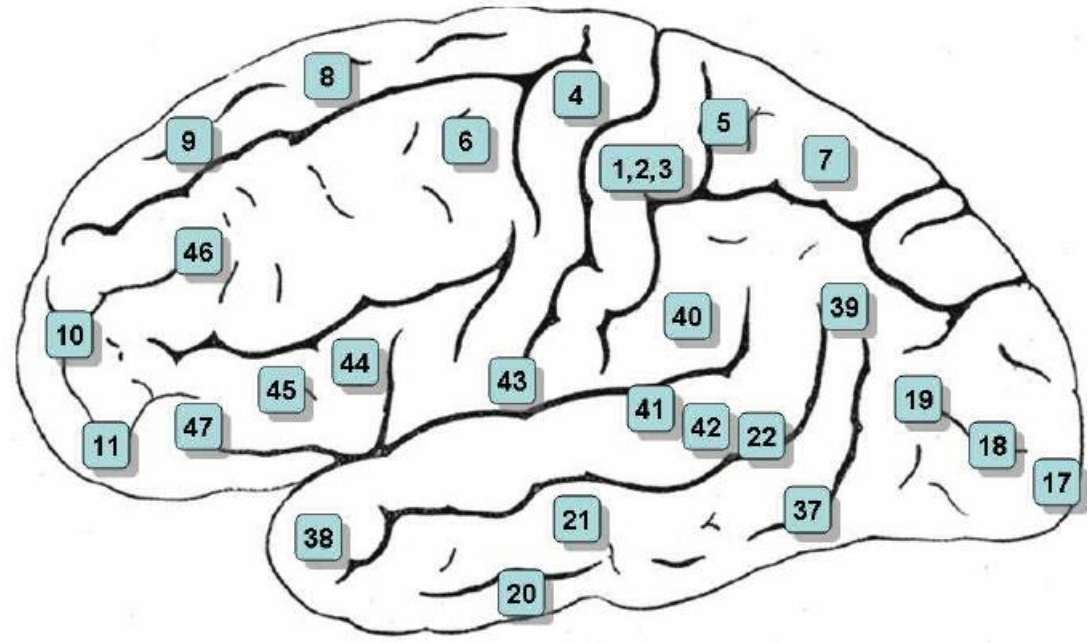
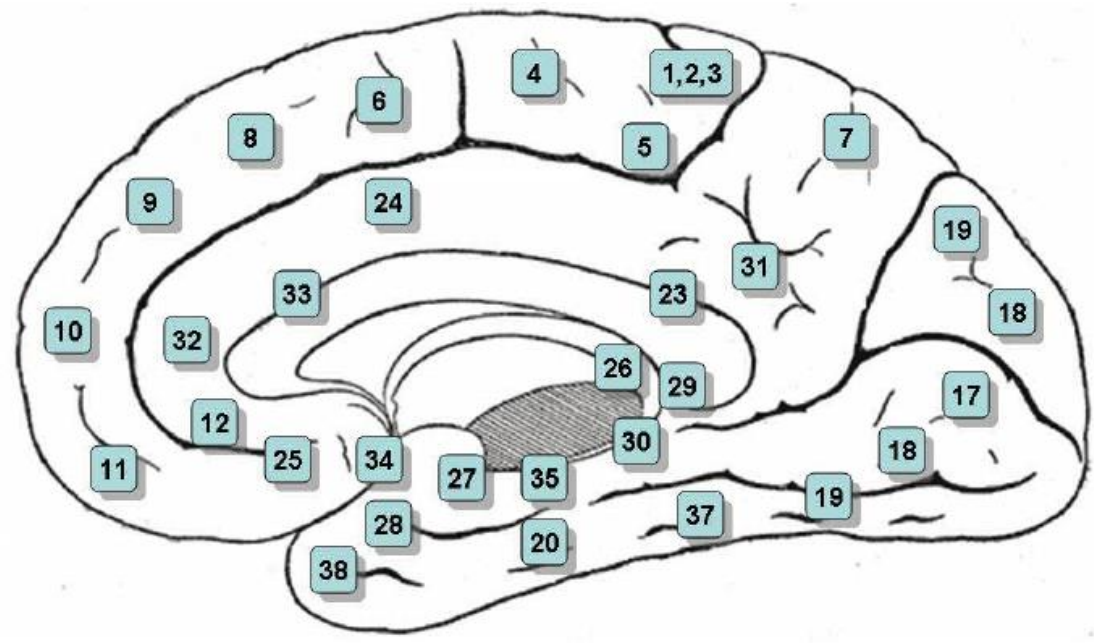


Figure 4

Illustration of Brodmann areas from a medial view, retrieved from Gray and Lewis (2000).



Three brain systems are considered to be key contributors of the dynamic pain connectome: the salience network (SN), the default mode network (DMN) and the antinociceptive system (AS) (Kucyi & Davis, 2015), which all consist of defined Brodmann areas. In the following section we will go through networks of the DPC, explaining core regions and nodes of each network. Then we will provide an overview of the BAs of the networks, and thereby also the BAs of the dynamic pain connectome.

1.7.1 The salience network. Activation of the salience network (SN) has been linked to processing of salient information, including nociceptive, emotional, social, cognitive and homeostatic information (Ullsperger et al., 2010). According to a meta-analysis conducted by Bartra et al. (2013), the network responds to salient information of both positive and negative value. With respect to pain, fMRI studies have demonstrated greater activation in the salience network when subjects attend to painful stimulus, compared to when they attend to something else (Kucyi & Davis, 2015).

1.7.1.1 Core regions. The anterior insula (aINS) and the anterior cingulate cortex (ACC) are considered to be key hubs of the SN (Seeley, 2019). In addition, the mid-cingulate cortex (MCC), the temporoparietal junction (TPJ) and the dorsolateral prefrontal cortex (dlPFC) are central areas (Kucyi & Davis, 2015). The network also consists of nodes in subcortical areas, including the amygdala, hypothalamus, ventral striatum, thalamus, and specific brainstem nuclei (Seeley, 2019). In the following section, important nodes of the salience network will be presented, along with their respective functions. Subcortical areas will not be further elaborated, as they are not directly detectable using EEG. See table 1 for an overview of the brain regions and corresponding Brodmann areas of the SN.

1.7.1.2 Important nodes and their function. The anterior insula (aINS) is considered to be a key node of the salience network, and is located at Brodmann area 13 (Ardila et al., 2016). Network analyses have demonstrated a critical role with respect to cognitive control and attentional processes (Menon & Uddin, 2010), and amongst others, it is found to be an important component in error detection (Ullsperger et al., 2010). According to Menon and Uddin (2010), the aINS functions as an "integral hub" that marks salient events, switches between large-scale networks (specifically the DMN and central executive network (CEN)), and initiates appropriate control signals and behavioral responses. The aINS has strong connections to several structures in the limbic system, including the amygdala, orbitofrontal cortex, olfactory cortex, ACC and superior temporal sulcus (Uddin, 2015). Both acute, chronic, physical and psychological pain activate the aINS (Uddin, 2015).

Another key component of the SN is the ACC, including Brodmann areas 24, 25, 32, 33 (Stevens et al., 2011). The ACC in general has strong functional connectivity to the aINS, and is thought to modulate responses in the sensory, motor and association cortex, following the marking of salient events by aINS (Menon & Uddin, 2010). Recently, a type of spindle neurons called "Von Ecomono neurons" has been located only in the cingulate (dACC and MCC) and insular cortices of the human brain (Stevens et al., 2011). Menon and Uddin (2010) hypothesize that these neurons ensure fast control signals from the ACC and the aINS, as part of the salience network. The ACC is reportedly found to be involved in functions like executive tasks, homeostatically incongruous physical states, and encoding of pleasant and aversive stimuli (Gasquoine, 2013). The area has connections both to the limbic system and to the prefrontal cortex, and is therefore thought to play an essential role in affect regulation and integration of neural information (Stevens et al., 2011). Abnormal neural activity in the ACC has been reported in several psychiatric conditions, in addition to chronic pain (Gasquoine, 2013).

The dorsal part of the ACC has been split off as a distinct anatomical area, called MCC, and includes Brodmann areas 24, 32 and 33 (Stevens et al., 2011). The MCC has strong connections to both cognitive and motor-related areas, and to pain- and motor-related areas of the thalamic nuclei (Stevens et al., 2011). The area is described by Stevens and collegues (2011) as "cognitive", being involved in tasks like conflict-monitoring, response-selection and execution. The anterior part of MCC is especially related to vulnerability to chronic pain (Vogt, 2016).

The dorsolateral prefrontal cortex (dlPFC) is located at Brodmann areas 46 and 9 (Gupta & Tranel, 2012). The area has been found to play a critical role in executive functions, such as working memory and selective attention (Curtis & D'Esposito, 2003). In addition, mounting evidence from chronic pain patients shows that activity in the dlPFC is associated with increased sensitivity to both painful and non-painful somatic stimuli (Hubbard et al., 2020). According to Hubbard and colleagues (2020), this can indicate impairments of somatosensory gating in patients with chronic pain (Hubbard et al., 2020). Furthermore, several studies have found a link between dlPFC-activity and pain catastrophizing (Ellingson et al., 2018; Gracely, 2004; Hubbard et al., 2020).

Lastly, the temporoparietal junction (TPJ), located at Brodmann area 39 (Bzdok et al., 2013), is an important node in the salience network. One of its main functions is to draw attention to changes in sensory input, and coordinate brain activity in order to elicit appropriate behavioral responses (Bosma et al., 2018). Research has demonstrated functional

deficits in the TPJ, as well as abnormal communication between the TPJ and other areas of the dynamic pain connectome, in people with chronic pain (Bosma et al., 2018).

Table 1

An overview of the brain regions and corresponding Brodmann areas of the salience network.

Brain region	Brodmann areas
Anterior insula (aINS)	13
Anterior cingulate cortex (ACC)	24, 25, 32, 33
Mid-cingulate cortex (MCC)	24, 32, 33
Temporoparietal junction (TPJ)	39
Dorsolateral prefrontal cortex (dlPFC)	46, 9
Amygdala	-
Hypothalamus	-
Ventral striatum	-
Thalamus	-
Specific brainstem nuclei	-

1.7.2 The default mode network. The default mode network (DMN) is a brain system that is activated when our mind is wandering (not thinking of anything specific), resting or if our attention is unengaged in the external sensory world (Andrews-Hanna et al., 2014; Leech & Sharp, 2014). Kucyi et al. (2013) found that this particular system is deactivated when attention is maintained on pain, and not deactivated when attention fluctuates away from pain. In addition, Kong et al. (2010) found a decrease of activity (BOLD-signal) in DMN core regions during painful stimulation of subjects. Impairments in DMN activity has also been linked to several different neurological and neuropsychiatric disorders (Mohan et al., 2016).

1.7.2.1 Core regions. The DMN comprises of several areas that are functionally connected to each other, and there seems to be consensus that posterior cingulate cortex (PCC)/precuneus/retosplenial cortex (Rsp), medial prefrontal cortex (mPFC), inferior parietal lobule (IPL) and subcortical areas within the medial temporal lobe (MTL) constitute core regions of the network (Buckner et al., 2008; Kucyi & Davis, 2015). See table 2 for an overview of the brain regions and corresponding Brodmann areas of the default mode network. Here we will examine the Brodmann areas that constitute the DMN, as well as possible functions of these nodes.

1.7.2.2 Important nodes and their function. PCC and precuneus seem to have a pivotal function in the DMN, as it appears to be the only node directly interacting with essentially all other nodes (Fransson & Marrelec, 2008). PCC includes Brodmann areas 23/31 and is located next to precuneus (BA 7) and Rsp (BA 29/30) in the medial inferior parietal lobe (Buckner et al., 2008; Leech & Sharp, 2014). Also, Brodmann areas 39 and 40 of IPL is part of DMN (Buckner et al., 2008). Leech and Sharp (2014) postulate that PCC is involved in internally directed thought and cognition, and could be important in regulating our attention, both internally-externally and the width of the attention span. Both PCC and precuneus are associated with self-referential and emotional introspective processes (Broyd et al., 2009).

mPFC is also an important part of the DMN. More specifically, dorsomedial prefrontal cortex (dmPFC), and parts of ventral medial prefrontal cortex (vmPFC) and anterior medial prefrontal cortex (amPFC) are important nodes of the network within mPFC (Andrews-Hanna et al., 2014). According to Jonker et al. (2017), dmPFC is associated with self-awareness, and could be part of a system that enable us to switch our attention from external to internal self-representations. dmPFC includes Brodmann areas 8, 9, 10, 24 and 32, whereas vmPFC comprises Brodmann areas 10, 24 and 32 (Buckner et al., 2008). amPFC includes BA 9, 10 and 32 (Schmitz & Johnson, 2006). According to Lieberman et al. (2019), vmPFC (as well as dmPFC) is linked to social processes, and amPFC is related to self-processes. In addition, both vmPFC and amPFC are associated with affective processes (Lieberman et al., 2019).

Lastly, there are several subcortical nodes in the MTL. They consist mainly of the hippocampus and parahippocampal formation, which are related to episodic memory function (Buckner et al., 2008). These nodes seem to communicate with the rest of DMN through entorhinalcortex (Ec) and PCC/Rsp (Greicius et al., 2009), but do not have corresponding Brodmann areas, as they are not cortical brain regions.

Table 2

An overview of brain regions and corresponding Brodmann areas of the default mode network.

Brain region	Brodmann areas
Posterior cingulate cortex (PCC)	23, 31
Precuneus	7
Retosplenial cortex (Rsp)	29, 30
Inferior parietal lobe (IPL)	39, 40
Dorsomedial prefrontal cortex (dmPFC)	8, 9, 10, 24, 32
Ventral medial prefrontal cortex (vmPFC)	10, 24, 32
Anterior medial prefrontal cortex (amPFC)	9, 10, 32
Subcortical areas of MTL	-

1.7.3 The antinociceptive system (AS). The AS is a descending pain modulatory system, that constitutes the third part of the pain connectome (Kucyi & Davis, 2015). It can be described as an endogenous control system, whose *main* function is to attenuate nociception and reduce pain (Yamamotová, 2019). However, it has later become evident that pain modulatory systems also can have a facilitatory effect (Kwon et al., 2014).

Key structures in the AS are the periaqueductal gray (PAG) and the rostral ventral medulla (RVM) (Hemington & Coulombe, 2015). PAG is an important node of the AS, and is mainly known for mediating pain suppression (Kucyi et al., 2013). The area receives direct input from the cortex, hypothalamus and amygdala (Yamamotová, 2019), and projects to the RVM, which again sends either inhibitory or facilitatory projections to the dorsal horn in the spinal cord (Hemington & Coulombe, 2015). As PAG and RVM are subcortical areas, they do not have corresponding Brodmann areas, and are not directly detectable with EEG.

According to Kucyi et al. (2013), when people engage in mind wandering away from pain, there are stronger functional connections between the PAG and the DMN, particularly the medial prefrontal cortex (mPFC). Furthermore, Kucyi et al. (2013) found that people who are more prone to mind wandering have stronger anatomical links and functional communication between the two areas. These individual differences could contribute to explain why some people are unable to disengage from pain (Kucyi et al., 2013).

1.8 Fibromyalgia

Fibromyalgia (FM) is primarily a chronic pain syndrome, and is a diagnosis given to patients with generalized pain without a physical explanation of the symptoms (Wolfe et al., 2010). It is also a condition characterized by unsatisfactory sleep, physical exhaustion (fatigue), and cognitive difficulties (i.e. fibrofog) (Häuser & Fitzcharles, 2018). In addition, FM patients often have comorbid disorders, which makes both the diagnostic process and the treatment challenging (Chakrabarty & Zoorob, 2007). FM affects many people, and has a worldwide prevalence of 2-3% (Sarzi-Puttini et al., 2020). Additionally, the prevalence is even higher in selected clinical samples (Neumann & Buskila, 2003). FM mostly affects women, and studies across cultures and ethnicity have estimated that approximately 90 % of FM patients are female (Yunus, 2001).

Unexplained widespread pain is the most important characteristic of fibromyalgia, and people with the disorder may experience hyperalgesia (increased pain responses to normally painful stimuli) or allodynia (pain responses to normally nonpainful stimuli) (Clauw, 2009). Also, muscular pain is the most prominent feature in most cases, and it is usual for the patients to have a diffuse tenderness in several body areas (Clauw, 2014). Earlier on, the FM diagnosis was given after a physical tender point examination of the patient, but now the diagnosis is based on subjective evaluations (Wolfe et al., 2010).

In addition to pain, FM has several accompanying ailments that can be debilitating for the patient. Sleep disturbances is reported by roughly 80% of the patients (Wu et al., 2017), but some studies have shown a prevalence of over 90% (Bigatti et al., 2008). It is established that poor sleep quality is associated with several mental health problems and psychiatric disorders (Freeman et al., 2020), and it also seems to have a mediating role between pain and fatigue (Nicassio et al., 2002).

Fatigue is a subjective symptom of malaise or physical exhaustion, and has a major impact on everyday functioning and quality of life (Sharpe & Wilks, 2002). It is an important component of the FM experience, and patients have rated it as a highly significant feature of their disorder (Crawford et al., 2011). Most FM patients experience fatigue (prevalence of 78-94%), with approximately 16-80% meeting the criteria for chronic fatigue syndrome (CFS; Finan & Zautra, 2010).

Fibrofog is the term used to describe subjectively experienced cognitive difficulties associated with fibromyalgia, such as forgetfulness, loss of mental clarity and inattentiveness (Kravitz & Katz, 2015). This type of dyscognition has a negative impact on several aspects of

the individuals lives (e.g. difficulties with attending to a conversation), but it is relatively understudied as a symptom (Williams et al., 2011).

In addition to several characteristic symptoms of FM, the patients often have comorbid medical or psychiatric disorders such as irritable bowel syndrome (IBS), CSF, migraine, anxiety, and depression (Buskila & Cohen, 2007; Hudson et al., 1992). The psychiatric comorbidity could be as high as 30-60%, and anxiety and depression are the most common comorbid disorders (Clauw, 2009).

1.8.1 Diagnostic criteria. The American College of Rheumatology (ACR) first defined fibromyalgia as a disorder in 1990 and have revised and simplified the diagnostic criteria since then. The ACR criteria is generally accepted for diagnosing FM, and provides a valid evaluation without a physical examination of the patient (Wolfe et al., 2010). The ACR questionnaire is based on self-report, and FM is therefore a diagnosis established through subjective evaluation of pain.

Widespread Pain Index (WPI) and Symptom Severity scale (SS) are important variables in this process, as they together form the Fibromyalgia Symptom scale (FS; total symptom pressure) in ACR criteria. ACR recommend following points as diagnostic criteria for fibromyalgia: 1) WPI ≥ 7 *and* SS ≥ 5 or WPI of 3-6 *and* SS ≥ 9, 2) Symptoms have been at a similar level for a minimum of 3 months, and 3) The patient does not have a disorder that could otherwise explain the pain (Wolfe et al., 2011; Wolfe et al., 2010). See method section ("questionnaires") for further elaboration of the ACR questionnaire, and appendix C for the Norwegian version.

1.8.2 Treatment. There are currently no standardized methods to treat fibromyalgia, and treatments are often ineffective (Macfarlane et al., 2017; Sarzi-Puttini et al., 2008). As previously stated, FM is a complex diagnosis with very different expressions. FM patients are heterogeneous as a group, and comorbidity is common. Because of its complexity, several domains could be of interest in treatment, such as pain, fatigue, overall quality of life etc., depending on the individual patient (Rahman et al., 2014). Several researchers suggest a multidisciplinary therapy, including both pharmacological and nonpharmacological treatments (Clauw, 2009).

To date, there are no healing medical treatments of FM, and traditional pain medications have little effect (Forseth & Gran, 2006). The use of antidepressants is frequent in FM treatment, such as tricyclic antidepressants (TCA), dual serotonin norepinephrine reuptake inhibitors (SNRI) or selective serotonin reuptake inhibitors (SSRI), recommended in the order they are listed. TCA is preferred because of its effectiveness, but SSRI is typically

better tolerated (Dharmshaktu et al., 2012). It seems like some patients experience symptom relief with the use of antidepressants, but in many cases the adverse effects outweigh the benefits (Häuser et al., 2012). In addition to antidepressants, there are other pharmacological treatments in clinical use for FM, such as antiepileptika (reduces pain, sleeping problems and tiredness), but this is not as regular as the aforementioned (Forseth & Gran, 2006).

The best studied nonpharmacological treatments are education, cognitive behavioral therapy (CBT) and exercise, which all display evidence of some improvement of FM patients' functioning (Clauw, 2014). Management of accompanying symptoms such as sleep disturbance is also recommended (Roizenblatt et al., 2011). At the same time, despite a multidirectional approach, treatment is often inadequate. This often results in reoccurrence of pain (Hackshaw, 2020).

More recent research has led to the development of promising treatment methods for fibromyalgia, such as neurofeedback training (NFT; Wu et al., 2021) and transcranial direct current stimulation (tDCS; Marlow et al., 2013), but more research is necessary to optimize the procedure and confirm the effect. NFT is a therapeutic application of EEG, and provides an operant conditioning procedure that supports the patient's ability to modify neurophysiologic dynamics of the brain (Kayıran et al., 2010). Transcranial direct current stimulation (tDCS), on the other hand, is a non-invasive brain stimulation technique, where application of low amplitude direct current to the scalp is thought to influence the excitability level of underlying neurons (Valle et al., 2009). Even though we have a growing understanding of fibromyalgia, the underlying causes of the disorder have not been fully identified. Future discoveries of FM pathophysiology and potential biomarkers could point us towards more suitable treatments tailored for the patients (Hackshaw, 2021).

1.8.3 Pathophysiology and biomarkers. The pathophysiology of fibromyalgia remains unclear. As a result, fibromyalgia is a condition with no known biomarkers, which means that we have no objective measures to differentiate FM as a disorder (Hackshaw, 2021). As of now, the FM diagnosis is merely based on subjective symptoms and the exclusion of somatic conditions that better explain these symptoms. This could lead to under-, over- and misdiagnosing of patients (Häuser et al., 2019). As previously stated, this could make treatment challenging.

Researchers and clinicians usually try to explain FM from a biopsychosocial perspective, and proposes several risk factors contributing to the pathophysiology of the disorder (Bradley, 2009). These include genetic factors, abnormal function of the autonomic and neuroendocrine systems, and environmental stressors (Bradley, 2009). At the same time,

the risk factors are also related to other conditions, such as psychiatric disorders (Arnold et al., 2006), CFS and irritable bowel syndrome (Aaron & Buchwald, 2003). Other factors include for example childhood problems, medical illnesses and somatic symptoms, which are factors directly or indirectly associated with pain (Creed, 2020). This implies a multiple causal pathway for developing fibromyalgia and chronic pain.

Per now, the best supported hypothesis for explaining FM pathophysiology is disturbances in pain processing, including augmented pain responses to experimental stimuli, as well as greater neurological activity in brain regions associated with pain processing (Bair & Krebs, 2020; Galvez-Sánchez & Reyes Del Paso, 2020; Hackshaw, 2021). Here, three promising and slightly different theories for explaining FM will be presented, namely the theory of central sensitization, the theory of predictive coding, and thalamocortical dysrhythmia. A common feature of the explanatory models is the proposition of a potential common underlying mechanism for developing fibromyalgia.

1.8.4 Central sensitization (CS). CS refers to the process of pain amplification by mechanisms in the central nervous system (CNS) (Harte et al., 2018). With the introduction of this concept, pain was no longer considered to be exclusively peripherally driven, but also influenced by central mechanisms (Harte et al., 2018). It includes a "prolonged but reversible increase in the excitability and synaptic efficacy of neurons in central nociceptive pathways" (Woolf, 2011), and leads to increased responsiveness to a variety of stimuli, e.g, pressure, temperature, light, and medication (Cagnie et al., 2014). Two common, clinically relevant manifestations of CS are hyperalgesia (increased pain responses to normally painful stimuli) and allodynia (pain responses to normally nonpainful stimuli) (Clauw, 2009).

The term was first introduced by Clifford J. Woolf (1983), at which point it was used to describe spinal mechanisms that enhanced ongoing nociceptive input following tissue damage from intense noxious stimuli. However, it has now been established that CS can occur both in the presence and absence of a peripheral injury or inflammation (Harte et al., 2018). Since the discovery of the phenomenon, it has become evident that various kinds of functional, chemical and structural plasticity can contribute to the sensitization of the central nociceptive system (Latremoliere & Woolf, 2009).

Central sensitization has been found to be present in almost all chronic pain conditions, including fibromyalgia (Harte et al., 2018). Today, CS is considered to be one of the most important pathophysiological factors in FM symptomology (Staud et al., 2007). Several experimental studies have shown that FM patients are more sensitive to nonspecific stimuli, for example pressure and temperature, which indicates the involvement of central

sensitization (Desmeules et al., 2003). Over time, researchers have attempted to develop clinical and evoked pain measurements that could function as CS markers and be used to aid and supplement the FM diagnosis (de la Coba et al., 2018). For instance, "quantitative sensory testing" (QST), which involves measuring and documenting sensory thresholds using direct patient feedback (Greer & Donofrio, 2009), has been widely used to derive markers of allodynia and hyperalgesia (Williams, 2018).

It is not yet known whether some people have higher risk of developing central sensitization than others, and if this in turn entails a larger risk of pain hypersensitivity and chronification (Woolf, 2011).

1.8.5 Predictive coding. Predictive coding has been proposed as a universal computational principle in the cortex, including the perception of pain (Song et al., 2021). It is now generally accepted that cognitive processes influence how we experience pain, but the exact mechanisms are yet to be completely understood (Pagnoni & Porro, 2014). The theory of predictive coding could potentially provide a better understanding of the development of chronic pain, including fibromyalgia.

The theory postulates that the brain constantly tries to predict the sensory world, and recent findings indicate that this also applies to pain perception. The framework of predictive coding is applied to placebo hypoalgesia with success, and findings suggest that the Bayesian formulation can directly account for differences in the extent and precision of expectations that contribute to pain and pain relief (Büchel et al., 2014). As fibromyalgia is a state of chronic pain without any clear cause, perhaps predictive coding could provide us with a better understanding. If experiences and expectations can influence how we perceive sensations, including pain, may also explain the development of FM.

As previously mentioned, beta rhythms seem to be more associated with top-down signaling, while gamma and theta could be more associated with bottom-up (Bastos et al., 2020). FM is a pain disorder without an objective painful stimulus, and therefore it may be relevant to consider top-down influence of sensory signals as a key contributor to the experienced pain. Potentially, due to the role of beta oscillations in top-down modulation, excess beta could be a potential biomarker for FM.

1.8.6 Thalamocortical dysrhythmia (TCD). TCD is described as a resonant interaction between thalamus and cortex, due to the generation of low-threshold calcium spike bursts in thalamus (Llinás et al., 1999). This results in coherent theta activity and is characterized by increased power at low frequencies. It is proposed as a possible causal- or contributing factor of neuropathic pain and disorders as fibromyalgia (Fallon et al., 2018).

Neuroimaging studies have proposed that fibromyalgia patients show altered thalamic structure and function, which could be linked to abnormal thalamocortical oscillations (Lim et al., 2016). Thalamus is a relay for pain signals (Brodin et al., 2016) and has extensive reciprocal connections with the cortex (Lim et al., 2016). Studies have found that disturbed thalamocortical activity could result in the constant perception of pain (Henderson et al., 2013), and chronic pain may be linked to functional, anatomical or biochemical changes in thalamocortical pathways (Groh et al., 2018).

We find further support for this hypothesis in studies on patients who suffer from chronic neurogenic pain, who also display an overactivation of pain related areas (e.g., ACC). Therapeutic lesions of these patients' thalamus (central lateral thalamotomy) led to a significant reduction of EEG overactivity in specific pain related areas (BA 24 and 32), as well as subjective pain relief (Stern et al., 2006).

1.9 Importance of the study

Fibromyalgia affects many people across the world (prevalence of 2-3 %), especially women (Yunus, 2001). The patients often undergo considerable suffering, and the condition has an adverse impact on quality of life (Häuser et al., 2019). In addition to the core symptoms of pain, fatigue, cognitive difficulties and sleep problems, the patients often have additional ailments such as affective problems and irritable bowel. This often affects daily activities and their ability to do work or housework (Bennett, 2005).

FM patients are a heterogenic group of people, which makes it a difficult diagnosis in many ways. The diagnostic process is very challenging, especially since there are no known objective measure or biomarker to confirm the disorder. There are also unclear boundaries between FM and several other illnesses, including psychiatric disorders (Bidari et al., 2018). Patients report to wait an average of 2.3 years and presenting to 3.7 different physicians before receiving a FM diagnosis, which emphasizes how difficult the diagnostic process is (Choy et al., 2010). Finding electrophysiological biomarkers could make the diagnostic process faster and easier, helping both the patient and health care professionals.

In addition to the fact that the diagnostic process is challenging, chronic pain patients often experience disbelief regarding their suffering (Wolfe, 2009). Fibromyalgia women are at risk of being stigmatized, both by health care professionals and by society in general, and there seems to be three themes contributing to stigmatization of FM-women: 1) Moralizing attitudes, including alleged laziness and failure to recover after receiving "medically correct" treatment, 2) Disbelief as to the reality of their pain, and 3) Pain's invisibility (Quintner,

2020). An objective measure to confirm an FM diagnosis could contribute to the destigmatization of the diagnosis and might improve the lives of the patients as well as helping healthcare workers provide proper treatment.

In addition to debilitating subjective symptoms, the financial and social costs are substantial (Bair & Krebs, 2020). Patients with FM are associated with considerably higher costs in primary health care settings compared to the general population (Sicras-Mainar et al., 2009). This is due to use of more pharmaceutical products, but also because of inefficiency in the diagnostic process. FM patients often have numerous clinical visits, examinations and specialist consultations (Häuser et al., 2019). At the same time, indirect costs make up most of the expenses, such as losses in productivity, fewer working hours, absence at work, disability, and early retirement, to mention some (Skaer, 2014).

To summarize, a better understanding of fibromyalgia, its pathophysiology and potential biomarkers could lead to earlier and more precise detection of the diagnosis. This could spare healthcare resources and societal costs, as well as giving the individual patient diagnostic confirmation and proper treatment. Per now, there are no standardized treatment for FM, and biomarkers could help the development of tailored treatments specifically for these patients. An objective measure to confirm the disorder could also remove stigma and disbelief regarding the FM diagnosis. Moreover, the FM research is now more relevant than ever after the covid-19 pandemic. FM patients are vulnerable, and isolation and pandemic-related stressors are likely to have a severe impact on this specific group (Mohabbat et al., 2020).

1.10 Aim and research questions

In the present study we wish to continue the search for FM qEEG (quantitative EEG) biomarkers, contributing to a better understanding of the disorder. The main purpose of the study was to investigate if FM patients have deviant brain activity in the dynamic pain connectome, and if this could provide potential biomarkers for the disorder. If this was the case, we wanted to see if specific areas within the DPC correlate stronger with perceived symptom intensity than other areas. This could contribute to a better understanding of FM symptomatology. Our study is a contribution to a series of several fibromyalgia studies at the EEG-lab (Eide, 2020; Ingvaldsen, 2019; Luckman & Gulbrandsen, 2019; Nordvoll & Bruun, 2021), but with some important alterations.

The use of standardized commercial normative databases is common in EEG-studies, for example The Human Brain Institute normative database for Mitsar in WinEEG (Bio-

Medical Instruments, 2021). Such normative databases have also been used in previous studies at the EEG-lab due to unavailability of other control groups (Eide, 2020; Ingvaldsen, 2019; Luckman & Gulbrandsen, 2019). This raises several problems when comparing the subject- and control group; 1) The Mitsar normative database consists of an unknown number of Russian subjects, which means that it contains a completely different population and culture than our subject group. By using our own control group, we ensure that they are age matched and from the same population as the subject group, 2) We do not know how the researchers explained the procedure to the subjects, which could influence the results. For example it is found that focusing on speed vs. accuracy make significant changes in the EEG recordings in VCPT-condition (Aasen, 2013; see method section for more information), and 3) We do not know their procedure for artifact correction. Thereby, by using the exact same procedure (instructions and artifact correction) for both subject- and control group, we remove several potential interfering factors. Lastly, and possibly an important point, 4) The use of different equipment on subject- and control group could be problematic, such as when a different amplifier is used for collecting normative data. Most amplifiers do not amplify the EEG signals in a linear manner, but will often display some attenuation at the highest (gamma) and lowest (delta) frequencies (Teplan, 2002). By using the same amplifier for both subject- and control group, we eliminate the different frequency characteristics from amplifiers, and the potential influence of measurement errors on the data. Thereby, using the exact same procedure (instructions and artifact correction) and equipment for both subject- and control group, we reduce possible interference from confounding variables. Hence, we also reduce the risk of false positive results (type 1 errors) (Field, 2018, p. 82).

We have also considered recommendations from the previous studies at the EEG lab regarding sample size, just as Nordvoll and Bruun (2021) did in their study. Our sample is much bigger than the previous studies (Eide, 2020; Ingvaldsen, 2019; Luckman & Gulbrandsen, 2019), which could increase the statistical power and minimize the chance of false negative results (type 2 errors) (Field, 2018, p. 82).

Lastly, we chose to conduct individual power spectra analyses as recommended by the most recent study at the EEG-lab (Nordvoll & Bruun, 2021). It is often more practical to investigate the average of a population than analyzing all subjects individually (Arah, 2009). Because of the strong heterogeneity of the FM population, a lot of information can be lost when computing a grand average of the power spectra brain activity. We hope that individual spectra analysis (comparing each FM subject's brain activity with the control group) could provide more information, with higher sensitivity and more precision. The individual analysis

also enables the examination of the connection between individual brain activity and subjective symptom pressure.

Building on existing research on fibromyalgia, as well as recommendations for future research from previous studies at the NTNU EEG-lab, the current study wishes to investigate the following research questions (RQ) and hypotheses:

1. Do fibromyalgia patients have deviant spectral power brain activity compared to healthy controls?
    - Hypothesis I: FM patients have more overactivation of beta frequency compared to other frequency bands.
    - Hypothesis II: FM patients have significantly less occipital alpha band frequency occipitally than healthy controls.
2. Do fibromyalgia patients have deviant brain activity in the pain connectome compared to healthy controls?
3. Does the amount of deviant activity within the pain connectome correlate with perceived symptom intensity (scores on ACR, FIQ or VAS) among FM patients?
4. Is specific BA within the pain connectome associated with perceived symptom intensity (ACR, FIQ or VAS) among FM patients?
    - Hypothesis I: There are no strong correlations between single Brodmann areas and perceived symptom intensity.
    - Hypothesis II: There is a stronger correlation between perceived symptom intensity and the salience network, compared to the default mode network.
5. Is deviant activity in DPC with *specific frequency bands* associated with symptom intensity (ACR, FIQ or VAS) among FM patients?
    - Hypothesis: Deviant beta band frequency in DPC correlate stronger with perceived symptom intensity.

2. Method

2.1 Subjects

For this study we used data from fibromyalgia patients collected in a long-term project at the EEG lab at NTNU. Participants were recruited through the Fibromyalgia Association (Fibromyalgiforeningen) in Sør-Trøndelag, as well as self-help forums for FM patients on Facebook. The subjects have previously participated in various studies at the lab (see Luckman and Gulbrandsen (2019) Ingvaldsen (2019) and Eide (2020) for more information). Data for the control group were also collected at the EEG lab. This group was essentially recruited through convenience and snowball sampling, where information was posted on social media with the encouragement of further recruitment. People who were interested (both study- and control group) received information about the relevant study and an informed consent schema per e-mail (see appendix B). The project was approved by the Norwegian Regional Ethics Committee (REK). All participants gave their informed consent for using the data material presented.

2.1.1 Study group. Initially ,73 women (age 18-72) were recruited for the study group, all diagnosed with fibromyalgia by authorized health care personnel. 5 were not included in our study as they did not meet the ACR diagnostic criteria for FM (Wolfe et al., 2010). In addition, 5 more participants were excluded because of noisy EEG recordings. Interference in the EEG of FM patients is not surprising, as muscular artifacts (e.g. due to pain) is known to interfere with the recordings (Reis et al., 2014). However, artifact correction was possible in most cases. Remaining participants did not have significant hearing- or visual impairment, as this could influence the EEG recordings when they are presented with visual or auditive stimuli. There were cases of comorbidity in the study group, including migraine and mood disorders, but no patients had severe psychiatric or neurological disorders.

For EEG analysis, we included a total of 63 women (N=63). Some of these used pharmacological medication during the test period and were not instructed to discontinue these. Unfortunately, the lists of pharmaceuticals and comorbid disorders among the FM patients are incomplete, and some medications are known to influence EEG (Blume, 2006; Kropotov, 2016; Kropotov, 2008).

For statistical analysis we had a slightly smaller selection than for EEG-analysis. Sadly, due to covid-19, we were not able to gather questionnaires from all the FM subjects. This made the sample size even smaller in the analysis of subjective symptom intensity, as we only received completed questionnaires from 50 or 51 subjects, on FIQ/VAS and ACR

respectively. Only these were included in our second part of analysis (n = 50 for FIQ and VAS, n = 51 for ACR).

2.1.2 Control group. For the control group, we used EEG-data from another project collected at the NTNU lab. The group contained 29 healthy subjects between the ages of 20-51, 24 females and 5 males, who reportedly had no chronic pain or known mental illness. Males were included in the group despite fibromyalgia being a "female disorder". We know that there are some neuroanatomical differences between men and women, but not all studies have found gender differences in EEG-recordings (Kaiser, 2007). We therefore chose to include the men, leading to a bigger control group and a larger basis for comparison.

2.2 Design considerations

2.1.1 Why EEG? One of the most important reasons why EEG was employed in this study was availability, as access to EEG equipment was provided through the NTNU lab. In addition, EEG as a method has several strengths compared to other brain imaging methods, including low costs, time-efficiency and mobility (Ploner & May, 2018). It is also generally available across several institutions (Morton et al., 2016). Therefore, potential findings of electrophysiological biomarkers retrieved with EEG could easily be implemented in the diagnostic process of patients. Another technical strength of the method is the temporal resolution, which is exceptional compared to other brain imaging methods, like fMRI. EEG can detect neural events occurring in milliseconds, which makes it suitable to study temporal aspects of pain (Sturzbecher & de Araujo, 2012).

2.1.2 Spectral analysis. In the current study, spectral analysis was considered a suitable method for investing potential EEG-biomarkers for FM patients. Spectral analysis is an extensively used EEG analysis method, and includes sectioning EEG oscillatory activity into broad, pre-defined frequency bands in the delta, theta, alpha, beta and gamma range (Newson & Thiagarajan, 2019). Countless studies have reported significant correlations between EEG spectra and cognitive states, and it is now widely acknowledged as one of the primary analysis methods within the neuroscience field (Kim & Im, 2018). Today, the spectral analysis approach dominates the EEG literature with respect to developing objective symptom biomarkers (Newson & Thiagarajan, 2019).

Another potential approach could be to investigate event-related potentials (ERPs). However, as a part of the thesis delimitation, we chose to focus on spectral analysis of the EEG-data. Furthermore, the current study aims to investigate stable deviances in brain activity, rather than deviances in specific cognitive operations. As opposed to spectral

analysis, which is considered to measure cognitive *states*, event-related potentials (ERPs) reflect specific cognitive *processes* (Herrmann et al., 2014). Thus, spectral analysis is considered to be a more suitable analysis method for the purpose of the study.

2.1.3 Individual analysis. We chose to conduct individual analyzes, although this is more time consuming and cumbersome than a grand average comparison (Arah, 2009). Grand average comparison is a mean of all the subjects' brain activity, which means that a lot of information about the patients can be lost in the process. Especially because of the heterogeneity of the FM population. Therefore, we could potentially find significant brain activity deviances that are not detectible when computing a grand average. Nordvoll and Bruun (2021) also recommended individual analysis as the next step in the search for FM electrophysiological biomarkers.

An additional advantage of analyzing the patients' brain activity individually, is that we can investigate if individual brain activity is associated with subjective symptom severity (measured with different questionnaires). This is not possible using grand average.

2.1.4 Questionnaires. We considered American College of Rheumatology (ACR) to be the most important measure of FM-symptoms, as this is the accepted diagnostic tool for fibromyalgia (Wolfe et al., 2010). In addition, Fibromyalgia Impact Questionnaire (FIQ) and the Visual Analog Scale (VAS) were included, as they measure important aspects of FM, such as impact on daily life and subjective experience of pain (Burckhardt et al., 1991; Crichton, 2001). This facilitates a stronger insight into the relationship between brain activity and FM symptomatology.

2.2 Apparatus

2.2.1 ACR. All participants were required to meet the FM-criteria provided by The American College of Rheumatology (ACR), as this is the generally accepted and validated diagnostic tool for fibromyalgia. This also applies without a physical examination of the patient (Wolfe et al., 2010). As previously stated, the ACR consists of Widespread Pain Index (WPI) and Symptom Severity scale (SS), which together form the Fibromyalgia Symptom scale (FS; total symptom pressure). The ACR questionnaire were scored according to guidelines presented in Wolfe et al. (2010).

WPI is a measure of the number of painful body parts the patient has experienced during the past week. The patient marks the painful areas, and each area gives one point to the WPI-score (maximum score of 19). See table 3 for an overview of body areas.

Table 3.

Possible painful body areas (19 in total) in WPI.

Left upper region	Right upper region	Left lower region	Right lower region	Axial region
Jaw, left Shoulder girdle, left Upper arm, left Lower arm, left	Jaw, right Shoulder girdle, right Upper arm, right Lower arm, right	Hip (buttock, trochanter), left Upper leg, left Lower leg, left	Hip (buttock, trochanter), right Upper leg, right Lower leg, right	Neck Upper back Lowe back Chest Abdomen

SS consists of part 2A and 2B. 2A measures fatigue, sleep satisfaction and cognitive symptoms, and the patient is instructed to score symptom severity over the past week: 0 = no problem, 1 = Slight or mild problems, generally mild or intermittent, 2 = Moderate, considerable problems, often present and/or at moderate level, or 3 = severe: pervasive, continuous, life-disturbing problems (Wolfe et al., 2016). 2B is a symptom severity scale of other somatic symptoms, such as muscle pain, depression, irritable bowel syndrome etc. Based on the quantity of symptoms (of a total of 33), the patient was given points of: 0 = no symptoms, 1 = few symptoms (1-11 symptoms), 2 = a moderate number of symptoms (12-21 symptoms), or 3 = A great deal of symptoms (22-33 symptoms). 2A and 2B were summarized and combined to form the total SS scale (Wolfe et al., 2010).

2.2.2 FIQ. Fibromyalgia Impact Questionnaire (FIQ) is a self-report scheme that measures the overall impact of FM symptomatology, both in everyday tasks and general quality of life (Burckhardt et al., 1991). Even though the FIQ score is not a requirement for receiving a FM diagnosis, it is confirmed to be a valid tool for assessment of FM, both in English and Norwegian (Fors et al., 2020). See appendix D for the Norwegian version of the questionnaire.

The scheme is composed of 10 items as described in Burckhardt et al. (1991). The first item has 11 questions related to physical functioning and ability to manage typical daily activities (e.g., doing laundry or climbing stairs). Item responses were reported on a Likert scale: 0 = always, 1 = most days, 2 = occasionally, or 3 = never. The participant could choose

to delete items from the list that they would not normally do. To obtain a valid sum score, the mean sum (S) of the scores (total scores divided by the number of activities they normally do from the list) is calculated. Next, the sum is normalized before it is added to the other item scores S x 1.33.

Item 2 and 3 includes scores ranging from 0-7. Item 2 measures how many days the patient felt good during the past week. This item is scored inversely, in the way that higher scores indicate less negative impact on the person's life (0=7, 1=6, 2=5, 3=4, 4=3, 5=2, 6=1, 7=0). Item 3 is scored directly and represents the number of days that the patient missed work the past week, including housework, because of fibromyalgia. Both items are normalized before summation with other scores (S x 1.43).

Items 4-10 are scored on a scale from 1-10, measuring different symptoms or consequences of the fibromyalgia. Examples of these items are "When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework? (1 = no problem with work, 10 = great difficulty with work)" or "How nervous or anxious have you felt? (1 = not anxious, 10 = very anxious)". These scores can be summed directly (without normalization) and added to the scores of items 1-3. The total FIQ scale has a maximum score of 100, and higher scores indicate a greater negative impact on the individual (Bennet, 2005).

2.2.3 VAS. Visual Analogue Scale (VAS) is a tool used for measuring characteristics that cannot easily be measured, e.g. pain, that is believed to range across a continuum (Crichton, 2001). VAS is a 100 mm horizontal scale, where the patient makes a mark reflecting their perception (Heller et al., 2016). In our study, VAS consists of three scales: pain (ranging from "no pain" to "unbearable"), fatigue ("no fatigue" to "severe fatigue") and fibrofog ("no fibrofog" to "severe fibrofog"). VAS is shown to be an easy-to-administer and valid measure of FM symptoms (Bigatti & Cronan, 2002). See appendix E for a Norwegian version of VAS.

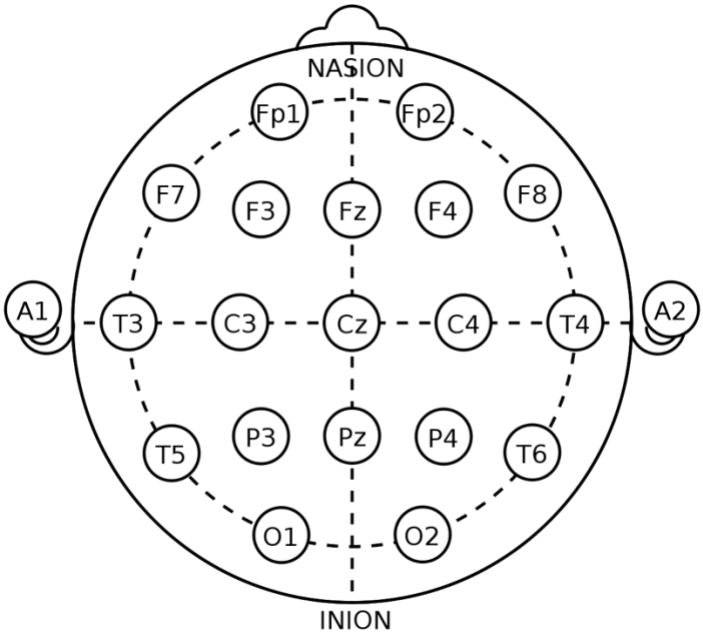
2.2.4 EEG. The data were obtained by using the standard procedure for electroencephalogram (EEG) as described in several studies (Demerdzieva & Pop-Jordanova, 2019; Høyland et al., 2017). EEG brain activity was recorded from a 19-channel tin electrode cap (Electrocap International Inc.) with an amplifier from Mitsar (St. Petersburg, Russia), version 202. The electrodes were placed according to the international 10-20 system on the scalp with reference to the earlobes (A1 and A2), allocated to following regions: Frontal (Fp1, Fp2, F3, Fz, F4, F7 and F8), temporal (T3, T4, T5 and T6), central (C3, Cz and C4), parietal (P3, Pz and P4) and occipital (O1 and O2) regions (see figure 5). The electrode positions are

measured in relation to known skull landmarks, namely nasion (in front), inion (in the back of the head) and the ear channels (from both sides) (Nisar & Yeap, 2015). Conductive gel (OneStep Cleargel, MedCat B.V.) was applied in all electrodes.

The input signals were filtered between 0.5 and 30 Hz and digitized at a sampling rate of 500 Hz. Impedance was kept below 10 kΩ for all electrodes. The data was collected and analyzed in Mitsars WinEEG software (version 2.140.113).

Figure 5.

10-20 system of electrode placement on the scalp, with reference to the earlobes (A1 and A2), nasion and inion.



2.3 EEG procedure

The EEG data in this study were collected by several lab assistants at the NTNU EEG-lab, including the authors of the thesis. This applies to the study group (FM-patients) as well as the control group. All assistants had prior necessary training and followed the same procedure for obtaining EEG-data. Ogrim and Kropotov (2020) explains this process thoroughly.

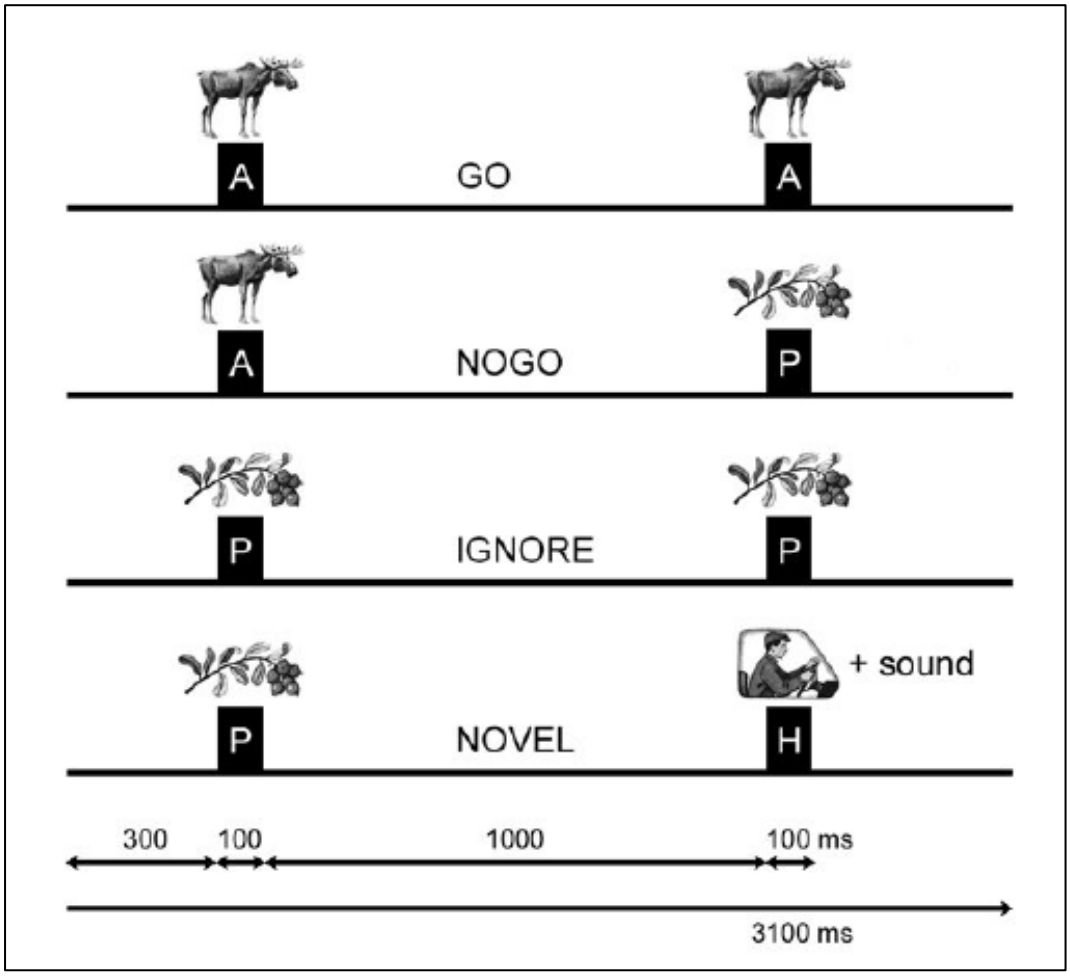
2.3.1 EEG recordings. EEG activity was measured in three conditions for all participants: 1) Eyes opened (EO), 2) Eyes closed (EC), and 3) Visual continuous performance task (VCPT) in psytask (1.50.12). EO and EC is a 6-minute resting EEG

registration (180 s each), whereas VCPT measures the persons cortical activation during attention demanding tasks for 20 minutes.

2.3.2 VCPT. In VCPT the subjects are presented with several visual stimuli, which are pictures of animals (a), plants (p) and humans (h; combined with sound). The pictures appear in paired sequences (a-a/a-p/p-p/p-h + sound), and the participants were instructed to push a button (mouse pad) as fast as possible only if the pictures show a-a (Go-condition). If the pictures show a-p (NoGo), the participants should discontinue to react, while p-p and p-h (+sound) are "ignore"-conditions. This is illustrated in figure 6. The trial consists of 400 paired pictures in total, and the subjects will have a small break every 100 pairs.

Figure 6.

Illustration of VCPT Go/NoGo task.



2.4 qEEG analysis

All data were artifact corrected and analyzed in WinEEG (Mitsar software version 2.140.113). Spectral analysis was conducted on all FM subjects and individually compared to the control group. Source localization was applied to significant ($p < .01$) positive deviances.

2.4.1 Artifact correction. The obtained data were artifact corrected before further analysis, as recordings may be affected by eye blinks, eye movements, cardiac activity, or other types of non-brain activity (Ille et al., 2002). Electromyogenic (EMG) artifacts, or muscle electrical activity, could also invalidate potential findings in EEG investigations and should be removed (McMenamin et al., 2010).

Artifact correction for eye blink was conducted by zeroing the activation curves of individual independent components corresponding to eye blinks (spatial filtration), in addition to horizontal eye movements (Ogrim & Kropotov, 2020). Also, epochs of the filtered EEG with excessive amplitude (>100 μV) and/or slow (>50 μV in the 0–1 Hz-band) and excessive fast (>35 μV in the 20–35 Hz-band) frequency activity was automatically excluded from further analysis. Manual artifact rejection was supplemented when needed (Ogrim & Kropotov, 2020).

2.4.2 Power spectra analysis. We conducted individual spectra analysis of all our EEG-data, which is a way of quantifying the amount of oscillatory activity of the different frequency bands in the raw EEG (qEEG). The spectral power is represented as topological distributions on the scalp surface, and indicates signal power at a temporal scale (Kim & Im, 2018). Each spectrum represents an average over four sequential epochs, where each epoch lasts 4 s (Kropotov, 2008, p. 127).

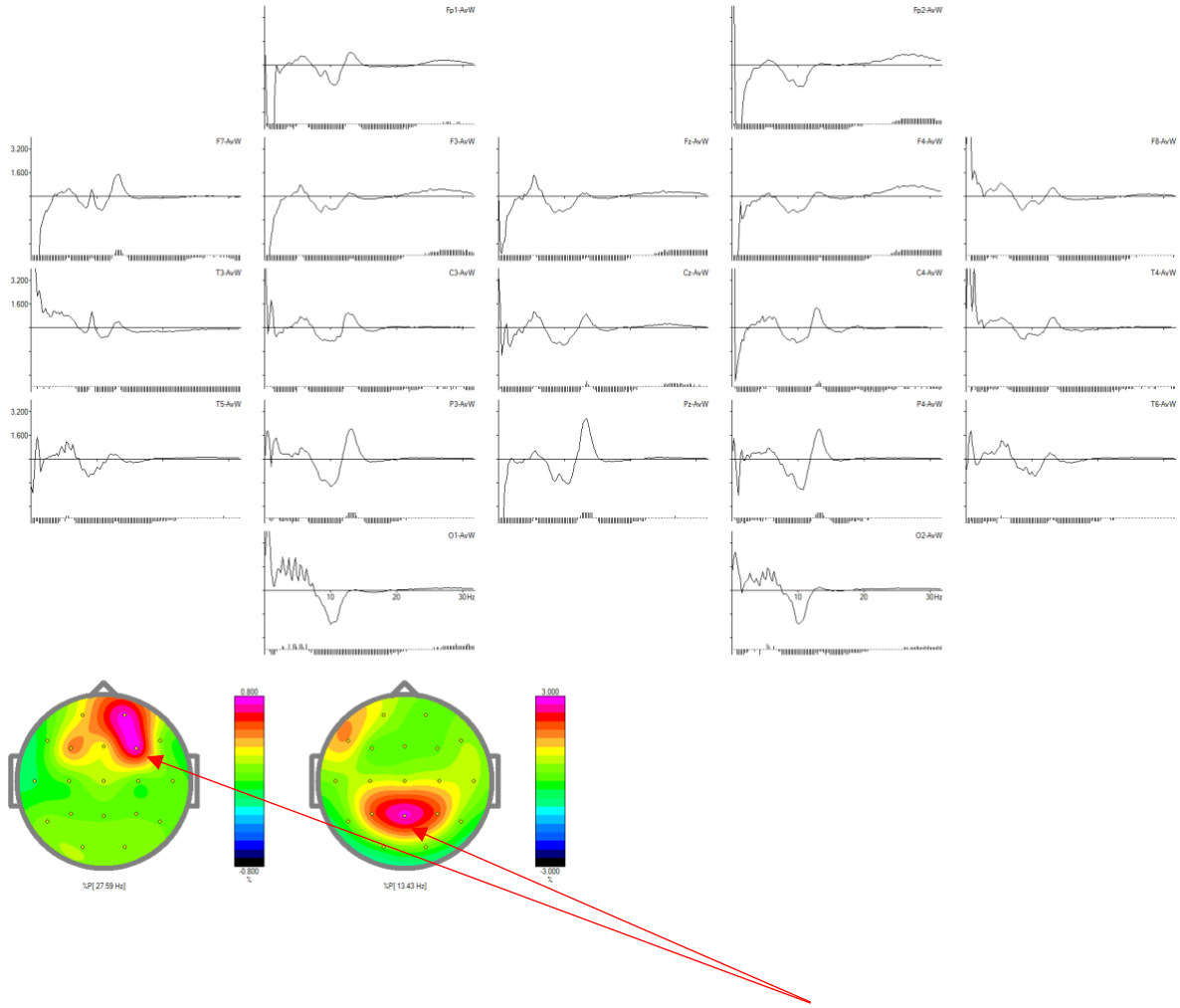
This study focuses on relative power (%P) over absolute power (mV^2). Absolute power represents the amount of spectral power of a specific frequency, while relative power indicates the proportion of each band to the given signal (Kim & Im, 2018). Both relative and absolute power are considered to be reliable parameters for analyzing EEG (Onton et al., 2006), but relative power has shown to have slightly higher test-retest-reliability (Salinsky et al., 1991).

We computed a difference curve and compared all individual spectra of FM subjects with the control group (as displayed in figure 7), in EO, EC and VCPT condition. Significant positive deviations ($p < .01$) in brain activity were chosen for further analysis, but we also reported if the patient had significantly ($p < .01$) less occipital alpha (RQ 1). This was the only negative deviance we investigated, as exporting data from EEG spectra to sLORETA negates the possibility to localize weaker amplitudes than normal.

As mentioned, gamma is hard to detect with EEG, and is especially prone to contamination from muscular artifacts (Tandle et al., 2015). Therefore, gamma was excluded in the power spectra analysis and from further examination.

Figure 7

Difference curves of fibromyalgia patient and control group revealing significant deviances from the norm.



Note. The two brain maps indicate a significant ($p < .01$) excess of beta rhythms at two different locations.

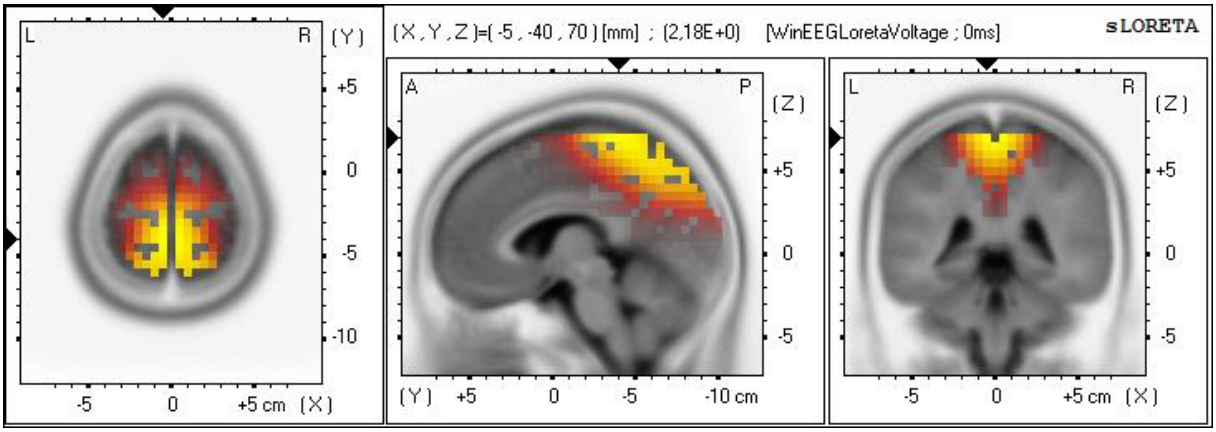
2.4.3 Source localization. Standardized low-resolution brain electromagnetic tomography (sLORETA) is a validated source localization technique for brain activity based on multichannel surface EEG recordings (Pascual-Marqui et al., 1994). This is the most popular brain imaging method because of its simplicity and high precision (Sadat-Nejad & Beheshti, 2021), and it has shown zero localization error (Pascual-Marqui, 2002). sLORETA

gives the best solution compared to similar methods (such as LORETA) in terms of localization error and ghost (spurious) sources (Grech et al., 2008). The technique takes into account variance due to noise from the EEG measurements, as well as biological variance in the actual signal (Jatoi, Kamel, Malik, & Faye, 2014).

sLORETA was applied for source localization to provide us with possible source generators of the deviant EEG activity (Brodmann areas), as explained by Jatoi, Kamel, Malik and Faye (2014). Figure 8 shows an example of source localization with sLORETA. If sLORETA was able to localize the source, the 5 most likely BA matches were reported (see appendix A). 5 BA matches were chosen as this corresponds to the EEG spatial resolution of 6 cm^2 (Nunez & Srinivasan, 2006, p. 41), and is also the default setting of sLORETA.

Figure 8

Source localization of deviant activity with sLORETA.



Note. The image displays beta activity in posterior cingulate cortex.

2.5 Statistical analysis

For the statistical analyses, Statistical Package for the Social Sciences (SPSS) was employed to investigate whether brain activity is related to symptom severity. This part of the study addresses research question 3) "Does the amount of deviant activity within the pain connectome correlate with perceived symptom intensity among FM patients?", research question 4) "Do specific BA within the pain connectome correlate with perceived symptom intensity among FM patients?", and 5) "Does deviant activity in DPC with specific frequency bands correlate with symptom intensity among FM patients?".

"Symptom intensity" of the FM patients were measured with ACR-, FIQ- and VAS-questionnaires, which are valid instruments for measuring FM symptoms. In addition to the total ACR-score (combined of WPI and SS-score), we chose to use WPI as a separate

variable, as this is a pain-specific measure (Wolfe et al., 2010). We found it relevant to investigate all characteristic symptoms of FM (e.g., fibrofog and fatigue). However, pain was considered to be the most important variable, as this is the main diagnostic criteria. In addition, since we focus on the dynamic *pain* connectome in this study, the pain symptoms are inevitably the most interesting to investigate.

Correlation analysis was chosen to investigate whether different kinds of brain activity in the DPC is related to symptom severity. Correlation is a statistical measure of how much two measurable quantities are related to each other (Field, 2018, pp. 333-368), and therefore we conducted several correlation analyses to investigate possible covarying variables.

2.5.1 RQ 3. "The amount of deviant activity within the DPC" was conceptualized to address research question 3. This was conceptualized this in several ways. First, we hypothesized that DPC deviances in *multiple* conditions could correlate with *higher* symptom scores, as this could indicate a dysfunctional DPC in a bigger part of the patient's daily life (during rest and activity). Thus, several correlation analyses between "number of conditions" (ranging from 0-3) and the different symptom scores (ACR total, WPI, FIQ and VAS pain/fatigue/fibrofog) were conducted.

Secondly, we investigated the possible correlations between the total number of unique BA deviances in the pain connectome (EO, EC and VCPT combined) in each FM patient, and their experienced symptoms. If the patient had deviances in a specific BA in more than one condition, these were only counted once, as we wanted to examine unique contributions to the perceived symptoms. The thought is that the scale of DPC activation will correlate with the experienced symptom intensity of FM patients, and larger scaled activation (more unique BA "hits") would mean higher scores on ACR, WPI, FIQ and VAS. Therefore, we conducted several correlational analyses to see if there were statistically significant correlations between the variables.

2.5.2 RQ 4. Furthermore, we wanted to investigate if there are different areas within the pain connectome that correlate more strongly with perceived symptom intensity (ACR, WPI, FIQ, VAS) among FM patients. The different areas we wanted to investigate (independent variables) were each specific Brodmann area, as well as the salience network and the default mode network separately. To separate SN and DMN, two new independent variables representing each network were computed in SPSS, by combining the BAs they consist of (as displayed in table 1 and 2).

Here we conducted several correlation analyses in EO, EC and VCPT conditions, to see if specific BA "hits" in itself (independent variables) correlate with symptom severity

(ACR, WPI, FIQ, VAS pain/fatigue/fibrofog) among FM patients. Then we conducted new correlation analyses to see if deviant activity in SN or DMN in EO, EC and VCPT condition correlate with symptom severity separately.

2.5.3 RQ 5. Lastly, we wanted to investigate if deviant activity in DPC with specific frequency bands correlate stronger with symptom intensity among FM patients. Delta band activity was not included, as few "hits" were identified in this frequency. In addition, it is may be challenging to differentiate between delta band brain activity and irrelevant noise and artifacts (Tandle et al., 2015). Therefore, we computed three new variables were computed: "Deviant theta band activity in DPC", "Deviant alfa band activity in DPC" and "Deviant beta band activity in DPC". Subsequently, correlation analyses were conducted to determine possible covariances between these variables and perceived pain intensity.

3. Results

3.1 Power spectra analysis

The total number of subjects were 63 (N = 63). Regarding RQ 1, significant (p <.01) deviances in power spectra brain activity were found in all FM patients compared to the control group. 57 of the subjects (90.5 %) showed deviance in EO condition, while all 63 of them (100%) showed spectral deviances in EC. In addition, all except 3 (n=60, 95.2 %) had deviant brain activity in the VCPT condition.

We found positive power spectra deviances in alpha, beta, theta, and delta frequency bands when we compared FM patients with the control group. Deviant increased beta activity was the most evident, as 85.7% (n=54) of the subject group had power spectra deviance in at least one of the conditions; 69.8% (n=44) in EO, 54.0% (n=34) in EC, and 79.4% (n=50) in VCPT. Secondly, 71.4% (n=45) had deviances in alpha band frequency in at least one of the conditions, whereas 39.7% (n=25) had alpha deviances in EO, 61.9% (n=39) in EC, and 42.9% (n=27) in VCPT condition. Slightly less of the FM patients had theta band deviances, with 43.9% (n=27) in at least one of the conditions; 19.0% (n=12) in EO, 30.0% (n=17) in EO, and 30.2% (n=19) in VCPT. Lastly, only a few of the subjects had power spectra deviances in delta band frequency; only 19.0% (n= 12) with deviance in at least one of the conditions; 1.6% (n=1) in EO, 11.11% (n=7) in EC, and 7.9% (n=5) in VCPT condition.

In addition to the deviant positive activity, we also found that 93.7% (n=59) had significantly (p<.01) less occipital alpha frequency.

3.2 Source localization

Source localization was used to investigate if fibromyalgia patients have deviant brain activity in the pain connectome compared to healthy controls (RQ 2). sLORETA was able to localize the deviant brain activity in 57 (90.5%) of the FM patients, of which 55 had deviances within the pain connectome. Thus, DPC-deviances were found in 87.3% of the FM patients, which were represented as theta, alpha and beta frequency bands.

As found in previous studies at NTNU, the current study identified deviant activity in most BA associated with the DPC. The only exception was BA 33, where no deviances were found. However, this coincides with previous findings at the EEG-lab (Eide, 2020; Ingvaldsen, 2019; Nordvoll & Bruun, 2021). See tables in appendix A for a summary of results.

Within the DPC, the most common deviance among FM was in BA 39 (71.4%, *n*=45) across conditions. This differs slightly from the most recent study at the EEG-lab, where they compared a grand average (as opposed to individual) power spectra of the FM patients to the norm. Nordvoll and Bruun (2021) found that BA 40 was the most frequent finding across conditions (40.63%), all though this is a lower percentage than we found for BA 40 across conditions (60.3%, *n*=38).

Deviances in BA 7, BA 31 and BA 39 were the most frequent finding (25.4%, *n*=16) in EO condition. In EC, BA 39 was the most frequent finding (54.0%, *n*=34), followed by BA 7 (39.7%, *n*=25), BA 31 (38.1%, *n*=24) and BA 40 (31.7%, *n*=20). In VCPT condition, deviance in BA 7 (37.1%, *n*=23) was the most frequent, followed by BA 39 and BA 40 (33.9%, *n*=21).

3.4 Statistical analysis

Since questionnaire information was only obtained from 51 (ACR) or 50 (FIQ/VAS) of the FM patients, the total number of subjects will be adjusted depending on the specific analysis (*n*=50, *n*=51, *N*=63).

3.4.1 RQ3. Investigating RQ 3, we found differences in the number of conditions (EO, EC, VCPT) in which FM patients showed DPC deviances (ranging from 0-3). Of the 63 participants, 14.3% (*n*=9) had no DPC deviances in any of the conditions. 14.3% of the participants (n=9) had deviances in just one condition, 31.7% (*n*=20) in two conditions, and 39.7% (*n*=25) in all three conditions. Correlation analysis of the 50/51 of the patients with questionnaire scores showed no association between deviances in multiple conditions and subjective symptom severity (ACR total, FIQ, VAS pain/fatigue/fibrofog) and WPI).

The total number of unique BA deviances in the pain connectome (EO, EC and VCPT combined) ranged from 0 to 12 among the FM patients, with a mean of approximately 5 areas (M = 4.81, SD = 3.05). Correlation analyses showed a significant moderate correlation between the number of BA deviances and WPI score (r = .32, n = 51, p < .05), but no significant correlation with VAS pain. However, when we examined deviances in EO, EC and VCPT separately, we found significant moderate correlations between the number of BA deviances and pain perception, measured with both WPI (r = .32, n = 51, p <.05) and VAS (r = .29, n = 50, p <.05), in the VCPT condition. There were no significant correlations in the two other conditions (EO and EC). Also, we found no significant correlations between the number of unique BA deviances and scores on ACR total, FIQ, VAS fatigue or VAS fibrofog.

3.4.2 RQ 4. Correlation analyses between deviant DPC activity in EO, EC and VCPT conditions, and perceived symptom intensity, was conducted. These indicated that none of the areas were associated with variance in total ACR score, the number of painful body parts (WPI), or variance in scores on FIQ and VAS (pain, fatigue, fibrofog).

When we combined the Brodmann areas into two independent variables (SN and DMN), we found significant differences in how the two networks correlates with perceived pain. Correlation analyses were conducted in all three conditions (EO, EC, VCPT). A significant, moderate correlation was found between deviant activity in SN in VCPT condition and the WPI index (perceived pain) (r = .37, n = 54, p <.01). There were no significant correlations between deviances in SN and VAS pain in VCPT condition, nor between SN and perceived pain (WPI and VAS pain) in EO or EC conditions. In addition, deviant activity in DMN did not have a significant correlation with perceived pain (neither WPI nor VAS) in any of the conditions (EO, EC, VCPT). Deviant activity in SN and DMN did not have a significant correlation with any of the other symptom scores (ACR, FIQ, VAS fatigue/fibrofog).

3.4.3 RQ 5. Correlation analyses of deviant activity in DPC in specific frequency bands and perceived symptom intensity, found no significant correlations between theta, alfa or beta frequency band and scores on ACR, WPI, FIQ or VAS (pain/fatigue/fibrofog).

4. Discussion

4.1 Main findings

As part of a continuous search for fibromyalgia biomarkers, the current study wished to investigate if fibromyalgia patients had deviant brain activity in the dynamic pain connectome (DPC). The first part of this investigation was conducted using spectral analysis, and subsequent source localization was executed to localize possible sources of the deviant EEG-activity. Lastly, after identifying potential biomarkers, we wanted to investigate possible correlations between individual spectral deviances and perceived symptom intensity.

4.1.1 Power spectra analysis and source localization. To answer research question 1, "Do fibromyalgia patients have deviant spectral power brain activity compared to healthy controls?", we conducted power spectra analysis of all individual fibromyalgia patients. The spectra were compared to the grand average power spectra of healthy controls, consisting of EEG-recordings collected at the NTNU EEG-lab. In accordance with what was expected based on existing literature and previous findings, significant deviances in oscillatory EEG-activity were found in all three conditions (EO, EC and VCPT). 90.5 % showed deviances in EO condition, 100% in EC condition and 95.2 % in VCPT condition. Spectral deviances were found in both beta, alpha and theta frequency bands in respectively 85.7 %, 71.4 % and 43.9 % of the subjects. This supports hypothesis I, as overactivation of beta oscillations were the most frequent (over theta and alpha). Lastly, the results supported our hypothesis that FM patients (93.7 % of the subjects) have significantly less occipital alpha band frequency than healthy controls.

With the second research question, "Do fibromyalgia patients have deviant brain activity in the pain connectome compared to healthy controls?", we wanted to investigate if the source of the power spectra deviances was located within the DPC. sLORETA was implemented for this purpose, uncovering DPC-deviances in 87.3 % of the FM patients, manifested as theta, alpha and beta oscillations. With the exception of BA 33, abnormal activation was found in all other BAs within the connectome. These results correspond with previous NTNU-studies (Eide, 2020; Ingvaldsen, 2019; Nordvoll & Bruun, 2021), as well as our hypotheses based on presented theory.

4.1.2 Statistical analysis. To answer the third research question, "Does the amount of deviant activity within the pain connectome correlate with perceived symptom intensity (scores on ACR, FIQ or VAS) among FM patients?", we conceptualized "the amount of deviant activity" as 1) The number of conditions (EO, EC and VCPT) with deviant activity in each individual patient (ranging from 0-3), and 2) the total number of unique BA deviances in

the pain connectome (EO, EC and VCPT combined) in each FM patient. Then we conducted correlation analyses to see if these variables correlate with perceived symptom intensity, measured with ACR, WPI, FIQ and VAS (pain/fatigue/fibrofog).

Correlation analysis showed no significant correlation between the number of conditions with deviant DPC-activity and experienced FM symptoms (ACR total, FIQ, VAS pain/fatigue/fibrofog) and WPI). At the same time, correlation analyses showed a significant moderate correlation between the number of BA deviances and WPI score (r = .32, n = 51, p < .05), but no significant correlation with VAS pain or any of the other symptom scores (ACR total, FIQ, VAS fatigue and VAS fibrofog). However, when we examined deviances in EO, EC and VCPT separately, we found significant moderate correlations between the number of BA deviances and pain perception, measured with both WPI (r = .32, n = 51, p <.05) and VAS (r = .29, n = 50, p <.05), in the VCPT condition. There were no significant correlations in the two other conditions (EO and EC). Also, we found no significant correlations between the number of unique BA deviances and scores on ACR total, FIQ, VAS fatigue or VAS fibrofog in VCPT condition. This could indicate that a larger area with deviant activity within the DPC is associated with more subjective pain (more painful body parts). Also, deviant activity within the DPC during an attention demanding task is associated with more painful body parts and more subjective pain intensity.

Next, we investigated research question 4: “Is specific BAs within the pain connectome associated with perceived symptom intensity (ACR, FIQ or VAS) among FM patients?”. Correlation analyses were conducted (in EO, EC and VCPT conditions) to see if deviant activity in individual BA areas of the DPC, the salience network or default mode network correlates with perceived symptom intensity by itself. As predicted, none of the Brodmann areas had significant correlations with any of the symptom scores, providing support for hypothesis I of RQ 4. Moreover, DMN did not show correlations with any of the symptom scores. However, a moderate correlation was found between deviant activity in SN and the WPI index (perceived pain) (r = .37, n = 54, p <.01), but only in the VCPT condition. No correlations were found between SN and perceived pain in EO or EC condition, nor between SN and any of the other symptom scores (ACR total, FIQ or VAS). This partially supports our hypothesis II of RQ 4, as SN did have stronger correlations with perceived symptom intensity compared to DMN. At the same time, this only applied during an attention demanding task (VCPT), and only in association with the number of painful body parts (widespread pain).

Lastly, to answer research question 5, “Is deviant activity in the DPC with specific frequency bands associated with symptom intensity (ACR, FIQ or VAS) among FM patients?”, we conducted correlation analysis between the three variables “Deviant theta band activity in the DPC”, “Deviant alfa band activity in the DPC” and “Deviant beta band activity in the DPC”, and perceived symptom intensity. Next, correlation analyses between specific frequency band deviances in the DPC and perceived symptom intensity were conducted. No significant correlations were found between theta, alfa or beta frequency band and scores on ACR, WPI, FIQ or VAS (pain/fatigue/fibrofog). This did not support our hypothesis, postulating that beta band frequency in the DPC would have stronger correlations with perceived symptom intensity.

4.2 Interpretation of the results

As expected, spectral deviances were found in all conditions (EO, EC and VCPT), and all FM patients had deviant spectral power brain activity compared to healthy controls. Of all the participants, deviant increased beta activity was the most evident (87.5%). In addition, 93.7% of the FM subjects had less occipital alpha than healthy controls. Since less occipital alpha is not thought to be FM specific (Mathewson et al., 2012; Mazaheri et al., 2010), we consider an overactivation of beta frequency to be more suitable as a potential biomarker for fibromyalgia. At the same time, 87.3 % of the FM patients showed power spectra deviances in the DPC in all analyzed frequencies, including theta-, alpha- and beta frequency. This could indicate that a general disturbance in the DPC may be another possible biomarker of FM. In the following sections, we propose the theory of predictive coding and thalamocortical dysrhythmia as possible explanatory models for FM.

4.2.1 Predictive coding and dysfunctional pain templates. Beta oscillations are known to be involved in top-down cortical processing. Top-down influence of pain perception might be an important contributor to FM symptoms, which indicates that the theory of predictive coding might be a suitable explanatory model for FM. This theory postulates that the brain constantly tries to predict the internal and external sensory world based on previous experiences, and thereby influences our perception of sensory signals.

Studies have found that prior pain experience may lead to a reactivity to external suggestion of pain (Bayer et al., 1998), which may indicate that painful experiences could trigger templates and expectation of pain. Also, studies have found that childhood trauma and neonatal pain could increase pain sensitivity in adult life, thus increasing the possibility of developing FM (Low & Schweinhardt, 2012). Furthermore, infections such as Epstein-Barr

virus, hepatitis C and parvovirus may trigger FM (Hawkins, 2013). This provides further evidence that prior pain experiences lead to anticipation of pain, and subsequent non-painful stimuli may be perceived as painful based on top-down modulation of the signals.

When considering our results and the theory of predictive coding, FM may be understood as a product of a dysfunctional pain template. This template may be used by the individual to interpret external and internal signals, thus leading to the subjective experience of pain without any objective cause. This would be visible through EEG-recordings, manifested as beta oscillations, making it a possible objective biomarker for the disorder. On the other hand, beta frequency band deviances within the DPC did not correlate with perceived symptom intensity in our study, and there were also significant deviances in alpha- and theta frequencies. This contradicts the theory of predictive coding as an explanatory model of FM, as beta frequencies are thought to facilitate top-down modulation. Since as much as 87.5% of the FM patients showed positive deviances in the DPC, augmented activation of this particular network may lead to the maintenance and aggravation of pain. Thalamocortical dysrhythmia is suggested as a possible cause for augmented activation of pain related areas (Fallon et al., 2018; Henderson et al., 2013), thus making it a possible explanation for the pathophysiology of FM.

4.2.2 Thalamocortical dysrhythmia. Theta oscillations has received an important role in the theory of TCD. Even though we did not find an overrepresentation of positive theta deviances in pain related areas in the FM patients, our findings support TCD as a potential mechanism for explaining FM. Since theta cross-couples and nests higher frequency oscillations, a disruption in the theta oscillations may cause changes in other frequency bands, causing disturbances in larger networks of the brain (Vanneste et al., 2018). According to findings from Stern et al. (2006), a therapeutic lesion of thalamus in patients with chronic neurogenic pain led to a significant reduction of EEG overactivity in areas within the DPC (BA 24 and 32), in addition to subjective pain relief. This overactivity was manifested as beta and theta, which could mean that TCD is not only detectable as theta in the EEG-signals. Potentially, a dysrhythmia in the thalamocortical pathways could lead to a disruption of cortical signals, which is detected through deviations of electrical activity in the cortex. If this dysrhythmia affects pain related areas of the brain, it could lead to augmented brain activity in these areas (Fallon et al., 2018), and thus a disturbance of pain signals. Consequently, this augmented brain activity in cortical pain processing areas could be manifested as chronic pain without any clear cause. Since most of our subjects showed positive deviances (overactivity of alpha, beta, or theta) within the DPC, TCD could be a likely explanatory model for FM.

Further support for the TCD hypothesis is that we did not find any evidence that beta-, alpha- or theta frequency band activity had an impact on symptom intensity. This could indicate that a general disruption of the activity in DPC may contribute to chronic pain, not just an overactivity of beta oscillations. However, we found that the number of BA deviances correlated positively with the number of painful body parts (WPI). This could imply that a more widespread overactivation of the DPC may be associated with greater subjective pain intensity.

In addition, deviant activity in individual Brodmann areas did not correlate with subjective symptom severity. In summation, this could mean that a bigger dysrhythmia in the thalamocortical pathways, causing disruptions of a larger area of the DPC, could lead to greater subjective symptom severity. This supports the theory that TCD could create a general oscillatory disturbance and augmented activity in the DPC, causing the constant perception of pain in FM patients.

4.2.3 Central sensitization. The present study did not aim to investigate specific hypotheses related to the presence of CS in FM patients. A core feature of central sensitization is pain hypersensitivity, manifested through i.a. increased pain responses to normally painful stimuli and pain responses to normally nonpainful stimuli. However, in order to investigate these aspect of the FM symptomology, other study designs involving evoked pain (e.g., quantitative sensory testing) would be more suitable.

As earlier stated, CS involves "increased excitability and synaptic efficacy of neurons in central nociceptive pathways" (Woolf, 2011). Furthermore, several forms of both functional, chemical, and structural plasticity could be contributing mechanisms to this phenomenon. The theory of predictive coding postulates that disrupted pain templates, manifested as overactivity of beta oscillations, could be an important contributor to FM symptomology. Similarly, thalamocortical dysrhythmia emphasizes the contribution of disruption of oscillatory activity in thalamocortical pathways. In addition to providing explanatory models of FM, both theories may also represent mechanisms through which central sensitization is developed or maintained. Thus, CS is considered to be compatible with the abovementioned theories of predictive coding and TCD.

4.2.4 Attention and pain perception. Our results also indicate that attentional processes could be disrupted in people with chronic pain. For instance, we found that the salience network is more strongly connected to pain perception than DMN, and it seems that those with more widespread pain have stronger activation of SN when performing in attention-demanding tasks. According to Kucyi and Davis (2015), the salience network is

more strongly activated when an individual attends to pain, which could indicate that disruption of attentional processes is an important contributor to FM symptomatology.

As proposed by Kucyi and Davis (2015), pain-attention-interactions largely depends on functional and structural connectivity within the DPC, and chronic pain populations show abnormal structural and functional connections in these areas. According to Tagliazucchi and colleagues (2012), reduced functional connectivity is related to increased alpha and beta power as shown with EEG. Our study shows that FM patients have increased alpha- and beta-activity in the DPC compared to healthy controls, which could indicate reduced functional connectivity. As reduced functional connectivity within the DPC has been associated with high degree of intrinsic attention to pain (IAP), it is likely that the FM patients included in our study also have reduced ability to redirect attention away from pain.

Lastly, our findings also shows that FM patients have significantly less occipital alpha than healthy controls. Occipital alpha has been proposed as an attentional mechanism that mediates suppression of distracting information (Foxe & Snyder, 2011). The reduction of occipital alpha-band oscillations in FM-patients can therefore be interpreted as additional evidence for disrupted attentional processes, that contributes to FM symptomology.

4.2.5 Non-pain symptoms. Our analyses did not find any correlations between deviant brain activity in the DPC and symptom severity on VAS fatigue/fibrofog. Nor did we find any correlations with the symptom scales ACR total and FIQ. Although we wanted to investigate if a greater overactivation in the DPC could lead to higher symptom severity in general, it makes sense that larger activation of the Dynamic *Pain* Connectome would only be associated with a stronger perception pf *pain*. A treatment intervention targeting the DPC could therefore result in a reduction of pain severity.

4.3 Limitations

There are many strengths, but also some limitations to the current study. Due to the covid-19 pandemic, government restrictions limited our access to NTNU and the EEG-lab. In addition to restrictions, FM patients could be at high risk when it comes to viral infections as some findings indicate that they have a weaker immune system (Behm et al., 2012). Both government restrictions and the risk of viral infection therefore made it difficult to increase the number of participants in the study, especially since EEG-recordings require direct physical contact.

Moreover, because of government restrictions, we were not able to gather questionnaires from all the FM subjects. This made the sample size even smaller in the analysis of subjective symptom intensity.

4.3.1 Design. Even though our sample size is relatively big compared to previous studies at the EEG-lab, a larger subject- and control group would have been beneficial because of the heterogeneity of FM patients. In addition, the subject group consisted only of women, which makes it difficult to generalize the findings to male FM patients. At the same time, the results are representative of most FM patients, as the majority are women.

Another limitation is that confounding variables could have influenced the patients' EEG-recordings. Many of the FM subjects had comorbid disorders, such as migraine, sleeping problems and fatigue. Unfortunately, additional diagnoses were not appropriately documented or controlled for, nor was the list of medication use. In this way, the EEG-recordings may have been influenced by other factors.

4.3.2 EEG-procedure and analysis. There are some general limitations of the EEG procedure and -analysis (see section 1.4.4.3). Furthermore, gamma oscillations are difficult to detect with EEG because of its low amplitude and high frequency, and delta oscillations may also be confused with muscular artifacts. Therefore, we chose to only focus on alpha-, beta- and theta band for further analyses. This could mean that valuable information about FM brain activity deviances may have been lost.

Moreover, a disadvantage with spectral analysis is that exporting data from EEG spectra to sLORETA negates the possibility to localize weaker amplitudes than normal. This could mean that important deviances in brain activity is not found when comparing FM patients to healthy controls.

At the same time, there are many advantages of the method. For instance, it is time- and cost effective, widely accessible and easily administered (see section 1.4.4.3 for elaboration).

4.3.3 Causality. The current study found an association between deviances in brain activity and the fibromyalgia disorder. However, the question of causality is not as easily answered. Some studies suggest that long term pain could lead to structural and functional changes in the brain (K. B. Jensen et al., 2013). Thus, we do not know the direction of the relationship between oscillatory deviances and the FM diagnosis. Furthermore, we do not have any additional anamnestic information about the subjects except gender and age. Therefore, other factors may have influenced the patient's brain activity, thus affecting our results.

4.4 Implications for future research.

We still do not have a clear answer to what causes or maintains fibromyalgia, and our study is only one of many steps towards finding answers regarding the pathophysiology of FM and potential biomarkers. We hope that future research will continue to expand the knowledge about the disorder, contributing to better, faster, and more specialized treatment options.

Even though we included more participants than previous studies at the EEG-lab (Eide, 2020; Ingvaldsen, 2019; Luckman & Gulbrandsen, 2019), we would recommend future studies to have even larger samples. This would minimize the risk of false negative results, as well as provide more accurate values. A bigger sample size would also make it easier to assess the representativeness of the subjects, as well as generalizing the results (Biau et al., 2008). Future research should also include men in the subject group, so that the results would be generalizable to both male and female patients with FM. It would also be interesting to investigate if there are gender differences in the manifestation of FM.

As mentioned, comorbid disorders and medications could influence the EEG-recordings. Future research should make a complete list of possible confounding variables and control for these in the analyses. Also, as there seems to be many factors contributing to FM symptoms, longitudinal studies could be useful to gain a deeper insight into the disorder. This type of study is especially beneficial for determining the association between risk factors and what causes and maintains a disorder, and it is a study type with continuous or recurring assessments to follow specific individuals over longer time periods (Caruana et al., 2015). This could provide a deeper insight into FM as a disorder, and it would enable us to see how brain activity develops over time. Ideally, a longitudinal study should start even before the subjects develop fibromyalgia.

Lastly, future research should aim to continue the search for electrophysiological deviances as possible biomarkers for FM. Conceivably, this will lead to further support of augmented brain activity in the DPC as a potential biomarker of FM, and predictive coding or thalamocortical dysrhythmia as explanatory models for FM.

4.5 Implications for diagnostic process and treatment.

Despite limitations of our study, we have presented solid findings that should be considered when developing a diagnostic process and treatment for FM patients in the future. The results strongly indicate that FM patients have electrophysiological abnormalities in the DPC that contribute to the disorder. This could mean that existing treatments for the patients,

such as regular CBT or exercise, may be inadequate and should be updated. We propose treatment methods that target the electrophysiological deviances more directly, such as tDCS and NFT, in addition to psychological interventions targeting attentional processes.

4.5.1 Diagnostic process. Even though more research is required before implementing the use of EEG in the medical examination of possible FM patients, our results clearly indicate deviances in the DPC as a possible biomarker of the disorder. EEG is cheap and easily accessible for clinicians, thus making it a convenient tool to support a potential diagnosis. We suggest more research on possible DPC biomarkers for FM and present the possibility of using EEG early in the diagnostic process. Future research should also aim to find electrophysiological inclusion and exclusion criteria for fibromyalgia.

4.5.2 tDCS. As mentioned, dysfunctional pain templates may be a possible contributor to the FM disorder, and treatment interventions targeting these templates should be considered. tDCS is thought to influence the firing of neurons when applying direct current to the scalp, which in turn could change activity in brain networks (Antal et al., 2017; Vecchio et al., 2021). Hence, tDCS could aid the reconsolidation of a faulty pain memories by changing the activity in pain related areas (such as DPC), and should be considered when testing new treatment methods for FM. Results from previous studies at the EEG-lab (Luckman & Gulbrandsen, 2019) implies that tDCS leads to the reduction of subjective symptom severity of FM patients. There was a significant reduction of VAS total, VAS pain and FIQ score, and 25% did not meet the ACR diagnostic criteria for FM after treatment. Even though the study had some limitations, such as not having a control group for the placebo effect, the results are promising in the FM research field. Future research should aim to replicate these findings. In addition, tDCS is non-invasive and seems to have few known adverse effects (Antal et al., 2017).

4.5.3 Neurofeedback training. NFT is another possible neurophysiological intervention that may be useful in treatment of the FM disorder. It is a technique where EEG is used to measure, process, and give the patient auditory and/or visual feedback about their brain state. It is a type of operant conditioning procedure that supports the patient's ability to modify neurophysiological dynamics of the brain (Kayıran et al., 2010). The treatment procedure is individually adapted to the patient, which is beneficial for treating FM patients due to the heterogeneity of the group.

Our results indicate that TCD may be a plausible explanatory model for FM, which strengthens the suggestion of NFT as a possible treatment method for the disorder. The exact mechanism of NFT is not clear, but the procedure is thought to enhance neural plasticity (Ros

et al., 2010), and normalize brain activity (Pineda et al., 2014). It is also applied to several patient groups with success (Beauregard & Lévesque, 2006; Pineda et al., 2014; Sacchet & Gotlib, 2016). Since there are many ways of performing NFT, we propose NFT of the sensory motor rhythm (SMR) or infra-low frequency NFT (ILF-NFT) for treating FM.

4.5.3.1 SMR NFT. The SMR is thought to be generated through thalamocortical interactions (Kayıran et al., 2010). As thalamocortical dysrhythmia could be a plausible explanation of FM, SMR NFT should be considered as a possible treatment option. Furthermore, the SMR is located at the sensory motor cortex (SMC), and previous research has discovered changes in resting state functional connectivity between SMC and the salience network in people with chronic pain (Kutch et al., 2017). Our results indicate that SN is more associated with subjective pain that other areas of the DPC, which strengthens the hypothesis of SMR NFT as an appropriate treatment method for FM. Kayıran et al. (2010) found a significant reduction of subjective symptom pressure (VAS pain and VAS fatigue) after SMR NFT with FM patients, which provide further support for this treatment.

4.5.3.2 ILF-NFT. ILF-NFT has also been suggested as a possible treatment for FM, and is a method proposed by Othmer and Othmer (2008) in the 21st century. This is a feedback technique that is non-conditional (unlike the other NFT-procedures), and is performed without any guidance from the therapist (Othmer & Othmer, 2006). Also, it only give signals to the patient below 0.1 Hz, and is thought to influence neuromodulation (Othmer & Othmer, 2017). Since the method targets the slower frequencies, and TCD is characterized by increased power at low frequencies, ILF-NFT could be a possible treatment for FM. Moreover, previous research has found that ILF-NFT has a good influence on the subjective perception of positive psychological changes (Grin-Yatsenko et al., 2021), and it has also been presented a reduction of pain in chronic pain patients after ILF training (Jensen et al., 2007). Also, since slower frequencies cross-couple with faster oscillations (Buzsáki, 2002), a modulation of slower frequencies may influence the faster ones. Previous studies at the EEG who completed ILF-NFT at fibromyalgia patients found significant reductions in FM symptoms after training (Eide, 2020; Ingvaldsen, 2019), but they did not have a sham-condition. More research is needed to confirm the effect, and to see if it is long-term.

4.5.4 Psychological interventions targeting attentional processes. Our results indicate that FM patients could have disrupted attentional processes compared to healthy controls, which is likely to be a contributor to FM symptomatology. According to Kucyi and Davis (2015), the role of attentional processes in chronic pain should receive more emphasis in the formation of therapeutical interventions, but they have not been sufficiently

investigated. However, it has been established that intrinsic attention to pain (IAP) and rumination are central elements of pain-attention-interactions. Although these processes have been referred to as relatively stable, individual characteristics, Kucyi and Davis (2015) questions whether IAP and rumination could be altered through different types of interventions. If this is the case, interventions targeted at these processes could potentially contribute to symptom relief for chronic pain patients.

Kucyi and Davis (2015) proposes several psychological interventions that should be further examined with respect to the chronic pain population. One example of a psychological intervention is cognitive behavioral therapy (CBT), which aims at modifying pain perception and reversion of central sensitization (Salomons et al., 2014). According to a recent systematic review, CBT is the most common psychological treatment for fibromyalgia (Albajes & Moix, 2021). However, our results indicate that psychological interventions such as classical CBT might not be sufficient as a treatment option for FM patients, as this patient group is characterized by identifiable, neural deviances in pain-related areas. In accordance with earlier studies, the current study suggests that potential psychological interventions should place a particular emphasis on attentional processes. For example, mindfulness meditation training has been proposed as a way of increasing awareness of attention to pain (Kucyi & Davis, 2015). This type of training has been shown to reduce ruminative thoughts, and may also reduce the increased intrinsic attention to pain in chronic pain patients (Kucyi & Davis, 2015). However, more research is needed in order to establish the efficacy of the treatment (Hilton et al., 2017).

Our study shows that FM patients have significant, electrophysiological deviances within pain-related areas of the brain, which indicates that standard psychological interventions such as CBT may be an insufficient treatment option. Thus, electrophysiological interventions could be a more suitable alternative compared to psychological interventions. However, attentional processes seem to be important in the development and maintenance of chronic pain. Therefore, we encourage the continuous study of these processes and interventions directed at these.

5. Conclusion

The aim of the study was to continue the search for fibromyalgia (FM) qEEG biomarkers by investigating if FM patients have deviant brain activity compared to healthy controls. We used position estimation procedure to source localize the deviant brain activity, uncovering if these deviations are localized in the Dynamic Pain Connectome (DPC). Furthermore, we wanted to see if specific areas within the DPC correlate stronger with perceived symptom intensity than other areas.

All of the FM patients had brain activity deviances compared to healthy controls, where increased beta oscillations were the most prominent. Also, 87.3 % of the subjects had deviances localized in the DPC. Furthermore, a larger scaled activation of the DPC is associated with higher subjective pain intensity. This may point towards augmented brain activity in DPC as potential biomarker of FM. In addition, the salience network seems to be more involved in FM symptoms than DMN, as deviant activity in SN during attention demanding task is associated with more subjective pain.

The results of the current study give a strong indication that FM patients have electrophysiological abnormalities in the DPC which contribute to the disorder, and our results suggest that predictive coding (dysfunctional pain templates) or thalamocortical dysrhythmia are plausible explanatory models for FM pathophysiology. Also, attentional processes seem to play an important part in the disorder. We propose treatment methods that target the electrophysiological brain activity deviances more directly, such as tDCS and NFT. In addition, research on psychological treatments targeting attentional processes are reccomended.

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Appendix

A. Tables from EO-, EC- and VCPT-condition showing deviant brain activity localized by sLORETA in specific frequency bands.
B. Informed consent schema from the different fibromyalgia studies at the EEG lab.
C. ACR questionnaire (Norwegian version)
D. FIQ questionnaire (Norwegian version)
E. VAS questionnaire for pain, fatigue and fibrofog (Norwegian version).

Appendix A

Table A1

An overview of Brodmann areas detected by sLORETA representing a significant (p<0.1) deviance of brain activity in each FM patient from healthy controls, in specific frequency bands in EO condition (N=73).

Eyes opened		
Patient	Brodmann areas	Frequency band
Fib 1	**7**, 18, 19, 21, 22, **31**, 37, **39**	Theta
Fib 2	6, **8**, **9**, **10**, **32**	Beta
Fib 3	-	-
Fib 4	1, 2, 3, 4, 5, 17, 18, 19, 37, **39**	Beta
Fib 5	6, **8**, **9**, 44, 45	Alpha
	2, **13**, 22, **40**, 42	Beta
	18, 19**, 31**, 37, **39**	Beta
Fib 6	-	-
Fib 7	20, 21, 22, 38, 47	Alpha
Fib 8	3, 4, 5, 6, **31**	Alpha
Fib 9	-	-
Fib 10	-	-
Fib 11	-	-
Fib 12	**10**, 11, **25**, **32**, 47	Alpha
Fib 13	20, 21, 22, 36, 37	Alpha
Fib 14	-	-
Fib 15	-	-
Fib 16	-	-
Fib 17	17, 18, 19, **30**, 37	Theta
Fib 18	**7**, 18, 19, 20, 21, 22, **31**, **39**, 41, 42	Alpha
Fib 19	5, **7**, 18, 21, 22, **31**, **40**, 41, 42	Beta
Fib 20	-	-
Fib 21	**7**, 17, 18, 19, **31**	Beta
Fib 22	4, 5, **7**, **31**, **40**	Alpha
	7, 19, 22, **39**, **40**	Beta
Fib 23	-	-
Fib 24	-	-
Fib 25	6, **8**, **9**, **10**, **32**	Theta
Fib 26	-	-
Fib 27	20, 21, 22, 37, **40**, 41, 42	Theta
	19, 21, 22, 37, **39**	Alpha
Fib 28	3, 4, 6, **7**, **8**, **9**, 17, 18, 19, 22, **30**, **31**, 37, **39**, **40**	Beta
Fib 29	-	-
Fib 30	**8**, **9**, **10**, **32**, **46**	Alpha
	10, 11, **13**, 21, 22, 38, 45, **46**, 47	Beta
Fib 31	5, **7**, 19, **39**, **40**	Beta
Fib 32	4, 6, **8**, 21, 22, **24**, **32**, **40**, 41, 42	Beta
Fib 33	**13**, 21, 22, 38, 47	Alpha
	9, **13**, 22, **40**, 41, 42, 44, 45, **46**	Beta
Fib 34	**10**, 11, 19, 20, 21, 22, 37, 45, **46**, 47	Beta
Fib 35	2, 3, 4, 5, **7**, 19, **31**, **40**	Alpha
Fib 36	3, 4, 6, **10**, 11, **24**, **25**, **31**, **32**, 47	Alpha
	7, 18, 19, **31**, **39**	Beta
	4, 6, **8**, **24**, **32**	Beta
Fib 37	-	-
Fib 38	-	-
Fib 39	-	-

Fib 40	**7**, 18, 19, **31**, **39**	Alpha
Fib 41	-	-
Fib 42	1, 2, 3, 4, 6	Alpha
Fib 43	-	-
Fib 44	**10**, 11, **25**, **32**, 47	Beta
Fib 45	-	-
Fib 46	**10**, 11, **32**, **46**, 47	Beta
Fib 47	6, 20, 21, 22, 38	Alpha
Fib 48	17, 18, 19, **23**, **30**	Alpha
Fib 49	-	-
Fib 50	-	-
Fib 51	20, 21, 22, 36, 37	Theta
Fib 52	1, 2, 3, 4, 6	Beta
Fib 53	-	-
Fib 54	-	-
Fib 55	**13**, 20, 21, 22, 36, 37, 38, 47	Theta
	7, 18, 19, **23**, **31**	Alpha
Fib 56	-	-
Fib 57	-	-
Fib 58	-	-
Fib 59	-	-
Fib 60	1, 2, 3, 4, 5, **7**, 17, 18, 19, **23**, **31**, 37, **39**	Beta
Fib 61	4, 5, 6, **7**, 18, 19, 22, **31**, 37, **39**, **40**	Alpha
Fib 62	-	-
Fib 63	3, 4, 6, **24**, **31**, 42, 43	Beta
Fib 64	20, 21, 22, 38, 41	Beta
	5, **7**, 19, **39**, **40**	Theta
Fib 65	-	-
Fib 66	-	-
Fib 67		-
Fib 68	17, 18, 19, **23**, **30**, **31**, **39**	Alpha
	3, 4, 6, **8**, **9**, 22, 42, 43	Beta
Fib 69	1, 2, 3, 4, 5, **7**, **40**	Beta
	10, 11, 17, 18, 19, **23**, **25**, **30**, **32**, 47	Theta
Fib 70	19, 21, 22, 37, **39**, **40**	Beta
Fib 71	-	-
Fib 72	**7**, 18, 19, **39**, **40**	Alpha
	10, **13**, 22, 45, **46**, 47	Beta
Fib 73	-	-

Note. EO = Eyes Opened, Brodmann areas in bold represents areas within the Dynamic Pain Connectome, patients shaded in blue are excluded from the analysis (see method section). The section is marked with a hyphen (-) if sLORETA was not able to source localize the deviant brain activity.

Table A2

An overview of Brodmann areas detected by sLORETA representing a significant (p<0.1) deviance of brain activity in each FM patient from healthy controls, in specific frequency bands in EC condition (N=73).

Eyes closed		
Patient	Brodmann areas	Frequency band
Fib 1	**13**, 18, 19, 20, 21, 22, **31**, 37, 38, **39**, **40**	Theta
Fib 2	17, 18, 19, 37, **39**	Alpha
Fib 3	-	-
Fib 4	5, **7**, 17, 18, 19, **31**, **39**, **40**	Alpha
Fib 5	3, 4, 6, 9, 43	Alpha
Fib 6	-	-
Fib 7	**13**, 21, 22, 38, 47	Alpha
Fib 8	5, **7**, 19, **39**, **40**	Alpha
Fib 9	18, 19, 21, 22, 37, **39**	Theta
Fib 10	3, 4, 5, **7**, **31**	Alpha
Fib 11	-	-
Fib 12	-	-
Fib 13	-	-
Fib 14	-	-
Fib 15	18, 19, 22, 37, **39**	Alpha
	19, 22, 37, **39**, **40**	Beta
Fib 16	-	-
Fib 17	3, 4, 5, 6, **7**, 20, 21, 28, 35, 36	Theta
	5, **7**, 18, 19, **31**, **39**, **40**	Alpha
Fib 18	**7**, 17, 18, 19, **31**, **39**, **40**	Alpha
Fib 19	**7**, 18, 19, **31**, **39**	Beta
	9, **10**, 11, 42, **46**	Theta
Fib 20	**7**, 17, 18, 19, **23**, **30**, **31**, **39**	Alpha
Fib 21	4, 5, **7**, 19, 22, **31**, **39**, **40**	Alpha
Fib 22	3, 4, 5, **7**, **31**	Alpha
Fib 23	-	-
Fib 24	17, 18, 19, **23**, **30**, **31**, 45, **46**, 47	Alpha
Fib 25	17, 18, 19, **30**, **31**, **39**	Alpha
Fib 26	-	-
Fib 27	5, **7**, 17, 18, 19, **23**, **30**, **31**, **39**, **40**	Alpha
Fib 28	1, 2, 3, 4, 6	Beta
Fib 29	-	-
Fib 30	20, 21, 22, 36, 37	Beta
Fib 31	21, 22, 37, **39**, **40**	Beta
Fib 32	18, 19, 21, 22, 37, **39**	Alpha
	22, **40**, 41, 42, 43	Beta
Fib 33	1, 2, 3, 4, 6	Beta
Fib 34	-	-
Fib 35	5, **7**, 17, 18, 19, 21, 22, **23**, 37, **39**, **40**	Alpha
Fib 36	**13**, 20, 21, 22, 38	Alpha
	6, **8**, **9**, **24**, **32**	Beta
Fib 37	-	-
Fib 38	-	-
Fib 39	-	-
Fib 40	**7**, 18, 19, **31**, **39**	Alpha
Fib 41	17, 18, 19, **23**, **30**	Alpha
Fib 42	**7**, 17, 18, 19, **31**, 37, **39**, **40**	Alpha
Fib 43	-	-
Fib 44	19, 21, 22, 37, **39**	Alpha
Fib 45	-	-

Fib 46	17, 18, 19, 37, **39**	Alpha
Fib 47	**7**, 17, 18, 19, **23**, **30**, **31**, **39**	Alpha
Fib 48	17, 18, 19, **23**, **30**	Alpha
Fib 49	-	-
Fib 50	-	-
Fib 51	-	-
Fib 52	**7**, 17, 18, 19, **23**, **30**, **31**	Beta
Fib 53	3, 4, 5, **7**, 19, **39**, **40**	Beta
Fib 54	18, 19, **30**, 37, **39**	Beta
	10, 11, **32**, **46**, 47	Theta
Fib 55	**7**, 18, 19, **31**, **39**	Alpha
	17, 18, 19, **23**, **30**	Theta
Fib 56	-	-
Fib 57	5, **7**, 18, 19, **30**, 37, **39**, **40**	Alpha
Fib 58	**6**, **8**, **9**, **24**, **32**	Alpha
Fib 59	-	-
Fib 60	**10**, 11, 18, 19, **30**, **31**, **32**, **39**, **46**, 47	Beta
Fib 61	4, 5, **7**, 17, 18, 19, **30**, **31**	Alpha
Fib 62	3, 4, 5, **7**, 19, **39**, **40**	Alpha
Fib 63	3, 4, 5, **7**, 19, **39**, **40**	Alpha
	23, **24**, 27, **30**, **31**	Beta
	7, 18, 19, **31**, **39**	Theta
Fib 64	20, 21, 22, 41, 42	Delta
	1, 2, 3, 4, 6, **7**, 17, 18, 19, 20, 21, 28, **31**, 38, 47	Alpha
Fib 65	19, 21, 22, 37, **39**	Beta
	3, 4, 5, 6, **7**	Theta
Fib 66	2, 3, 4, **7**, **13**, 19, 22, **31**, **39**, **40**, 42, 43	Alpha
Fib 67	-	-
Fib 68	17, 18, 19, 20, 21, 22, **23**, **30**, 37, **39**, **40**, 41, 42	Alpha
Fib 69	19, 22, 37, **39**, **40**	Alpha
	17, 18, 19, **23**, **30**	Theta
	10, 11, **25**, **32**, 47	Delta
Fib 70	17, 18, 19, 21, 22, **23**, **30**, **31**, 37, **39**	Beta
Fib 71	17, 18, 19, **30**, 37	Beta
Fib 72	5, **7**, 19, **39**, **40**	Alpha
	1, 2, 3, 4, 5, **40**	Beta
Fib 73	-	-

Note. EC = Eyes Closed, Brodmann areas in bold represents areas within the Dynamic Pain Connectome, patients shaded in blue are excluded from the analysis (see method section). The section is marked with a hyphen (-) if sLORETA was not able to source localize the deviant brain activity.

Table A3

An overview of Brodmann areas detected by sLORETA representing a significant (p<0.1) deviance of brain activity in each FM patient from healthy controls, in specific frequency bands in VCPT condition (N=73).

VCPT		
Patient	Brodmann areas	Frequency band
Fib 1	**10**, 11, 19, 21, 22, 37, **39**, 45, **46**, 47	Theta
Fib 2	2, 5, **7**, **39**, **40**	Beta
	6, **8**, **9**, **24**, **32**	Beta
Fib 3	-	-
Fib 4	3, 4, 5, **7**, 20, 21, 22, 38, 41, 45, **46**, 47	Alpha
	1, 2, 3, 4, **40**	Beta
Fib 5	18, 19, 22, 37, **39**, **40**	Beta
Fib 6	-	-
Fib 7	20, 21, 22, 41, 42	Alpha
Fib 8	-	-
Fib 9	-	-
Fib 10	-	-
Fib 11	**9**, **10**, 45, **46**, 47	Beta
	20, 21, 22, 41, 42	Alpha
Fib 12	3, 4, 5, 6, **7**, 17, 18, 19, 20, 21, 22, **23**, **30**, **39**, **40**, 41, 42	Alpha
Fib 13	19, 20, 21, 22, 37	Beta
Fib 14	-	-
Fib 15	17, 18, 19, 37, **39**	Alpha
	2, 3, 4, **8**, **9**, **10**, **13**, 20, 21, 22, 38, **40**, **46**	Beta
Fib 16	-	-
Fib 17	-	-
Fib 18	18, 19, 22, 37, **39**	Alpha
Fib 19	**7**, 19, 22, **39**, **40**	Beta
Fib 20	1, 2, 3, 4, 6	Alpha
Fib 21	18, 19, **31**, **39**, 37	Alpha
	18, 19, **30**, 37, **39**	Beta
Fib 22	2, 5, **7**, **39**, **40**	Beta
Fib 23	-	-
Fib 24	17, 18, 19, 37, **39**	Alpha
Fib 25	5, **7**, 19, **39**, **40**	Beta
	21, 22, 37, **39**, **40**	Beta
Fib 26	-	-
Fib 27	**10**, 11, 19, 22, **25**, **32**, 37, **39**, **40**, 47	Alpha
	17, 18, 19, **30**, **31**	Theta
Fib 28	**7**, 17, 18, 19, **31**	Beta
Fib 29	18, 19, 20, 21, 37	Beta
Fib 30	**7**, 18, 19, **31**, **39**	Theta
	1, 2, 3, 4, 6	Beta
Fib 31	**10**, 11, 20, 21, 22, 41, 42, 45, **46**, 47	Beta
	1, 2, 3, 4, 5, 6, **31**	Beta
Fib 32	1, 2, 3, 4, 6, **10**, 11, **25**, **32**, 47	Beta
Fib 33	**10**, 11, **13**, 21, 38, 45, **46**, 47	Theta
Fib 34	-	-
Fib 35	5, **7**, 18, 19, 22, **23**, **31**, **39**, **40**	Alpha
Fib 36	6, **8**, **9**, 22, **24**, **32**, 38, 45, **46**, 47	Alpha
	5, **7**, 19, **39**, **40**	Beta

Fib 37	-	-
Fib 38	-	-
Fib 39	-	-
Fib 40	**7**, 18, 19, **31**, **39**	Alpha
Fib 41	-	-
Fib 42	1, 2, 3, 4, 6, 19, 22, 37, **39**, **40**	Alpha
Fib 43	-	-
Fib 44	1, 2, 3, 4, 5, 6, **7**, **40**	Alpha
Fib 45	-	-
Fib 46	**10**, 11, 45, **46**, 47	Beta
Fib 47	**7**, 18, 19, **31**, **39**	Beta
	17, 18, 19, **23**, **39**	Beta
Fib 48	3, 4, 5, **7**, **40**	Alpha
	1, 3, 4, 6, **24**	Beta
Fib 49	-	-
Fib 50	-	-
Fib 51	-	-
Fib 52	2, 3, 4, 5, 6, **8**, **9**, **24**, **32**	Alpha
Fib 53	3, 4, 5, 6, **7**	Beta
	5, **7**, 19, **39**, **40**	Beta
Fib 54		
	17, 18, 19, **30**, **31**	Beta
Fib 55	**10**, 11, 45, **46**, 47	Theta
	2, 3, 5, **7**, **13**, 21, 22, **39**, **40**	Alpha
Fib 56	-	-
Fib 57	**10**, 11, 45, **46**	Beta
Fib 58	**10**, 11, **32**, **46**, 47	Beta
	2, 3, 5, **7**, **40**	Theta
Fib 59	**7**, 17, 18, 19, **31**	Beta
Fib 60	1, 2, 3, 4, **7**, 17, 18, 19, **31**, **40**	Beta
	17, 18, 19, **23**, **30**	Beta
Fib 61	2, 3, 5, **7**, **10**, 11, **25**, **32**, **40**, 47	Alpha
Fib 62	3, 4, 5, **7**, **40**	Alpha
Fib 63	1, 2, 3, 4, 6	Theta
	1, 2, 3, 4, 6	Beta
Fib 64	1, 2, 3, 4, 6	Alpha
	13, 20, 21, 22, 38	Beta
	20, 21, 22, 41, 42	Delta
Fib 65	1, 2, 3, 4, 6	Beta
Fib 66	4, 5, 6, **7**, **31**	Theta
Fib 67	-	-
Fib 68	3, 4, 5, 6, **7**, **13**, 19, 22, **24**, **31**, 32, **39**, **40**	Alpha
	3, 4, 6, **8**, **9**	Beta
	3, 4, 6, **8**, **9**	Beta
Fib 69	18, 19, 22, 37, **39**	Alpha
	5, **7**, 19, **39**, **40**	Beta
Fib 70	19, 21, 22, 37, **39**	Beta
	19, 20, 21, 22, 37	Beta
Fib 71	**10**, 11, **25**, **32**, 47	Beta
Fib 72	20, 21, 22, 36, 37	Alpha
	20, 21, 22, 41, 42	Beta
	17, 18, 19, **33**, **39**	Delta
Fib 73	-	-

Note. VCPT = Visual Continuous Performance Task, Brodmann areas in bold represents areas within the Dynamic Pain Connectome, patients shaded in blue are excluded from the analysis (see method section). The section is marked with a hyphen (-) if sLORETA was not able to source localize the deviant brain activity.

Appendix B

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 klinisk hovedoppgave ved Psykologisk Institutt (NTNU, Dragvoll), i samarbeid med studentene Astrid Sæten Skre, Kristine Fjeldal Venli og førsteamanuensis Stig Hollup.

For å opprettholde krav til smittevern ønsker vi at alle deltakere møter med munnbind. I tillegg vil forsøksmedarbeiderne bruke munnbind, og desinfeksjonsmidler vil være tilgjengelig.

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 4 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 an på den individuelle tidsplanen vi legger opp. Vi ser for oss ca. 2-3 økter i uka over en periode på ca. 6 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 Astrid Sæten Skre (tlf: 412 03 198, e-post: astriss@stud.ntnu.no) eller Kristine Fjeldal Venli (tlf: 994 71 602, e-post: kristfv@stud.ntnu.no).

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. 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 Astrid Sæten Skre (tlf: 412 03 198, e-post: astriss@stud.ntnu.no) eller Kristine Fjeldal Venli (tlf: 994 71 602, e-post: kristfv@stud.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

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

Fibromyalgia Impact Questionnaire (FIQ)

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

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

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

0 1 2 3 4 5 6 7

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

0 1 2 3 4 5 6 7

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

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

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

15: Hvor kraftig har smerten din vært?

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

16: Hvor trøtt har du vært?

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

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

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

18: Hvor kraftig har stivheten din vært?

Ingen stivhet ☐☐☐☐☐☐☐☐☐☐ Veldig stiv

19: Hvor nervøs eller engstelig har du følt deg?

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

20: Hvor deprimert eller trist har du følt deg?

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

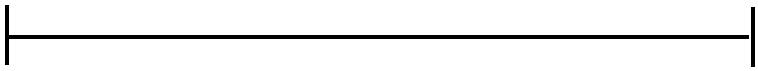
Appendix E

VISUELL ANALOG SKALA (VAS)

I løpet av den siste uken:

Smerte

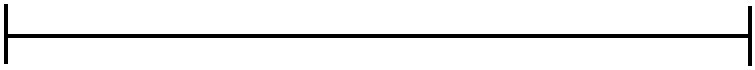
Hvor kraftig er smerten din? Sett et kryss på linjen.



Ingen smerte — Utholdelig smerte

Fatigue/trøtthet

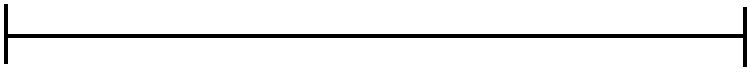
Hvor kraftig er din fatigue/trøtthet? Sett et kryss på linjen.



Ingen fatigue — Kraftig fatigue

Fibrotåke

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



Ingen fibrotåke — Kraftig fibrotåke

Astrid Sæten Skre & Kristine Fjeldal Venli

Towards an Understanding of the Hidden Pain: a qEEG Study of Fibromyalgia

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