Graduate thesis

NTNU
Norwegian University of Science and Technology
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Department of Psychology

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Transcranial direct current stimulation as a treatment option for patients with fibromyalgia

A pilot study of symptom relief and possible underlying mechanisms in brain activity related to treatment-outcome

Graduate thesis in Clinical Psychology
Supervisor: Stig Arvid Hollup
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Kunnskap for en bedre verden

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Abstract

Studies have shown an effect of transcranial direct current stimulation (tDCS) over the primary sensorymotor and motor cortex (S1/M1) on pain reduction. In this study, we investigated the effect of 5 consecutive sessions (20 minutes) of 2 mA anodal tDCS over M1 in 16 subjects with fibromyalgia (FM). Self-reported perception of pain, fatigue, and fibrofog were measured approximately 7 days before treatment, 7 days after treatment and at least 3 months after the end of treatment. Adverse effects were registered. Additionally, an EEG recording of the subjects was conducted to investigate possible deviances related to chronic pain before and after treatment in three conditions; eyes opened, eyes closed and VCPT. The qEEG patterns were hypothesised to be able to predict treatment-outcome with tDCS in subjects with FM. A significant reduction in pain, fatigue and fibrofog was observed in the treatment condition. Results indicate that tDCS may have a significant effect on pain reduction in subjects with FM, and that this effect is lasting over 3 months. The best outcome group, defined by the greatest symptom reduction on subjective measures, were found to have significantly less oscillatory correlates to default mode network activation in resting state compared to the worst outcome group, pre-treatment. The best outcome group were also found to have significantly more oscillatory correlates to default mode network activation in resting-state post-treatment. Further research should focus more specifically on the effects of tDCS within the framework of an RCT-design with a larger sample size.

Keywords: Fibromyalgia, Pain, Transcranial direct current stimulation (tDCS), EEG, dynamic pain connectome, central sensitization

Preface and Acknowledgment

Chronic pain is a major health issue around the world. Fibromyalgia is a diagnosis characterised by chronic pain, in addition to several symptoms affecting the patients' quality of life. Being diagnosed with fibromyalgia can be a relief for some, getting answers for their symptoms and more suitable treatment. Nevertheless, the available treatment is not good enough. Participants in the current study describes a life filled with obstacles affecting their professional as well as their personal life. Having an invisible illness raises much stigma, making it difficult for patients to feel understood and believed. Some have to step down at work and some lose contact with close friends. The patient group describe feelings such as shame and sadness over their loss of function, which in turn influences their self-perception.

The stigma and lack of specialised treatment for this patient group have been some of the motivational factors behind our work. We believe that a broader understanding of the maladaptive changes in the functional connections of the brain can lead to a greater acceptance of the diagnosis, as well as more specialised treatment options for fibromyalgia. Through this thesis, we hope to contribute to a broader understanding of the "fibro-brain", as well as strengthening the field of neuromodulating treatment options for this patient group.

Much work has gone into this project, starting in February 2018. We've aquired a great deal of knowledge from creating a project from scratch; deciding the research design, recrutting participants, collecting EEG and self-reported data, administering treatment, plotting, analysing and interpreting data, and lastly writing it all up. First of all, we would like to thank all the participants in this study for their contribution. For many of you, making the travel to our lab posed a significant change in your daily routine, and we want you to know how much we appreciate it. Your experiences and stories have been an eye-opener to what it is like living with an invisible illness, and we are grateful for your trust and openness. We would also like to thank Sigrid Hegna Ingvaldsen for being an excellent lab-partner and friend throughout this process. Finally, we would like to thank our supervisor, Stig Arvid Hollup, for always making yourself available with guidance and support. You always inspire us to think for ourselves, by never giving a straight answer to anything.

Hei. Mitt navn er Fibromyalgi. Nå tar jeg over livet ditt. Du får aldri danset mer. Jeg tar fra deg din store lidenskap. Du får aldri jobbet mer. Ei heller være sosial. For det har du ikke krefter til. Du får av meg en utmattelse så kraftig at du må hvile selv etter noe så enkelt som å ta en dusj.

Jeg skal sørge for at du mesteparten av tiden strigråter av de enorme smertene jeg gir deg eller skulle ønske du kunne forlate denne verden for å kunne slippe for så i bare et sekund. Hukommelse og konsentrasjon skal fibrotåka ødelegge. Du kommer til å skjelve, alt kognitivt blir vanskelig og balansen din blir ustødig. Med det følger også ekstrem svimmelhet. Du tåler verken varme eller kulde. Din indre termostat er ødelagt. Glem søvn. Og ønsk depresjon velkommen. Du klarer ikke hverdagen som alle andre. For det andre klarer på noen timer, må du bruke flere dager på. Og har du en "god" dag, og gjør det du må eller har lyst til, så straffer jeg deg. Da blir du sengeliggende av smerter i flere dager etterpå. Det finnes ingen kur. Og med meg følger så mye forskjellig og annet brutalt, at du blir aldri klok på meg. Ei heller helsevesenet. Nå er jeg sjefen. Jeg bestemmer hvordan hverdagen din blir. Og ikke glem at hver dag er annerledes. Du vet aldri hvilken dag du våkner til. Men en ting kan jeg love deg. De uutholdelige smertene kommer til å være der. Hver eneste dag. Hele døgnet. Jeg ser dine tårer, ditt sinne, din frustrasjon og oppgitthet. Men jeg bryr meg ikke. For jeg har kommet for å bli. Vi blir aldri venner, jeg og du. Jeg har tatt over, og du vil kjempe imot. Men det klarer du aldri. For jeg har overtaket. Du blir til tider hjelpeløs. Det betyr ingenting for meg. For jeg er Fibromyalgi. Jeg fører ingenting godt med meg og jeg er et ubarmhjertig monster. Og du har å finne deg i at jeg er med deg resten av livet. Som en samboer du aldri blir kvitt …

(Pasient med fibromyalgi, personlig kommunikasjon, 2019).

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List of Abbreviations

a……..	Animal (in the VCPT-task)
ACC……	Anterior cingulate cortex
ACR……	American College of Rheumatology
ADHD……	Attention Deficit Hyperactivity Disorder
BG……..	Basal Ganglia
BOLD…….	Blood-Oxygen-Dependent Imaging
CNV……	Contingent negative variation
CS……...	Central sensitization
DLPFC……	Dorsolateral prefrontal cortex
EC……...	Eyes Closed
EEG.....	Electroencephalography
EO……...	Eyes opened
ERP…….	Event related potential
FIQ……..	Fibromyalgia Impact Questionnaire
FM……...	Fibromyalgia
fMRI……..	Functional magnetic resonance imaging
FWER…….	Familywise errer rate
h……..	Human (in the VCPT-task)
HPA……	Hypothalamic-pituitary-adrenal gland
HT……...	Hypothalamus
LTD…….	Long term depression (of synaptic strength)
LTP…….	Long term potentiation (of synaptic strength)
M…….	Mean
Mdn…….	Median
MWUT……	Mann-Whitney U test
M1……...	Primary motor coretx
N1……...	N100 negative waveform (ERP)
p……..	Plant (in the VCPT-task)
PAG……	Pariaqueductal grey
PBN…….	Parabrachial Nucleus of the thalamus
PCC…….	Posterior cingulate cortex
PET…….	Positron-emission Tomography

PFC……. Prefrontal Cortex

P3 ……... P300 positive waveform (ERP).

qEEG…….... Quantitative Electroencepholagrapy

SD……... Standard deviation

SS…… Symptom severity score (ACR)

S1…… Primary somatosensory cortex

tDCS …….. Transcranial Direct Current Stimulation

VAS…… Visual Analogue Scale

VCPT…….. Visual Continuous Performance Task

WPI……. Widespread pain index (ACR)

WSRT……. Wilcoxon Signed Rank Test

Δ……. Aritmetic difference ($\Delta x = x_1 - x_2$)

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

%P……... Relative spatial power density in percent

1. Introduction

Fibromyalgia (FM) is a chronic pain diagnosis with a prevalence of 3-5% in Europe (Fagerlund, Bystad & Aslakssen, 2013). FM is difficult to diagnose (Sarzi-Puttini et al., 2018), and the diagnostic process can typically take more than two years and visits to several physicians (Choy et al., 2010). In the treatment of FM, there has been recommended a multicomponent approach, including both pharmaceutical and non-pharmaceutical interventions (Marlow, Bonilha & Short, 2013). However, no single treatment option has been proven effective in reducing all symptoms of FM, and the effects on pain are seldom large (Marlow et al., 2013; Marcus, Bernstein, Haq & Breuer, 2014). Besides, especially the pharmaceutical treatment options often report a high number of dropouts and adverse effects (Marlow et al., 2013). Transcranial Direct Current Stimulation (tDCS) has been proposed as a treatment option for FM, and research is promising on pain reduction. tDCS is a non-invasive brain stimulation with limited side-effects, that can be used for modulating cortical excitability and firing rate of individual neurons (Stagg & Nitsche, 2011; Boggio, Zaghi, Lopes & Fregni, 2008). The first part of this study aims to investigate whether tDCS can reduce the core symptoms in FM patients and if the effect can outlast the stimulation.

As pain perception in itself is a subjective phenomenon, pain processing is influenced by and interact with ongoing neural activity (Kucyi & Davis, 2015). Studying FM, some potential markers for chronic pain have been proposed in the framework of CS as well as the dynamic pain connectome. Napadow et al. (2010) hypothesised that the default mode network had altered functional connectivity in FM patients. Altered functional connectivity is associated with plastic neuronal change (Kuner & Flor, 2017), which introduces the relationship between structural change in the nervous system and neuronal activity in chronic pain (Yun et al., 2007; Nielsen & Henriksson, 2007). Electroencephalography (EEG) is a non-invasive technique measuring scalp electrical activity generated by structures in the cortex (Teplan, 2002). Even though EEG only measures electrical activity on the scalp, literature shows that it can be utilised to identify the location of the neural electrical sources within the cortex (Bénar & Gotman, 2002). The second part of the study aims to investigate deviances in the subject's EEG patterns and possible differences between different treatment-related outcomes. Finding differences in the qEEG data of different treatment-outcomes may contribute to better and more specific guidelines in the future use of tDCS as an intervention for FM.

1.1 Fibromyalgia

Fibromyalgia (FM) is a diagnosis given to patients with widespread chronic pain when no alternative explanation for the pain can be identified (Williams & Clauw, 2009). The population prevalence of FM is 3-5 % in Europe and is more prevalent in women than in men (Fagerlund et al., 2013). Some of the most characteristic symptoms of FM are widespread pain, fatigue, and fibrofog (i.e., cognitive symptoms) (Katz, Heard, Mills, & Leavitt, 2004), hereafter referred to as the core symptoms of FM in this thesis. A variety of additional symptoms and comorbid disorders may also be present, such as irritable bowel syndrome (IBS), depression, headaches, and sleep disturbance (Häuser, Thieme, & Turk, 2010). Regarding the perception of pain, FM patients often display both hyperalgesia and allodynia (Williams & Clauw, 2009; Sörensen, Graven-Nielsen, Henriksson, Bengtsson, & Arendt-Nielsen, 1998; Oudejans, Smit, van Velzen, Dahan, & Niesters, 2015). Hyperalgesia is defined as increased pain to normally painful stimuli, while allodynia is defined as pain to normally non-painful stimuli (Williams & Clauw, 2009). Fibrofog refers to disturbances in memory and mental clarity, which include experiences of forgetfulness, sensory overload, blurring, and a reduced ability to follow conversations due to difficulties with processing information (Katz et al., 2004, p. 53). According to Glass (2008), the FM population frequently report cognitive difficulties, that are verified using neuropsychological tests.

Studies have also shown that FM patients report being fatigued to a higher degree than the general population (Wolfe, Hawley, & Wilson, 1996). According to Nicassio, Moxham, Schuman and Gevirtz (2002), there are many possible perspectives on FM fatigue, including the roles of both pain, sleep, and depression associated with FM. The core symptoms of FM, combined with additional symptoms and common comorbid disorders, may lead to a generally reduced quality of life, which has been shown through several studies (e.g. Verbunt, Pernot, & Smeets, 2008; Gormsen, Roseberg, Bach, & Jensen, 2010; Moore et al., 2010; Mas, Carmona, Valverde, & Ribas, 2008).

1.1.1 Diagnostic criteria. FM is difficult to diagnose (Sarzi-Puttini et al., 2018), and the diagnostic process can typically take more than two years and visits to several physicians (Choy et al., 2010). The 1990 American College of Rheumatology (ACR) classification criteria consist of *a)* a 3-month history of widespread chronic pain on both sides of the body and above and below the waist, and *b)* the presence of 11 out of 18 tender points (Sarzi-Puttini et al., 2018). These so-called "tender points" include sensitive areas on the body in which applying pressure will cause pain, examined by a physician. There were several issues regarding the 1990 ACR classification criteria, where especially the examination of tender points was rarely performed

in primary care and often performed incorrectly (Fitzcharles & Boulos, 2003). Also, patients who had periods of improvement could fail to satisfy the diagnoses according to the 1990 ACR criteria (Wolfe et al., 2010).

The ACR 2010 diagnostic guidelines provide more practical criteria for the diagnostic process of FM and include an alternative to the tender-point examination as well as a wider variety of symptoms based on new research (Wolfe et al., 2010). The new guidelines include a widespread pain index (WPI), a symptom severity score (SS-score) for fatigue, sleep and fibrofog, and a list of multiple somatic additional symptoms (Sarzi-Puttini et al., 2018). The examination of tender points is replaced by the WPI and is no longer a necessity in the diagnostic process. According to Wolfe et al. (2010), the WPI strongly correlates with tender points and can, therefore, be used as an alternative in the diagnostic process. The ACR 2010 guidelines can be especially useful in the evaluation of patients with variability in symptoms over time (Wolfe et al., 2010).

1.1.2 Treatment. In the treatment of FM, there has been recommended a multicomponent approach, including both pharmaceutical and non-pharmaceutical interventions (Marlow et al., 2013). No single treatment option has been proven effective in reducing all symptoms of FM (Marlow et al., 2013). Amongst the pharmaceutical treatment options, antidepressants and simple analgesics such as paracetamol can be considered. Stronger opioids such as Tramadol should be used with caution due to long-term side-effects (Carville et al., 2008). The effects on pain following these recommendations are seldom large (Marcus et al., 2014), and especially the pharmaceutical treatment options often report a high number of dropouts and adverse effects (Marlow et al., 2013). The non-pharmaceutical treatment options can include exercise, transcranial direct current stimulation (tDCS), neurofeedback training, cognitive behavioural therapy, and physical therapy. With a growing understanding of possible mechanisms behind FM, several studies have shown that neuromodulation of cortical excitability can lead to symptom reduction in FM patients, with fewer dropouts and adverse effects (e.g. Fagerlund, Hansen & Aslaksen, 2015; Valle et al., 2009; Fregni et al., 2006b).

1.1.3. Theories about cause and effect. Conclusions are yet to be made about the cause of FM due to unclear mechanisms underlying chronic pain (Fregni & Pascal-Leone, 2007). The physiological basis of FM may include a genetic predisposition, an abnormal stress response to triggers, dysfunction in the HPA axis (Hypothalamus, Pituitary gland, and Adrenal glands) and the autonomic nervous system, and functional abnormalities in pain processing (Williams & Clauw, 2009). Research has shown abnormalities in both ascending and descending pain pathways which may relate to CS in the brain of FM patients. Studies show abnormalities in

both neurotransmitters that facilitate pain transmission, and neurotransmitters known to inhibit pain transmission (Clauw, Arnold & McCarberg, 2011). These findings suggest that the FM-brain display an augmented response to pain signals. This state of central overactivation may include several areas of the brain, including thalamic nuclei and limbic and cortical regions (Fregni & Pascual-Leone, 2007). According to Flor and Turk (1996):

> Chronic pain patients display increased perceptual and pain sensitivity that is mirrored in cortical hyperreactivity to both sub- and suprathreshold painful stimulation. (...) It is important, therefore, to recognize that chronic pain may lead to massive plastic changesin spinal and supraspinal mechanisms related to the processing of non-nociceptive and nociceptive information. These changes may induce a type of processing of nociceptive and non-nociceptive information that is quite different from that of a person without chronic pain. (pp. 74-75).

1.2 Chronic pain

According to Treede et al. (2015), different subtypes of chronic pain have different characteristics. Central to chronic pain, however, is the persistence of pain for at least three months. Furthermore, the cause of the pain is relevant. Often, in the case of chronic pain, the nociceptive signalling leading to pain is not caused by noxious stimuli that warns of actual cell damage. Thus, understanding the basic neuronal pain processing is relevant for understanding chronic pain.

1.2.1 Neural processing of pain. Figure 1 illustrates a basic conceptual outline of the afferent pain pathway. For a more detailed description, see Almeida, Roizenblatt and Tufik, (2004). Peripheral nociceptive neurons innervate the dorsal root ganglia of the spinal segments. All the dorsal root ganglia of a spinal segment are organized to be innervated by corresponding areas of the skin, muscles and other organs (Takahashi & Nakajima, 1996). Noxious stimuli originating in a certain area causes exitability in the sensory neurons in the area, which in turn progress to the dorsal horn of the corresponding segment. From the dorsal horn of the spinal segment, the pain pathway leads through the spinal segment and up through the spinothalamic tract. As illustrated, there is not a single conceptual nociceptive signalling pathway in the brain. fMRI-studies have identified afferent signalling through thalamus, insula, and the anterior cingulate cortex (ACC), to primary sensorimotor (S1) and motor cortex (M1) (Peyron et al., 2004; Almeida, Roizenblatt & Tufik, 2004). Other models show afferent signalling through the parabrachial nucleus (PBN), amygdala, prefrontal cortex (PFC), the basal ganglia (BG) and thalamus (Strobel, Hunt, Sullivan, Sun & Sah, 2014). The sensory components of pain are closely related to the former model and hypothesised to give information about the intensity

and anatomical origin of the noxious stimuli. The latter model is hypothesised to give information about the emotional valence and sense of danger related to pain sensation. (Neugebauer, Li, Bird, & Han, 2004; Treede, & Apkarian, 2008; Zhang et al., 2015; Talbot, Madden, Jones, & Moseley, 2019). However, Talbot et al. (2019), conclude that these systems do not work separately, and must be viewed as interactive and dynamic.

As shown in Figure 1, the thalamus is involved in both these models of afferent pain processing, further illustrating a complex network of neuronal interaction, indicating that the concept of afferent signalling alone cannot explain pain processing. Nociceptive modulation is one such example. Nociceptive modulation may directly modulate afferent nociceptive signals in the vertebrae through descending inhibition. Descending inhibition is, in turn, associated with the periaqueductal grey (PAG) (Gebhart, 2004). Tracey et al. (2002) identified an association between the PAG, pain perception and level of distraction. In their study, PAG-activation was positively correlated with level of distraction, and negatively correlated with subjectively reported level of pain. Thus, introducing the role of attention in the understanding of pain.

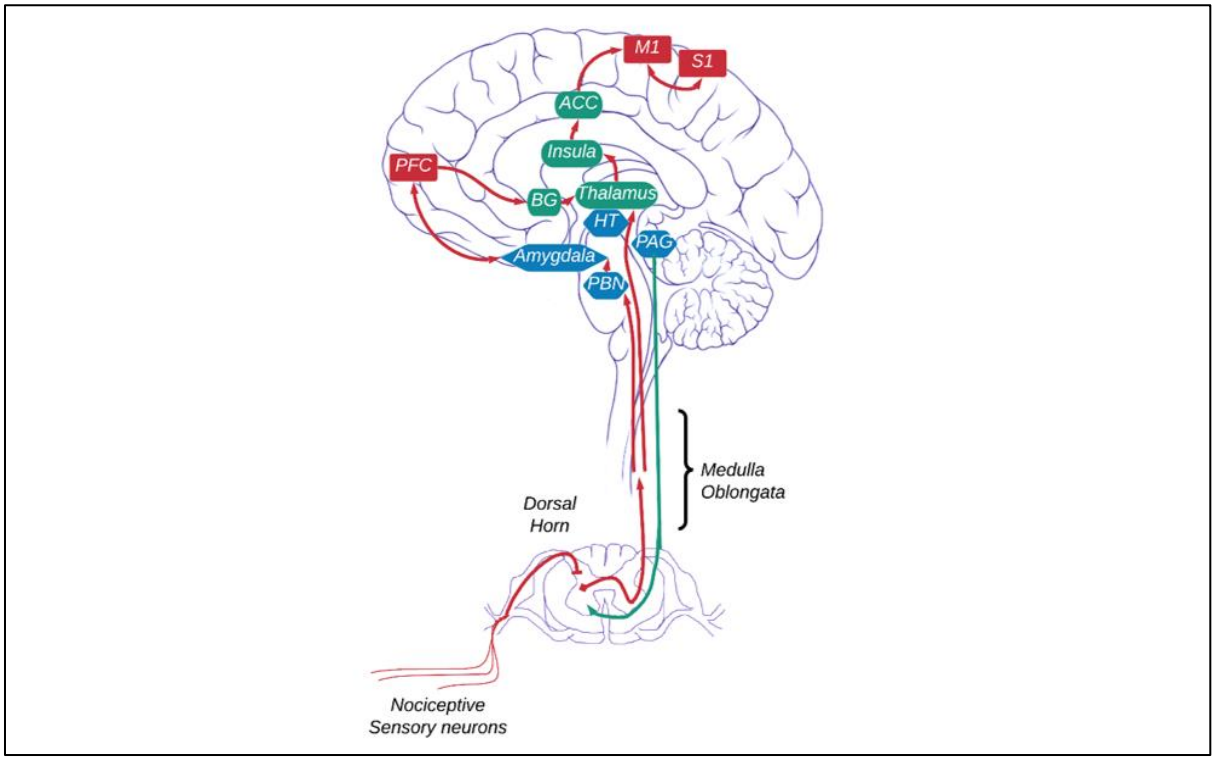


Figure 1. Conceptual illustration of the ascending nociceptive pathway and descending inhibitory pathway. Red arrows indicate the ascending pathway. Green arrows indicate the descending pathway. Blue markers are indicating limbic areas, green markers are indicating subcortical areas, and red markers are indicating cortical areas. AAC, Anterior Cingulate Cortex; BG, Basal Ganglia; HT, Hypothalamus; PBN, Pariabrachial Nucleus; PAG, Pariaqueductal Gray; PFC, Prefrontal Cortex; S1, Primary sensory cortex; M1, Primary motor cortex.

1.2.2 The dynamic pain connectome. As pain perception in itself is a subjective phenomenon, pain processing is influenced by and interact with ongoing neural activity (Kucyi & Davis, 2015). Studies using fMRI in combination with EEG have found nociceptive stimuli not only to change spatial neuronal activity (e.g. thalamus, insula, ACC and S1), but also to change spatiotemporal neuronal activity (Mouraux, Guerit, & Plaghki, 2003; Gross, Schnitzler, Timmermann, & Ploner, 2007). Spatiotemporal neuronal activity refers to an understanding of neuronal information processing as dependent on both neuroanatomical orientation (spatial) and frequency, synchrony, and phase of activation (temporal). In other words, the communication of different anatomical orientations in the brain is made possible by time-dependent connections. Some of the most commonly used measurements of spatiotemporal connectivity are fMRI measurements of functional connectivity and corresponding EEG measurements of oscillatory frequency and power (Greicius, Krasnow, Reiss, & Menon, 2003; Chen, Feng, Zhao, Yin, & Wang, 2008).

As previously mentioned, pain influences neuronal activity. Inversely, neuronal activity influences the perception of pain. Preexisting spatiotemporal neuronal states is found to influence whether a threshold stimulus is perceived as painful or not (Boly et al., 2007). Thus, the dynamic pain connectome refers to the variability of pain caused by the spatiotemporal communication within the brain. The three systems included in the theoretical framework of the dynamic pain connectome are, *1)* the default mode network, *2)* the salience network, *3)* the antinociceptive system. These three central neural systems have been identified to influence attention away from, and towards pain (Kucyi & Davis, 2015).

The default mode network is associated with mind wandering. Higher activation is correlated with less cognitive effort and more mind wandering. Furthermore, the default mode network activation is associated with increased mind wandering away from pain (Greicius et al., 2003). Although different researchers propose somewhat different anatomical areas of origin, there seems to be an agreement regarding three anatomical areas central to the default mode network. Increased activity in the ACC, posterior cingulate cortex (PCC) and precuneus are associated with more mind wandering, and increased default mode network activation. Studies on functional connectivity in combination with EEG, have identified correlations between increased alpha activity, increased beta activity, altered frontal theta activity, and decreased delta activity (Scheeringa et al., 2008; Jann et al., 2009; Hlinka, Alexakis, Diukova, Liddle, & Auer, 2010, Neuner et al., 2014).

The antinociceptive system is closely related to the aforementioned descending pain. Kyuci et al. (2013) identified functional connectivity between the default mode network and

the antinociceptive system, indicating that default mode network activation is associated with descending inhibition through the antinociceptive system.

The salience network is associated with attending to pain rather than away from pain. Functional connectivity between the anterior insula, the medial cingulate cortex, and the dorsolateral prefrontal cortex, is correlated with activation of the salience network (Seeley et al., 2007). Goulden et al. (2014), hypothesise that the salience network activation is involved in switching between other networks like the default mode network. To our knowledge, there are few consistent findings on the temporal properties of the salience network. However, Otti Guendel, Wohlschläger, Zimmer and Noll-Hussong (2013) found a significanty difference in the frequency of functional connectivity between patients with chronic pain and healthy controls. Even though this does not give information about the associated frequencies of phase locking of the salience network, it illustrates the importance of researching the dynamic pain connectome in the context of chronic pain.

1.2.3 The dynamic pain connectome in patients with chronic pain. There are few studies and yet inconsistent findings on specific oscillatory frequencies regarding chronic pain, and even fewer concerning the dynamic pain connectome. An increase in theta activity is identified as a possible marker for chronic pain (Stern, Jeanmonod, & Sarnthein, 2006). Altered theta activity is associated with a decreased default mode network activation and mind wandering away from pain (Scheeringa et al., 2008). Furthermore, this relationship has been identified in the context of chronic pain through studies on FM patients (Fallon, Chiu, Nurmikko, & Stancak, 2018). Napadow et al. (2010) hypothesised that the default mode network had altered functional connectivity in FM patients. Altered functional connectivity is associated with plastic neuronal change (Kuner & Flor, 2017). This introduces the relationship between structural change in the nervous system and neuronal activity in chronic pain (Yun et al., 2007; Nielsen & Henriksson, 2007).

1.2.4 Central sensitization. According to Fleming and Volcheck (2015), Central Sensitization (CS) refers to an amplification of afferent sensory signals which can cause a variety of symptoms. Additionally, CS is the result of neuronal plasticity. In short, this refers to a process where amplified signalling develops through neuronal change, which in turn is made possible by neuronal activity (Woolf, 1983; Bliss & Collingridge, 1993). Research on CS has focused primarily on amplification of neuronal signalling found in the afferent nociceptive pathway. Sensitization in the wide-dynamic-range-neurons in the dorsal horn of the spinal cord is prevalent even in regular acute pain stimulation, leading to enhanced neuronal pain signalling (Woolf, 1983; Campbell & Meyer, 2006).

According to Nielsen and Henriksson (2007), longstanding or permanent CS is considered an expression of plastic changes in both the dorsal horn of the spinal cord and the primary sensory cortex (p.466). This lowering of the threshold of pain signalling is, in turn, closely related to both allodynia and hyperalgesia (Latremoliere, & Woolf, 2009). Both allodynia and hyperalgesia are identified in FM patients through extensive research on quantitative sensory testing and nociceptive flexion reflex testing and is viewed by many as indirect evidence of CS in FM patients (e.g. Desmeules et al., 2003; Meeus & Nijs, 2007). As CS is made possible by neuronal activity, interplay between the mechanisms of CS and neuronal pain modulation through networks like the dynamic pain connectome seems probable (Ploner, Sorg & Gross, 2017). Emerging evidence illustrates the interplay between neural network activation and CS. Alshelh et al. (2016) identified deviances in spatiotemporal activity in the dorsal horn, the salience network, thalamic areas and the S1, between chronic pain patients and healthy controls. Furthermore, some emerging evidence indicates that also other sub cortical areas such as the hippocampus are affected by CS in chronic pain (Mutso et al., 2012; Mutso et al., 2013). These findings underscore the importance of further research on chronic pain within a framework of both structural and spatiotemporal factors. Future research must involve the use of EEG, as well as fMRI and other imaging techniques, to better understand the relationship between neuronal activity and structural plasticity.

1.3 EEG

Electroencephalography (EEG) is a non-invasive technique that measures scalp electrical activity generated by structures in the cortex (Teplan, 2002). These changes are presented as spikes, transients and rhythms (Kaiser, 2007). Even though EEG only measure electrical activity on the scalp, literature shows that it can be used to find the location of the neural electrical sources within the cortex (Bénar & Gotman, 2002). When recording an EEG, electrodes are most often positioned on the scalp according to the International 10-20 system. The electrodes are labelled in terms of their underlying brain areas. Compared to imaging techniques (e.g. fMRI, PET), EEG has the advantage of detecting changes in brain activity approximately a thousand times faster. On the other hand, the imaging techniques have better spatial resolution and can detect activity in deeper structures of the brain that do not contribute to the electrical field on the scalp (Kaiser, 2007).

1.3.1 qEEG. Quantitative Electroencephalography (qEEG) is a quantification of the raw data recorded with EEG. The qEEG breaks down complex brain waves into components for analysis. The analysis often includes a comparison of different frequencies in spatial power density (hereafter power) or amplitude at various sites of the brain, in addition to a comparison

with a normative database (Donaldson, Mueller, Donaldson, & Sella, 2003). The comparison with a normative database has been used to identify abnormalities in oscillatory activity in several conditions (Hargrove et al., 2010), and is shown to have high sensitivity and specificity (Prichep, 2005).

The level of sensitivity and specificity will depend on the normative database in question (Field, 2013). The qEEG provides an assessment of the mean spectral magnitude or power for different brain frequency bands (Kaiser, 2007). The nomenclature of brain frequency bands differs in the literature. According to Kane et al. (2017) brain frequency bands are defined as delta (0.1 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), beta (13 – 30 Hz), and gamma (30 – 80 Hz), which refers to the rhythmic activity patterns at different temporal scales in the brain (Fröhlich, 2016).

1.3.2 ERP. In addition to a frequency band assessment, the qEEG provide information about event-related potentials (ERP). ERP components are expressions of time-locked changes in cortical activity. They can be observed as curves with characteristic peaks when extracted from the EEG background activity (Ogrim et al., 2014). These time-locked potentials from multiple trials are averaged together to an observable event that provides information about a series of cognitive operations, from before the stimulus is presented until after a behavioural response is made (Woodman, 2010). The averaged event allows us to visualise, measure and compare a person's response during a trial. ERP components are labelled according to their polarity (e.g. P for positive waves and N for negative waves), and their latency (e.g. 100 if the component has its peak approximately 100 ms after stimulus onset). According to Begleiter et al. (1998), ERP characteristics are to some extent determined by biology, and may, therefore, be used as biomarkers for some diseases.

One way to obtain information about a person's ERP components is to record an EEG during a Visual Continuous Performance Task (VCPT). The Go/NoGo protocol is one example of the VCPT. In the Go/NoGo protocol, the subject is presented with four different conditions and instructed to act only for the go-condition, to withhold their response for the no-go condition, and to ignore the other two conditions. Because of the length of this task and the large number of distractor stimuli, this task requires a high level of sustained attention, selective attention and inhibitory control/impulsivity (Silvana & Nada, 2009). Research indicates that different diagnostic groups have some characteristic differences in their components and behavioural measures (e.g. Papaliagkas, Anogianakis, Tsolaki, Koliakos, & Kimiskidis, 2009; Wiersema, Van Der Meere, & Roeyers, 2009). As described within the framework of the dynamic pain connectome, chronic pain is attention-demanding and can be hypothesised to

interfere with the brain's attentional processes and inhibitory control. The VCPT also provides information about behavioural measures such as reaction time (RT) and reaction time variability (RTvar), which have been used as measures of the attentional processes involved in chronic pain. It has been argued that long reaction times may be related to impaired automatic processing and direct thinking, while very short reaction times may be related to limited inhibition (Nydén, Gillberg, Hjelmquist & Heiman, 1999).

The N100 component (hereafter N1) is a negative component with an average peak approximately 130 to 200 ms after the onset of the first stimulus (Brodeur et al., 2008). N1 is thought to reflect a process of discrimination in focus/attention (Vogel & Luck, 2000) and is associated with both feature integration and encoding of information (Sumich, Castro & Kumari, 2014). The P300 component (hereafter P3) is a positive component with a peak approximately 300 to 500 ms after the imperative stimulus. P3 has been widely studied, but the exact cognitive processes behind the component is still unknown (Brunner et al., 2013). The P3 paradigm can be divided in two; the P3 Go and the P3 NoGo, which are hypothesised to reflect different mechanisms. P3 Go is evoked by a Go-imperative stimulus (i.e. requires an action like pushing a button), and P3 NoGo is evoked by a NoGo-imperative stimulus (i.e. requires inhibition of an action). According to Brunner et al. (2013), the P3 NoGo is thought to reflect inhibitory and evaluative processes. The Contingent Negative Variation component (hereafter CNV) refers to a slow, negative potential that occurs between the cue and imperative stimulus (Leynes, Allen & Marsh, 1998). In a VCPT cued Go-NoGo task with a short inter-stimulus interval, the CNV can be located between 600 to 1100 ms after the onset of the first stimulus. The CNV is thought to represent a preparation potential for both cognitive and motor activity, and can be located at central sites (Cz, Fz) (Leynes et al., 1998).

1.3.3 qEEG abnormalities in FM patients.

Abnormalities in brain frequency bands. According to Jensen, Hakimian, Sherlin and Fregni (2008), there has been proposed a link between the subjective experience of pain and EEG activity. However, it can prove difficult to reliably identify a unitary EEG pattern for FM patients because of the complexity of the disorder (Hammond, 2010). The disorder's complexity, including a wide variety of symptoms and many common comorbid disorders, will have an impact on the patient’s EEG pattern. Nevertheless, some EEG abnormalities in FM has been proposed. Some research proposes that pain is associated with a relative reduction in amplitude in slower wave activity (delta, theta, alpha) and relatively higher amplitudes of faster wave activity (beta) (Jensen et al., 2008, p.193). However, a review of the literature on EEG

patterns in chronic pain showed increased alpha and theta power at resting state (dos Santos Pinheiro et al., 2016). An interesting finding from Donaldson et al. (2003) show a negative relationship between alpha and theta activity in the FM population. Their results indicate that the level of psychological stress and experienced pain may be a factor in the relationship between alpha and theta activity. The patients with the highest levels of psychological stress and experienced pain in their study displayed enhanced theta and reduced alpha amplitudes compared to healthy controls.

Abnormalities in ERP components. The previously mentioned literature review on EEG patterns in chronic pain also revealed that ERP components are altered in chronic pain patients (dos Santos Pinheiro et al., 2016). The most consistent finding in ERP components is a reduced amplitude of P3 in FM patients compared to healthy controls (e.g. Glass, 2006; Yoldas et al., 2003). The reduced P3 amplitude has also been observed in depressed patients (Hansenne, Pitchot, Moreno, Zaldua & Ansseau, 1996). Some studies have found an increased P3 latency in the FM population (Alanoğlu et al., 2005). There has also been shown an increased N1 amplitude in patients with chronic pain when presented with pain-related information (dos Santos Pinheiro et al., 2016). As previously mentioned, N1 represents an early process of discrimination in focus/attention and can be related to the processing of sensory information. According to Choi, Lim, Kim and Chung (2016), abnormal sensory information processing is a common feature in the FM population. Therefore, abnormalities in the amplitude and latency of the N1 component may be present, as an indicator of an abnormal process of early processing/discrimination of sensory information. Studies have also shown deviances in the CNV component related to chronic pain. CNV amplitude is modulated by attentional aspects (Schneider, Palomba & Flor, 2004), and could be altered in the FM population. Migraine patients display a stronger total CNV (i.e. more negative) compared to controls (Siniatchkin, Gerber, Kropp & Vein, 1998). Another study found that mean negative CNV-amplitudes were significantly larger during periods of induced pain than during control conditions and concluded that deep somatic pain augments CNV amplitude (Stude et al., 2003).

1.3.4 Neuromodulation to normalise brain activity. According to Krames, Peckham, Rezai and Aboelsaad (2009), neuromodulation is "the process of inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral or autonomic nervous systems (…) and is inherently non-destructive, reversible, and adjustable" (p. 3). Neuromodulation has been used to treat pain from many different causes (Thimineur & De Ridder, 2007). If FM patients are shown to have abnormalities in brain function, then techniques of neuromodulation could prove beneficial in

modifying brain activity and reduce symptoms (Fregni et al., 2006b). Neuromodulating techniques are adjustable (e.g. change of placement of electrodes in tDCS or change of frequency training protocol in Neurofeedback), which make them suitable for individualised treatment plans. The individual adjustments of neuromodulating techniques, such as tDCS, could use EEG findings to differentiate between patients and possibly predict treatment outcome.

1.4 Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) has received increased attention in recent years as a treatment option for FM. tDCS involves applying direct current (DC) over the scalp with sponge electrodes soaked in a saline solution (DaSilva, Volz, Bikson, & Fregni, 2011). It is a non-invasive brain stimulation tool with limited side-effects, that can be used in modulating cortical excitability and network rhythmical activity (Stagg & Nitsche, 2011; Boggio et al., 2008). Anodal and cathodal stimulation has opposite effects on cortical excitability; generally it has been shown that anodal stimulation enhances while cathodal stimulation reduces cortical excitability. tDCS has been shown to affect chronic pain conditions such as FM (Fregni et al., 2006b; Fagerlund et al., 2015).

1.4.1. Mechanisms of tDCS. Even though the underlying mechanisms of tDCS are still somewhat unclear, the leading hypothesis is that the cortical stimulation may interfere with maladaptive plastic changes associated with chronic pain (Boggio et al., 2008). Stimulation at the primary sensorymotor and motor cortices (S1/M1) seems to induce changes in neuronal resting-state potential in targeted areas of the brain. In turn, these changes in neural activity may lead to changes in other structures of the brain such as the thalamus, which can have an impact on the afferent nociceptive signal transmission (Fagerlund et al., 2013). Studies have shown that stimulation of M1 reduces pain in humans with spinal cord injury, as well as reduce their thalamic hyperactivity (Fregni et al., 2006a; Lenz, Kwan, Dostrovsky & Tasker, 1989). Changes in thalamic activity may also influence endogenous pain modulation through other areas central to the perception of pain (Fagerlund et al., 2013). Findings suggest that stimulation of M1 causes pain reduction in chronic pain patients, possibly by modulating M1-thalamic inhibitory connections involved in the processing of pain (Valle et al., 2009).

Studies have shown that the effects of tDCS can outlast the stimulation period for hours, weeks, and maybe months (Rroji, van Kuyck, Nuttin & Wenderoth, 2015; Stagg & Nitsche, 2011). The lasting effect of the stimulation suggests that LTP (Long-Term Potentiation) and LTD (Long-Term Depression) like effects may be involved (Caumo et al., 2012). More specifically, findings support that anodal tDCS over M1 may modulate NMDA receptor-

dependent processes that are involved in synaptic plasticity mediated by an LTP-like mechanism (Rroji et al., 2015). Thus, it is hypothesised that tDCS may counteract the plastic changes found in CS.

1.4.2. Electrode montages. Various montages can be used when administering tDCS. The most common electrode montage for chronic pain places the anode over left M1 and the cathode over the contralateral supraorbital ridge (Fp2) (Stagg & Nitsche, 2011). In order to stimulate the left M1, the anode must be placed on C3 according to the 10-20 electrode placement system. Studies have also examined the effect of stimulation of the dorsolateral prefrontal cortex (DLPFC). A meta-analysis proposed that M1 stimulation is more likely to reduce pain than DLPFC stimulation because M1 modulates the sensory component of pain while DLPFC is more related to attention and the cognitive aspect of pain (Zhu et al., 2017). According to Zhu et al. (2017), the anodal stimulation over the DLPFC did not significantly reduce pain or improve FM-related function compared to sham. Hence, the majority of tDCS research for chronic pain focuses on M1 stimulation.

tDCS may also stimulate adjacent cortical areas because of the large electrode size and bipolar montage, which in turn may reduce the focality of the stimulation. Increased focality can be achieved by reducing the size of the active electrode, increase the size of the reference electrode, or using an extracephalic reference (Nitsche et al., 2008). It has been shown that electrodes situated over the frontal poles and orbitofrontal cortices, can affect brain functions (Kincses, Antal, Nitsche, Bártfai & Paulus, 2004). Therefore, an alternative to placing the cathode over Fp2 can be to use an extracephalic placement (e.g. the shoulder).

1.4.3. Safety parameters. Most studies on anodal left M1 stimulation for chronic pain uses sponge or rubber electrodes sized between 25 cm2 and 35 cm2, with current intensities between 1 mA and 2 mA and a stimulation duration of 10 to 20 minutes (Stagg & Nitsche, 2011). Studies have shown that tDCS delivered at a level of 2 mA applied to motor areas is safe for use in both healthy controls and patients with different neurological disorders (Poreisz, Boros, Antal & Paulus, 2007). In a study by Roizenblatt et al. (2007) with 5 daily sessions of M1 stimulation (2mA, 20 min), the reported adverse effects were minor and uncommon and were equally distributed in the active stimulation and sham group. tDCS related changes in cortical excitability are prone to extinction but can be strengthened with additional treatment sessions (Valle et al., 2009). Findings suggest that tDCS should be administered more than once to increase behavioural effects (Nitsche et al., 2008). The literature indicates that often, at least 5 sessions are administered. Some studies have also suggested to increase the number of sessions to 10 daily sessions (Valle et al., 2009).

1.5 Importance of this study

FM has a relatively high prevalence in the population, with a generally reduced quality of life. Chronic pain can also be an economic burden for the individual, as well as for the public (Zaghi, Heine & Fregni, 2009). Data suggest that there is considerable cost in the management of the symptoms of FM compared to the general population, due to the cost of disability benefits (Arnold & Clauw, 2017). A study examining the FM-related costs and loss of productivity found that those who had a paid job lost an average of 5.6 days due to pain over three months (Lacasse, Bourgault & Choinière, 2016). Amongst the unemployed, an average of 25.1 days of housework was lost due to pain. Findings from the same study states that prescribed medication leads to the highest costs. Hence, the importance of identifying effective treatment for this population is obvious. As previously stated, no single treatment option has been proven effective in reducing all symptoms of FM and effects on pain and function are seldom large (Marlow et al., 2013; Marcus et al., 2014). Both antidepressants, exercise, cognitive behaviour therapy and patient education could give pain relief but are not satisfactory efficient (Talotta et al., 2017). Especially the pharmaceutical treatment options often report a high number of dropouts and adverse effects, underscoring the importance of identifying treatment options with fewer adverse effects (Marlow et al., 2013).

tDCS provides a relatively affordable treatment option if it can be proven effective in pain reduction and increase of daily function. tDCS has been shown to affect chronic pain conditions such as FM, with only minor and uncommon adverse effects (Fregni et al., 2006b; Fagerlund et al., 2015; Roizenblatt et al., 2007). Because tDCS is easy to apply and carry little risk of adverse effects, it can be designed for home use with comprehensive instructions and patient education (Zaghi et al., 2009). A commercial tDCS kit for home use costs approximately 120$. Compared to other treatments, such as medication, physical therapy and CBT, tDCS is low in cost. Studies have shown that tDCS has a significantly higher effect than placebo, and that the efficiency of tDCS is montage specific (i.e. anodal M1 stimulation for chronic pain) (Fregni et al., 2006b). However, according to Jensen et al. (2008), it has yet to be examined whether effective tDCS treatment is associated with changes in EEG.

As there is yet little knowledge of the relationship between neuronal activity and structural plasticity concerning chronic pain, researching the effects of tDCS through parallel investigation of self-reported symptoms and qEEG-measurements might offer new insights into alterations of neuronal activity as a result of tDCS. Furthermore, it might yield indications of markers for individual treatment plans. qEEG has previously been used to predict treatment-

outcome of tDCS in depression (Al-Kaysi et al., 2017), and to predict clinical outcome of Ritalin in children with ADHD (Ogrim et al., 2014).

To summarize the importance of this study; *(a)* Patients with FM report a generally reduced function and quality of life, *(b)* Managing FM involves a considerable cost for the individual as well as for society, (*c)* No treatment option has been proven to be effective in reducing all symptoms of FM, and the treatment effects on pain is seldom large, *(d)* tDCS has been shown to reduce pain in FM patients and is a cost-effective option with few adverse effects, and *(e)* qEEG might serve as an objective tool to differentiate between the responders and non-responders of treatment with tDCS for chronic pain.

1.6 Aim and hypothesis

In this study, we have two aims. First, to investigate whether tDCS can reduce the core symptoms in FM patients, measured by self-reported symptom scores. Secondly, if treatment-related changes can be observed with qEEG, measured by EEG-recordings. In the first part of this study, we hypothesise that tDCS will provide a significant reduction in the self-reported perception of pain, fatigue and fibrofog and that this effect will last for more than three months. This assumption is based on previous research where tDCS has been shown to have effects for chronic pain conditions such as FM (Fregni et al., 2006b; Fagerlund et al., 2015). Findings support that anodal tDCS over M1 may modulate synaptic plasticity mediated by an LTP-like mechanism (Rroji et al., 2015). Following these findings, we hypothesise that the changes in self-reported perception of pain will be observable three months after treatment.

In the second part of the study, we investigate the subject's EEG recordings by comparing their brain activity pre- and post-treatment against the normative database. We hypothesise that there will be observable deviances in the subject's qEEG patterns related to the dynamic pain connectome, and that tDCS will have an effect on normalising these maladaptive plastic changes associated with chronic pain. Also, we hypothesise that there will be differences in the qEEG patterns of the best-outcome group and the worst-outcome group. These differences may contribute to better and more specific guidelines in the future use of tDCS as an intervention for FM.

The current pilot study seeks to investigate the following hypotheses:

1. If maladaptive plastic changes in the brain cause fibromyalgia, neuromodulation of cortical excitability with tDCS will give a significant reduction in the self-reported perception of pain, fatigue and fibrofog.

2. If tDCS gives a significant reduction in the self-reported perception of pain, fatigue and fibrofog, these changes will be observable three months after treatment due to lasting plastic neuronal changes.
3. If maladaptive plastic changes in the brain causes fibromyalgia symptoms, there will be significant deviances in the subjects' qEEG data compared to the normative database. The same deviances should be significant and observably inverse compared to post-treatment. The observed deviances pre-treatment should tend toward normalisation post-treatment.
4. If subjects differ in self-reported treatment-related outcome, there will be significant deviances between the best-outcome group and the worst-outcome group in their qEEG data that could help predict individual treatment-outcome in future studies.

2. Method

2.1 Subjects

This study was conducted by collecting data from 17 female subjects suffering from FM (*M*=45.8 years, *SD*=8.4). The subjects were recruited through the Fibromyalgia Association (Fibromyalgiforeningen) and a Facebook group consisting of FM patients. Subjects had to live in proximity to Trondheim during the study. The subjects were invited to declare interest by e-mail, where they would receive information regarding the study. All interaction with the subjects in the recruitment process was conducted by e-mail. All subjects gave their written informed consent to participate in this study, which was approved by the Regional Committees for Medical and Health Research Ethics (REC).

All subjects in this study were diagnosed with FM according to the American College of Rheumatology criteria (ACR), were above the age of 18 and under the age of 70, were female, were willing to complete all study procedures and capable of giving their informed consent. Subjects were excluded if they had a physical condition that could explain their symptoms. Many of the subjects had other diagnoses such as migraine, fatigue and different forms of rheumatism, in addition to FM. Unfortunately, other diagnoses and ongoing treatment were not properly documented. However, the subjects were told to report changes in their standard treatment, such as changes in medication or undergoing surgery. One subject reported to being diagnosed with a physical condition, explaining many of her symptoms, and was therefore excluded. 16 women (*M*=45.6 years, *SD*=8.6) were included for further analysis.

2.2 Design

The study was designed to investigate the effect of anodal tDCS on pain, fibrofog, and fatigue. The tDCS was administered over 5 consecutive days. Before and after receiving treatment, the subjects filled out a series of questionnaires regarding their symptoms (ACR, FIQ, VAS for pain, fatigue, and fibrofog). Also, all subjects conducted an EEG recording to investigate possible treatment-related outcome differences. All measures were conducted approximately 7 days pre-treatment and 7 days post-treatment. The subjects received an envelope by mail after a minimum of three months after end of treatment consisting of the same questionnaires that were administered pre- and post-treatment for the study follow-up. Also, the follow-up included a survey of whether the subjects had continued treatment with tDCS during the three months. Outcomes were evaluated by these measures. 13 women (*M*=45.1 years, *SD*=9.0) took part in the follow-up. The study design is presented in Figure 2.

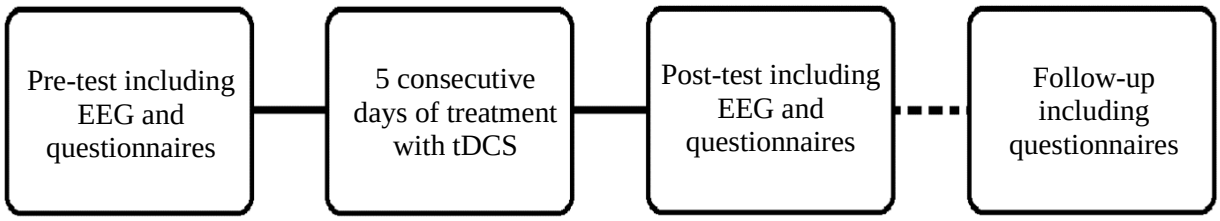


Figure 2: Illustration of the study design. Pre- and post-tests were conducted approximately 7 days before and after the treatment period. The follow-up was conducted by mail at least 3 months after the end of treatment. EEG, electroencephalogram; tDCS, transcranial direct current stimulation.

2.3 Apparatus

2.3.1 EEG. In this study, the EEG was recorded using a computer-controlled 19-channel electroencephalographic system from Mitsar (Mitsar Co, Ltd, Saint Petersburg, Russia), with a sampling rate of 500 Hz. A 19-electrode cap from Electro-Cap Inc (electro-cap.com) with pre-mounted tin electrodes according to the 10-20 international standard montage system was used for recording from the scalp. This system provides a standardised method for the electrode placement used in EEG. Additional reference electrodes on both ear lobes were also used (Klem, Lüders, Jasper, & Elger, 1999). A conductive gel was used to help bridge the current flow between the scalp and the electrodes (Mihajlović, Garcia-Molina & Peuscher, 2012). Quantitative data was obtained with the WinEEG software (Mitsar Co, Ltd). Eye blinks and other artifacts were removed by performing an independent component analysis. EEG data was visually inspected after correction to ensure an adequate artifacts correction. A filter was set for

epochs with excessive amplitude (>100 microvolts), in addition to a high pass filter for slow waves (0.53 Hz) and a low pass filter for fast waves (30 Hz). These frequency activities were excluded from further analysis. Comparisons were then made between the grand average of the subject's EEG spectra, ERPs (P3 NoGo, N1 and CNV) against the normative database. Comparisons were also made between the pre- and post-treatment reaction time and reaction time variability. Lastly, comparisons were made between the self-reported best-outcome group (n=5) and the self-reported worst-outcome group (n=5). The best- and worse-outcome groups were determined by self-report on the FIQ.

2.3.2 Visual Analogue Scale. The Visual Analogue Scale (VAS) is a widely used psychometric response scale (Grilo, Treves, Preux, Vergne-Salle & Bertin, 2007), considered to be a good measure for pain intensity (Price, McGrath, Rafiji & Buckingham, 1983). The VAS is a continuous scale comprised of a 100 mm horizontal line, on which subjects are asked to mark their symptom intensity (Kliger et al., 2015). In this study, the subjects were given three VASes in Norwegian to rate their level of pain, fatigue, and fibrofog (See Appendix D). The VAS for pain had extremes labelled as “no pain” to “unbearable pain”. The VAS for fatigue had extremes labelled as "no fatigue" to “severe fatigue”. The VAS for fibrofog had extremes labelled as "no fibrofog” to “severe fibrofog”. All subjects were asked to fill out the VASes both pre- and post-treatment, on the same day as the EEG recordings. Also, the VASes was distributed in the follow-up.

2.3.3 American College of Rheumatology. The American College of Rheumatology (ACR) consists of preliminary diagnostic criteria for FM, as well as a measurement of symptom severity (Wolfe et al., 2010). The subjects in this study were asked to fill out a Norwegian translation of the ACR 2010 diagnostic guidelines (See Appendix B) both pre- and post-treatment, on the same day as the EEG recordings. Also, the ACR was distributed in the follow-up. The Norwegian version of the ACR was translated by a translator.

The ACR consists of two parts; the Widespread Pain Index (WPI) and a symptom severity (SS) score. The following criteria must be met to fulfil the diagnostic criteria for FM; *1)* WPI $\geq$ 7 and SS score $\geq$5, or WPI from 3 - 6 and SS score $\geq$9, *2)* symptoms have been present at a similar level for at least 3 months, *3)* the patient does not have a disorder that would otherwise explain the pain.

Part 1 consists of the WPI, where the subject is asked to check each area where they have felt pain over the last week. Part 1 is scored with a WPI Index score between 0 and 19, where each area of pain counts as 1. The Symptom Severity Score consists of two parts, Part 2a and 2b. In Part 2a, the subjects are asked to indicate their level of symptom severity the past

week on a 4-point Likert Scale ranging from “0 = No problem” to “3 = Severe problems”. The symptoms being measured are “Fatigue”, “Waking unrefreshed” and “Cognitive symptoms”. In Part 2b, the subjects are presented a list of 34 symptoms they may or may not have experienced over the last week. These symptoms include, for example, “Muscle pain”, “Irritable bowel syndrome”, and “Insomnia”. Part 2b is scored from 0 to 3, depending on the number of other symptoms reported. Part 2a and 2b are added together and gives a total SS-score ranging from 0-12.

2.3.4 Fibromyalgia Impact Questionnaire. The Fibromyalgia Impact Questionnaire (FIQ) is a validated specific tool to measure the symptomatology of FM, and the effect on the patient’s life (Bennett, 2005). The subjects in this study were asked to fill out a Norwegian translation of the FIQ (See Appendix C) both pre- and post-treatment, on the same day as the EEG recordings. Also, the FIQ was distributed in the follow-up. The Norwegian version of the FIQ was translated by a translator.

The FIQ consists of 10 questions. The first item is related to the ability to perform large muscle tasks (Bennett, 2005), and contains 11 statements such as “climb stairs” and “make beds”. These statements are rated on a 4-point Likert scale from “0 = Always” to “3 = Never”, making the highest possible raw-score 33. In item 2 and item 3, the subject is asked to mark the number of days they felt good, and the number of days they missed work or housework because of FM, from 0 to 7. Item 3 is scored directly, while item 2 is scored inversely so that a high number will indicate impairment. Items 4 through 10 ask the subject to rate symptoms such as fatigue, pain, anxiety, and depression on a 10-point Likert scale from 1-10. All items undergo a normalisation procedure so that each item is expressed in similar units with a maximum score of 10, with 0 indicating no impairment and 10 indicating considerable impairment. The maximum possible score on the FIQ is 100. Bennett (2005) states that the average FM patient scores about 50 and severely afflicted patients usually score over 70 (p. 157).

2.3.5 Adverse effects. Adverse effects were registered by all subjects after the treatment period, as suggested by Fregni et al. (2015) in their recommendations for the safe use of tDCS. They were asked to report the occurrence of 13 symptoms during or after treatment with tDCS (See Appendix E). Before rating the symptoms, the subjects were instructed to report symptoms that had occurred in a more considerable degree than usual, so that the symptoms of FM would not be confused with the adverse effects. These symptoms included numbness under electrode, redness under the electrode, itching under electrode, burning under the electrode, pain under the electrode, nausea, fatigue, nervousness, insomnia, headache, difficulty in concentrating, acute mood changes and changes in visual perception. The questionnaire had categorical rating

scales, and were rated as “0=none”, “1=very mild”, “2=mild”, “3=moderate”, “4=severe” and “5=very severe”.

2.4 Procedure

2.4.1 Transcranial direct current stimulation. tDCS was administered using a stimulator from The Brain Stimulator©, a battery-driven device that provides a constant current of a maximum of 2 mA. In this study, subjects received 5 daily sessions (Monday-Friday, 1 week) of anodal stimulation of the left primary somatosensory and motor cortices (S1/M1). A constant current of 2 mA was applied for 20 minutes. The electrode montage was unilateral and monopolar. The anode was placed from Cz to T3, covering C3, according to the 10-20 system, see Figure 3. The cathode was placed on the ipsilateral shoulder. Most studies regarding tDCS and anodal M1 stimulation place the cathode above supraorbital regions (e.g. Fagerlund et al., 2015; Fregni et al., 2006b). However, it has been shown that electrodes situated over the frontal poles and orbitofrontal cortices, can affect brain functions (Kincses et al., 2004). Therefore, in this study, the cathode was placed on the shoulder.

Previous studies have primarily tried to stimulate the M1, even though the S1 is involved in most physical sensations, including chronic pain. In this study, the electrode sponges (35 cm2) were designed in an elliptic shape (4,5 cm x 11 cm) to match the area of both the primary somatosensory and motor cortices (S1/M1). Before the sponges were applied, the hair was moved away from the site of stimulation to increase conductance. The sponges were soaked in a saline solution (NaCl and water) and applied to the scalp. Conductance was controlled with a multimeter attached to the electrodes before each session, with acceptable levels of 1.8 to 2 mA. A cap made of non-conductive material was used to hold the electrodes in place during the stimulation.

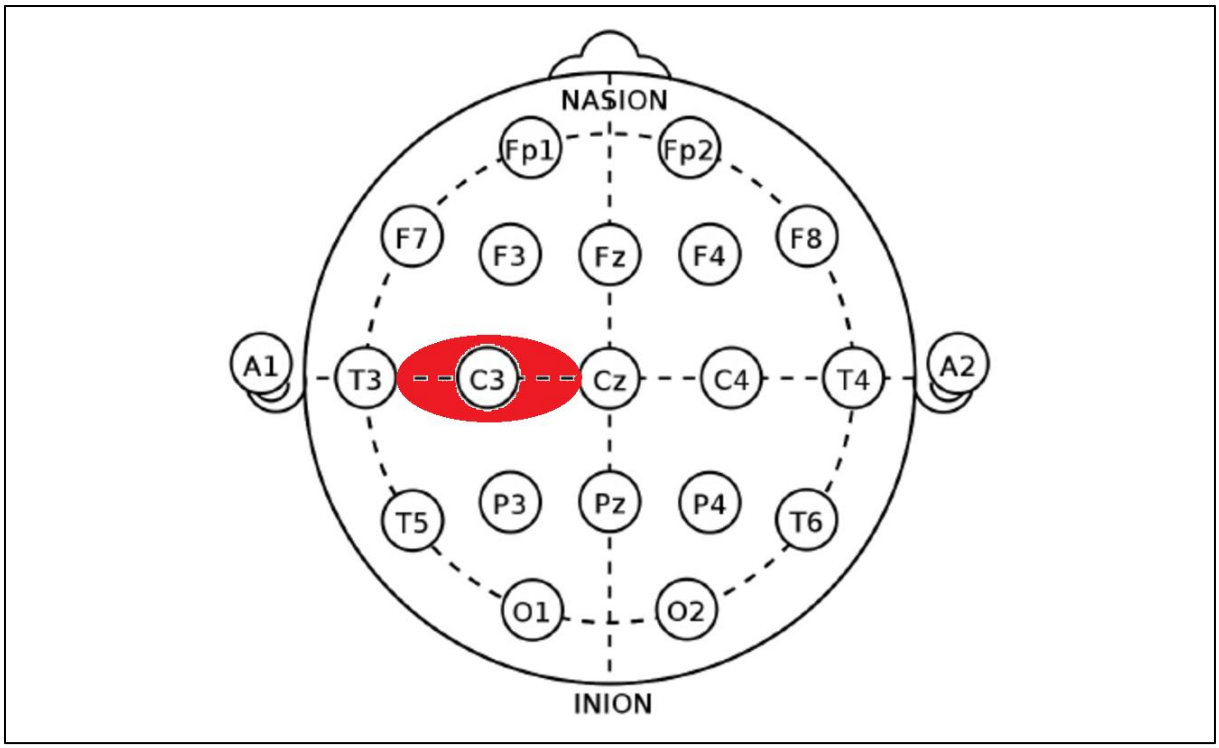


Figure 3: Sponge position of the anodal electrode marked according to the 10-20 system.

2.4.2 EEG and VCPT recordings. The EEG was recorded for two resting conditions and a visual continuous performance task (VCPT), following the standard protocol at the NTNU EEG-lab. Before the recording, subjects were seated in a chair 100 cm from a 22`` screen in a sound-isolated room and instructed to relax to avoid excessive artefacts. The resting conditions include 180 seconds with their eyes opened (EO) and 180 seconds with their eyes closed (EC). After recordings of resting conditions, the subjects were given instructions on the VCPT, a Go/NoGo task.

For the VCPT, a software tool "PsyTask" from Mitsar was used (Mitsar Co, Ltd). The task had a duration of 400 trials (20 minutes). Each session consisted of 100 trials, with a short break in between sessions to reduce tiredness and to secure the well-being of each subject. Trials consisted of a pair of stimuli with inter-stimulus intervals of 1000 ms. Each stimulus was presented for 100 ms. The inter-trial interval was 3500 ms.

In the VCPT, the trials are divided in four conditions; *1)* a-a (animal-animal), *2)* a-p (animal-plant), *3)* p-p (plant-plant) and *4)* p-h (plant-human). The p-h condition was presented together with a novel sound. Each session consisted of a presentation of 100 pairs of stimuli with equal probability for each category and stimulus. The subjects were instructed to press the left mouse button as fast as they could when the image of an animal was followed by an identical

image of an animal (a-a). They were instructed to withhold their response in condition a-p and to ignore the conditions p-p and p-h. The procedure is represented schematically in Figure 4.

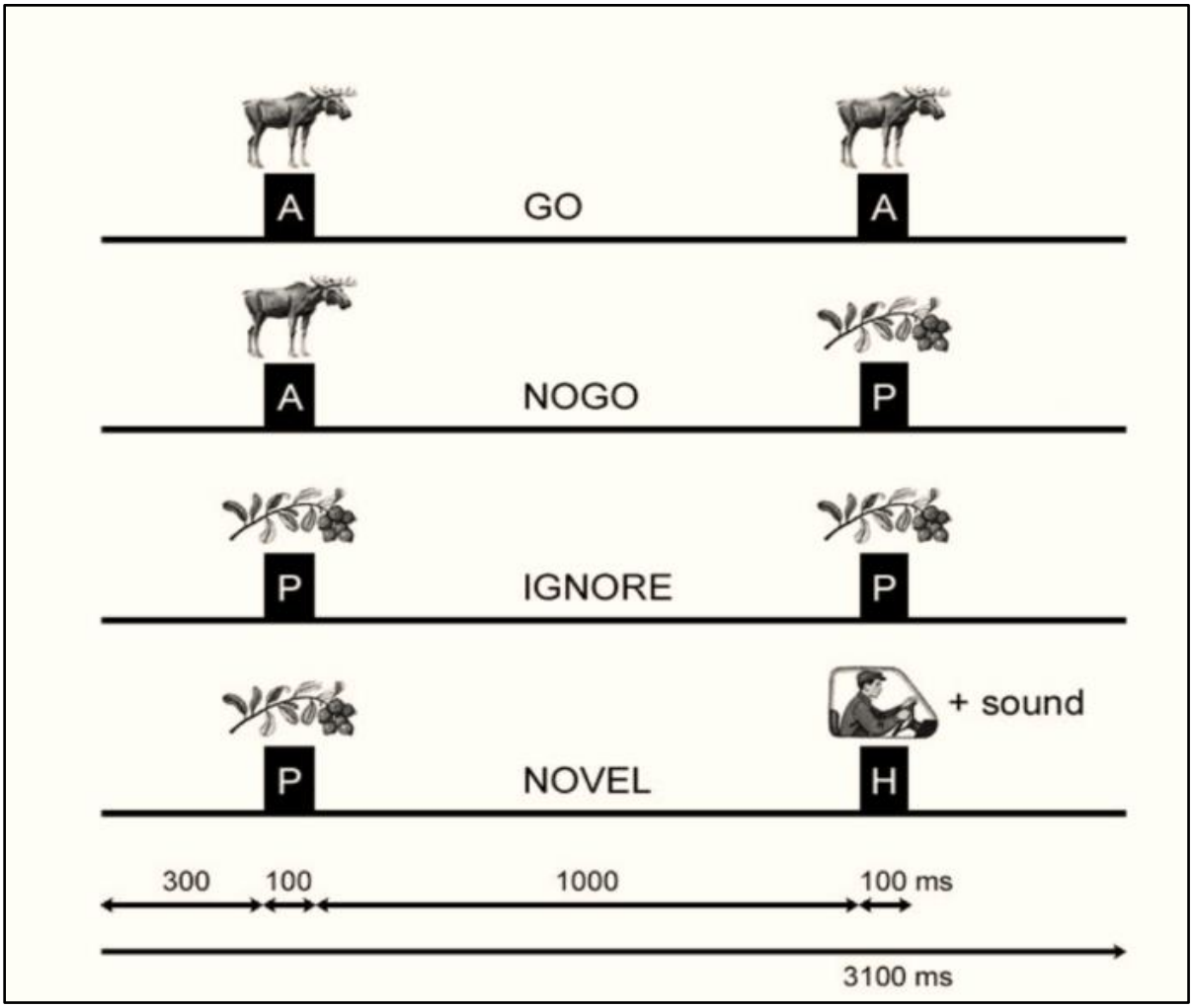


Figure 4: Schematic representation of the VCPT, A Go/No-Go task. A, animal; P, plant; H, human.

2.5 qEEG Analysis

A set of qEEG analyses was used to investigate hypothesis 3 and 4. Initial qEEG analyses included grand average of power spectra analysis and grand average of ERP analysis to compare both pre- and post-treatment groups to the normative database. The analyses were conducted to investigate if deviances in accordance with the presented literature were identifiable, and exploratively to investigate whether other consistent deviances were observable. Secondary qEEG analysis included grand average of power spectra analysis, grand average ERP analysis, and Frequency Band analysis, to compare the pre- and post-treatment groups to exploratively investigate whether the treatment condition contributes to change in spatiotemporal neuronal activity and whether these changes are consistent with eventually observed deviances compared to the normative database. Tertiary qEEG analysis included

grand average of power spectra analysis, grand average ERP analysis, and frequency band analysis, to compare the best- and worst-outcome groups both pre- and post-treatment to exploratively investigate whether any markers for treatment outcome are observable. Mitsar's normative database, "Database 1", was used in comparisons (Mitsar Co, Ltd)

An important note to all the analysis run in WinEEG is that parts of the test statistic is not available to report. WinEEG lacks reports on standard deviation. Thus, the standard deviations are not reported in the results section of the thesis.

2.5.1 qEEG spectra analysis. The individual power spectra were calculated both pre- and post-treatment. The power spectra were computed by the fast Fourier transformation method, following these parameters; Hanning time window and epoch length of 4 seconds with 50% overlap. The parameters were set according to the parameters of the normative database, for comparative reasons.

The internal analysis engine in WinEEG identifies power spectra trough Fourier transformation defined by the parameters as mentioned above. In short, the Fourier transformation estimates the power of every infinitesimal frequency in a defined range, and in practice, the observable output yields the estimated power at a frequency resolution of 1/100 Hz (Guevara, Ramos, Hernández-González, Zarabozo & Corsi-Cabrera, 2003; Mitsar Co, Ltd, Saint Petersburg, Russia). The estimated power for all frequencies in the range of 3Hz to 30Hz constitutes the individual power spectra. All the individual power spectra were then used to calculate grand averages of power spectra in the resting state conditions (Eyes opened and Eyes closed) for both groups pre- and post-treatment, and best- and worst-outcome within the internal engine. Thus, calculating average power and standard deviation for every point of frequency resolution between 3 and 30 Hz. The grand averages for pre- and post-treatment were then compared to the normative database in WinEEG. The comparisons were run with the internal analysis engine of WinEEG, yielding parametric comparisons of the means for each point of frequency resolution. Both absolute spatial power density and relative spatial power density (hereafter respectively absolute and relative power) are reported for each condition. However, data regarding the assumptions of each parametric test has not been evaluated as WinEEG provides no such output. This issue will be addressed in section 4.5.4.

2.5.2 ERP Analysis. As mentioned in section 1.3.2, the most consistent findings of deviant ERP components in chronic pain includes the N1, P3 NoGo and CNV. Accordingly, the ERP components (N1, P3 NoGo and CNV) were calculated for all subjects both pre-and post-treatment, as well as for the best- and worst-outcome groups by the internal analysis engine

of Mitsar WinEEG 2.129.100 software**.** The baseline was adjusted to the mean voltage 50 ms before S1 for the CNV and N1 component and to 50 ms before S2 for the P3 NoGo component.

Properties of the ERP components (i.e. peak amplitude and latency), were visually inspected and reported for each subject and the grand averages; all subjects pre- and post-treatment, and best- and worst-outcome group pre- and post-treatment. The peak amplitude was defined as the highest amplitude within a pre-defined timeframe, or by visual inspection of a distinct peak outside this timeframe. For the CNV, determining the peak can pose a challenge due to its shape and lack of a distinct peak. The peak of the CNV was therefore defined as the highest amplitude between 600-1100 ms after the presentation of stimulus 1. The timeframe for N1 was set to 130 – 200 ms after the presentation of stimulus 1 and the timeframe for P3 NoGo was set to 300-480 ms after the presentation of stimulus 2 (Grane et al., 2016; Ogrim, Aasen, & Brunner, 2016; Brodeur et al., 2008).

Latencies were determined by the peak latency method, a widely used method for determining latencies (Kiesel, Miller, Jolicœur & Brisson, 2008). The latency of an ERP component is defined by the latency of its maximum amplitude. The peak latency method involves determining the latency of a component by visual inspection of its peak and the associated latency. The ERP components and their properties were compared to a normative database of age-matched controls.

2.6 Statistical Analysis

A series of statistical analysis on the self-report variables were run in SPSS to investigate hypothesis 1 and 2. The Wilcoxon Signed-Rank Test was used to investigate potential differences in self-reported symptoms pre- and post-treatment-condition. The Mann-Whitney U Test was used to investigate and identify differences between the best- and worst-outcome groups. The related samples Friedman's two-way analysis of variance by ranks was used to investigate potential differences in self-reported symptoms pre-treatment, post-treatment and follow-up. All the tests mentioned above are non-parametric. The reason they were chosen is related to the assumption of normality.

2.6.1 The assumption of normality. To examine the assumption of normality that is essential for any parametric analysis of differences of means, the Kolmogorov-Smirnov, and Shapiro Wilk tests of normality was applied to all variables (Field, 2013). Furthermore, normality was visually examined through Q-Q-plots and histograms. More importantly, all pairs of pre- and post-test variables were calculated into difference-scores and subjected to the formerly mentioned test of normality. Although most of the pre- and post-test variables were found to be normally distributed, almost none of the difference-scores were found to be

normally distributed (Appendix G and H). This might be caused by the small sample size. Accordingly, the analysis of differences between pre- and post-treatment responses were carried out through non-parametric tests (Field, 2013). Choosing the non-parametric test over the parametric counterparts sacrifices statistical power and, therefore, increases the probability of a type II error. Nevertheless, it is necessary as the difference scores are not normally distributed.

2.6.2 Wilcoxon Signed Rank Test. The Wilcoxon Signed-Rank Test (WSRT) is a non-parametric test that compares two dependent samples, or in this case, repeated measurements of one sample. In contrast to the student's t-test, it does not rely on the mean and standard deviation, but rather on pairs of observations concerning the median.

The WSRT is based on three main assumptions. The first assumption is that the dependent variable must be measured at the ordinal or continuous level. The VAS is measured at a continuous level. While the items of the FIQ is measured at the ordinal level with Likert-scale items, the total score is assumed to be at the continuous level. The second assumption states that the independent variable should consist of related groups or matched pairs. In this study, the independent variable consists of one group being tested under different conditions (pre- and post-test), which is analogous to related groups. The third assumption states that the distribution of differences between groups must be relatively symmetrical (Field, 2013). The assumption of symmetry was evaluated through visual inspection of the boxplots of the difference scores (Benjamini, 1988). To our knowledge, there is no absolute critical threshold for evaluating the criterion of symmetry through inspection of box plots. For transparency in the evaluation of symmetry, all boxplots are provided in Appendix F. By our evaluation, the assumption of symmetrical distribution of difference scores are met, as none of the boxplots shows efinitive indications of assymetry.

2.6.3 Mann-Whitney U Test. As the WSRT is valid only for related groups, all comparisons of the best- and worst-outcome groups were analysed with the Mann-Whitney U Test (MWUT). MWUT is a non-parametric test that compares two independent samples. In contrast to the independent samples t-test, it does not rely on the mean and standard deviation, but rather on pairs of observations concerning the median.

The MWUT is based on three main assumptions, and one additional assumption to investigate the median. The first assumption is that the dependent variable must be measured at the ordinal or continuous level. As mentioned above, this holds true for analysis of the VASes and FIQ. The second assumption states that the independent variable must consist of two categorical groups. The MWUT is used to investigate differences between the best-outcome and worst-outcome groups, which in turn is theoretically categorical. This assumption is

explained further in 3.1.2 analysis of best outcome-versus-worst outcome. The third assumption is that there should be independence of observations. All subjects were tested independently with no information about tentative results. Thus, one test-subject should not be able to influence another. The fourth, additional assumption is needed if one wants to infer differences between the medians of the groups rather than the distributions, which is dependent upon equal distributions in the groups (Field, 2013). The distributions were evaluated through visual inspection of difference-score histograms and found not to be equal (Appendix I).

2.6.4 Related samples Friedman's two-way analysis of variance by ranks. The related samples Friedman's two-way analysis of variance by ranks (hereafter Friedman's test) were utilised to investigate differences in self-reported symptoms pre-treatment, post-treatment and in the follow-up. Friedman's test is based on three assumptions. The first assumption is that the test-subject needs to be measured at three different times. The assumption holds true as the FIQ were distributed pre-treatment, post-treatment and in the follow-up. Assumption 2 is that the subjects must be a random sample of the population. As mentioned in section 2.1, the test-subjects were recruited through the Fibromyalgia Association and a Facebook-page for FM patients. Thus, one can argue that there was no systematic selection in the recruitment process. The third assumption is that the dependent variables should be measured at the ordinal or continuous level (Field, 2013). As mentioned above, this holds true for analysis of the FIQ.

2.6.5 Family-Wise Error Rate. When analysing a sample mean multiple times the family-wise error rate will inflate the alpha value, increasing the chance of a type I error. In many cases, utilising the Bonferroni correction for a stricter alpha value counteracts this issue. Bonferroni correction is a simple transformation of the alpha-value, where the predefined alpha of .05 is divided by the number of tests that are run on a sample. This correction increases the probability of a type II error in each analysis but decreases the probability of a type I error (Field, 2013).

One can argue that analysing both the FIQ and the VASes is another example of multiple testing. However, it is assumed that the VAS Total and FIQ are measurements of approximately the same symptoms, and therefore correlates highly. Consequently, we assume no family-wise error rate in these comparisons. There are three different VASes in this study, and the average VAS Total is also calculated. Therefore Bonferroni-correction was used in the analysis of the pre-post-treatement analysis of the VASes. The follow-up analysis is also run by multiple comparisons. The small sample size of this study limits the statistical power. Accordingly, the four different VASes was not applicable for follow-up analysis, and only the FIQ were subjected to follow-up analysis.

In this study, EEG-analysis of groups and the normative database in sections 3.2.1-3.2.3 analyse the same samples twice. Furthermore, each of the comparisons are analysed, both trough absolute and relative power. Accordingly, each sample is analysed four times in practice. The reason why the Bonferroni Correction is not utilised in this part of the research is that the analysis is tied to Hypothesis 3. Hypothesis 3 states that there will be significant deviances *A)* in the subjects' pre-test qEEG data compared to the normative database, *B)* these deviances should be significantly and observably inversely related to the post-test qEEG data, and *C)* the observed deviances pre-treatment should tend toward normalisation post-treatment. The family-wise error rate inflates each of the alpha values, as shown in equation 1.

$$\alpha_{FW} = 1 - (1- \alpha_{PC})^{n} \quad (1)$$

Where FW is the Family-Wise inflated alpha value, PC is the per contrast alpha, and n is the number of analysis on the same sample. In the analysis of Hypothesis 3, two analysis are run on each sample (n=4), and the predefined alpha per contrast is 5% (α_{PC} = .05). Thus, leading to a family-wise inflated alpha value of approximately 19% (α_{FW} = .185). The alpha value is utilised to decide whether to reject the null hypothesis. In the case of Hypothesis 3, the null hypothesis is dependent on all three of the analysis. Consequently, the alpha value which is the basis of deciding whether or not to reject the null hypothesis, is the combined probability of making a type-I error for both A and B, and a type-II error for C. To calculate the alpha value of the actual decision whether to reject the null hypothesis, we will use the specific probability rule of multiplication illustrated in equation 2.

$$P(A \text{ and } B) = P(A) * P(B) \quad (2)$$

The rule states that the probability (P) of any number of co-occurring events (A and B) is equal to the multiplied probability of each event. The probability of a type-I error is given by the family-wise alpha value (α_{FW} = .0975) in condition A and B of hypothesis 3, as illustrated in equation 3. Equation 4 illustrates the probability of committing a type-I error when condition A and B are co-occurring.

$$P(A)=P(B)= \alpha_{FW} \quad (3)$$

$$P(A \text{ and } B) = P(A) * P(B) = (\alpha_{FW})^2 = .0344 \quad (4)$$

$$P(C) < 1 \Rightarrow P(A) * P(B) * P(C) < P(A) * P(B) \quad (5)$$

The probability of condition C is given by the probability of a type-II error and is not calculated in this study. Nevertheless, the probability of a type-II error is less than one. Accordingly, the concurrence of A, B and C is less likely to be identified by chance than A and B alone, as illustrated in Equation 5. Equation 6 illustrates that the alpha value of Hypothesis 3 (α_{H3}) is dependent on the probability of concurrently and falsely identifying A, B and C as true.

$$P(\alpha_{H3}) = P(A) * P(B)* P(C) < (\alpha_{FW})^2 \quad (6)$$

The probability of falsely rejecting the null hypothesis when identifying significant p-values with an alpha per contrast of 5% and a family-wise alpha of approximately 19% in both A B, is less than 3.4% ($\alpha_{H3} < .0344$). Therefore, one can argue that the alpha probability of falsely rejecting the null hypothesis of hypothesis 3 is, in fact, lower than the suggested alpha level of .05. It is important to note that individual EEG-findings related to Hypothesis 3, A, B and C, should be evaluated with utmost care, as the individual alpha-values are inflated by multiple comparisons. The limitations of the current approach of correction is discussed in section 4.5.2.

3. Results

3.1 Subjective measures

3.1.1 Analysis of pre-treatment vs post-treatment: effects of treatment condition

VAS: Total. A WSRT with a Bonferroni-adjusted alpha level of .0125 (.05/4) indicated that the post-test ranks (*Mdn* = 1.38) of the VAS were significantly lower than the pre-test ranks (*Mdn* = 1.91) of the VAS (Z = -2.534, p = .011). The effect size was calculated according to Rosenthal, Cooper and Hedges (1994) and was found to be moderate (r = -.45). These results imply a tendency to report a lesser total of pain, fibrofog and fatigue after the treatment condition.

VAS: Pain. A WSRT with a Bonferroni-adjusted alpha level of .0125 (.05/4) indicated that the post-test ranks (*Mdn* = 0.42) of the VAS pain item were significantly lower than the pre-test ranks (*Mdn* = 0.63) (Z = - 2.871, p < .004). The effect size was found to be moderate (r

= -.51). This finding implies a tendency to report less subjective pain after the treatment condition.

***VAS: Fatigue*.** A WSRT with a Bonferroni-adjusted alpha level of .0125 (.05/4) indicated that the post-test ranks (*Mdn* = 0.53) of the VAS fatigue item were not significantly lower than the pre-test ranks (*Mdn* = 0.70) (*Z* = - 2.045, *p* = .041). The effect size was found to be low (*r* = -.36). This finding implies a nonsignificant tendency to report less subjective fatigue after the treatment condition.

VAS: Fibrofog. A WSRT with a Bonferroni-adjusted alpha level of .0125 (.05/4) indicated that the post-test ranks (*Mdn* = 0.47) of the VAS "fibrofog" item were not significantly lower than the pre-test ranks (*Mdn* = 0.57) (*Z* = - 2.188, *p* < .029). The effect size was found to be moderate (*r* = -.38). This finding implies a nonsignificant tendency to report less subjective fibrofog after the treatment condition.

***FIQ*:** A WSRT with a Bonferroni-adjusted alpha level of .0125 (.05/4) indicated that the post-test ranks (*Mdn* = 43.5) of the FIQ were significantly lower than the pre-test ranks (*Mdn* = 64.2) (*Z* = - 3.361, *p* < .001). The effect size was found to be large (*r* = -.59). This finding is indicative of a tendency to report fewer and less severe symptoms of FM after being subjected to the treatment condition.

***ACR: Diagnostic Criteria for Fibromyalgia*.** The ACR diagnostic criteria were evaluated pre- and post-treatment, see Figure 5. Before treatment, all subjects met the ACR diagnostic criteria for FM. However, after the treatment, 25% of the subjects did not meet the diagnostic criteria of the ACR guidelines.

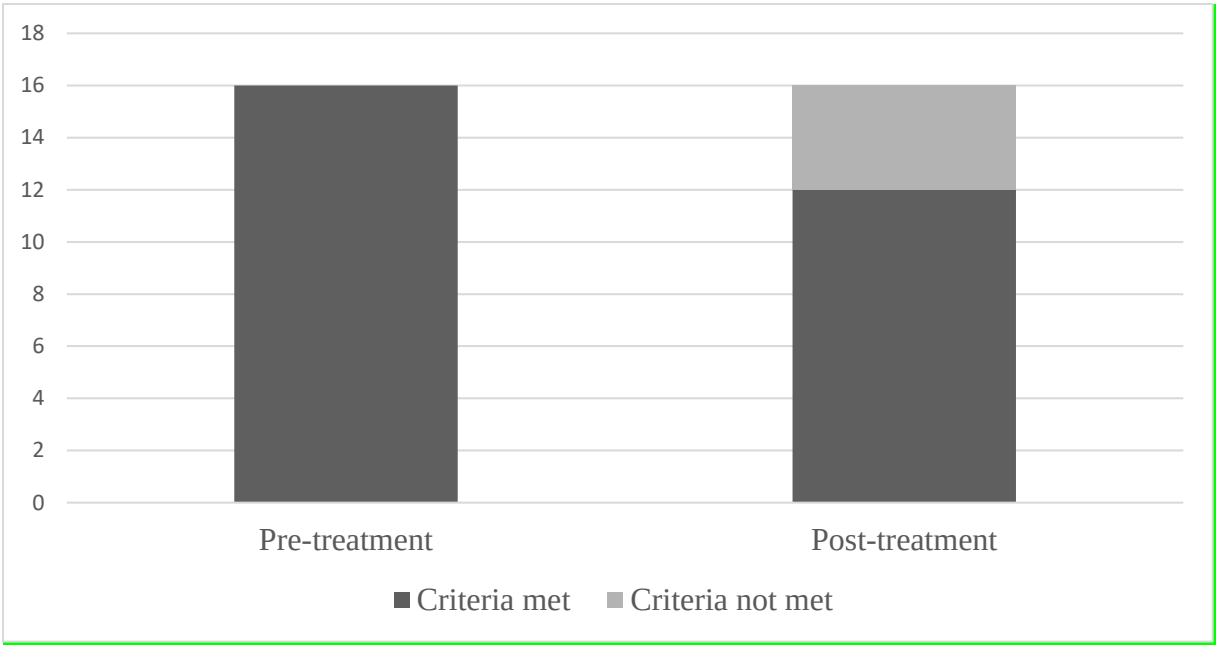


Figure 5: Diagram illustrating the number of subjects who met the criteria for the American College of Rheumatology 2010 diagnostic guidelines pre- and post-treatment.

3.1.2 Analysis of best-outcome and worst-outcome groups. The best- and worst-outcome groups were defined as the 5 subjects with respectively the highest and lowest FIQ difference scores. This operationalisation implies that the outcome is dependent on relative change rather than severity of symptoms after treatment. MWUT analysis indicated that the best-outcome group ranks (*Mdn* = 28.3) of the FIQ difference scores were significantly higher than the worst-outcome ranks (*Mdn* = 1.1) (U = 0.00, p < .001). MWUT analysis of the difference scores of the VAS Total indicated the same significant differences (U = 0.00, p < .001) between the best-outcome group ranks (*Mdn* = 0.89) and the worst-outcome group ranks (*Mdn* = -0.14). MWUT analysis indicated that the best-outcome group ranks (*Mdn* = 53.7) of the FIQ pre-test scores did not differ significantly from the worst-outcome ranks (*Mdn* = 60.3) (U = -1.358, p = .175). These results suggest that the best- and worst-outcome groups differ significantly in the self-reported symptom relief, but not in the self-reported symptoms pre-treatment.

3.2 EEG

3.2.1 Initial analysis of treatment group pre-treatment vs the normative database

Grand average of power spectra analysis. Comparisons of the EO-condition pre-treatment to healthy controls revealed significant differences in the alpha frequency bands at parietal sites (P3) in absolute power. Comparisons of the EC-condition pre-treatment to healthy controls revealed significant differences in the alpha frequency band at parietal sites (P4) in

absolute power, and significant differences in the beta frequency band at central sites (C3, Cz) in relative power. Significant differences are shown in Table 1, with a visual representation of topographies in Figure 6 and Figure 7.

Table 1:

Significant differences in grand average of power spectra in all conditions pre-treatment compared to the normative database

			Eyes Opened				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
P3	P3	12,94*	Positive	-	-	-	-
			Eyes Closed				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
Fp(1)	**P4**	**12,21****	Positive	C3	C3	17,58*	Positive
			Positive	C3	C3	24,14*	Positive
-	-	-	-	C3	Cz	26,37*	Positive

*Note. Source refers to source analysis by WinEEG visually inspected in topographies. *p<.05, **p<.01*

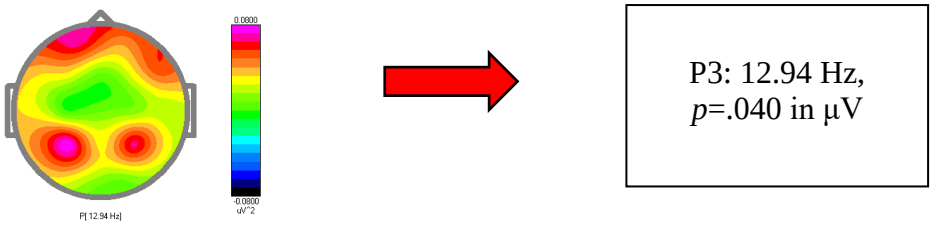
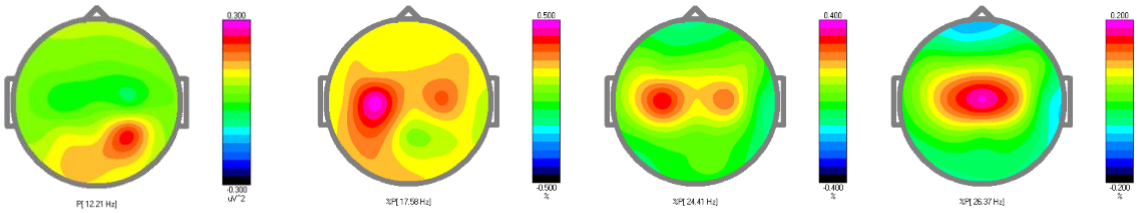


Figure 6: Significant differences in grand average of power spectra in Eyes Closed pre-treatment compared to the normative database in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.



P4: 12.21 Hz, *p*=.005 in µV	C3: 17.58 Hz, *p*=.024 in %P	C3: 24.14 Hz, *p*=.025 in %P	Cz: 26.37 Hz, *p*=.022 in %P

Figure 7: Significant differences in grand average of power spectra in Eyes Opened pre-treatment compared to the normative database in absolute power (µV), displaying cortical area determined by WinEEG, frequency and level of significance.

Grand average of ERP analysis. An analysis of the ERP components pre-treatment to norm-database was conducted with WinEEG. The analyses showed significant deviances in all ERP components (P3 NoGo, N1 and CNV). Subjects showed significant deviances in N1 amplitude on all relevant sites for the N1 component (O1, O2, T5 and T6), indicating a more powerful negative potential. Significant deviances in CNV amplitude were also identified on all relevant sites (Cz and Pz), indicating a more powerful negative potential. Significant deviances in N1 and CNV are presented in Figure 8. Also, the subjects showed significant deviances on all relevant sites for the P3 NoGo component (Cz, Fz), indicating an earlier and more powerful positive potential, see Figure 9.

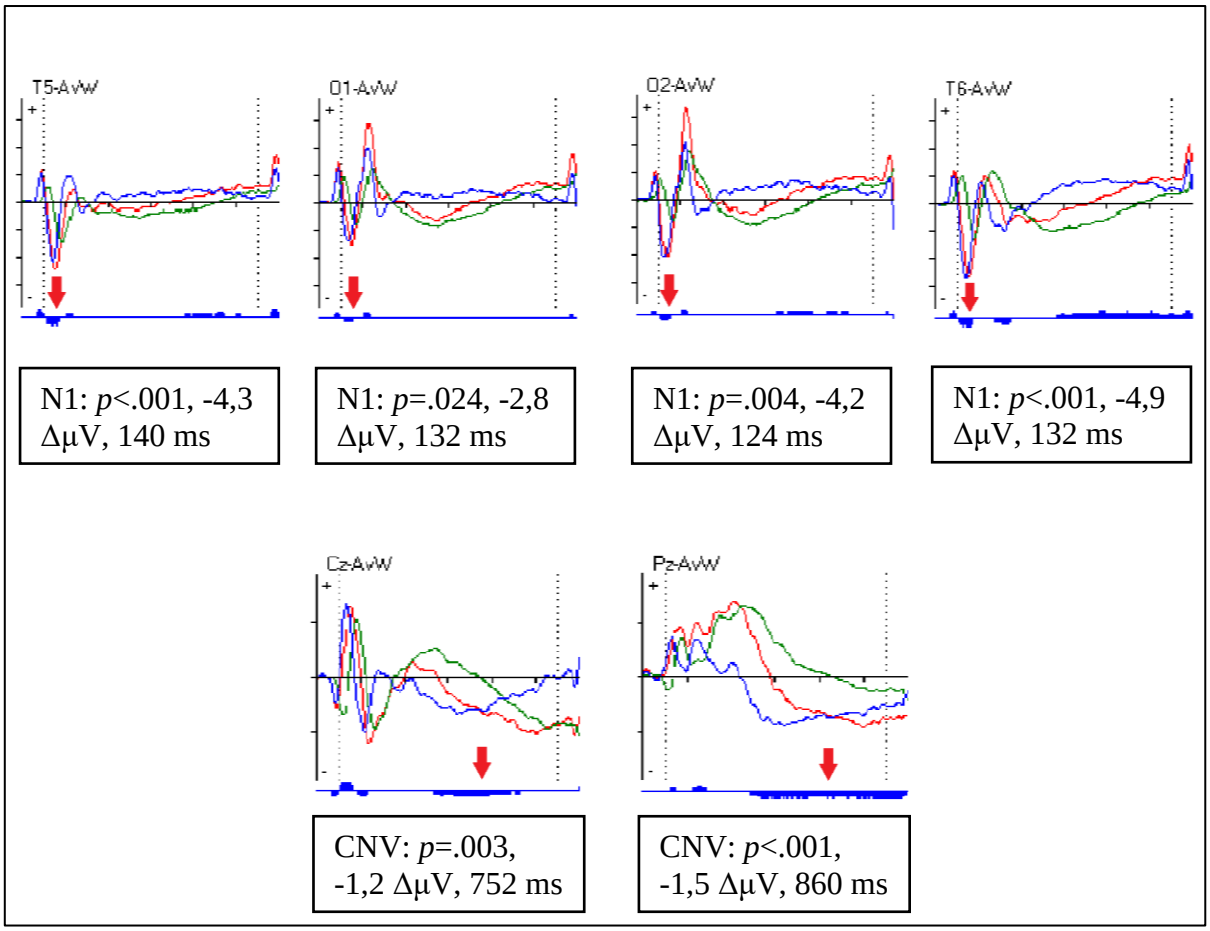


Figure 8: Subjects' grand average of ERP pre-treatment compared to the normative database. The figure illustrates significant deviances in the the N1 and CNV component with amplitude, latency and significance level for the difference-score. Positive upward deflection for positive potentials.

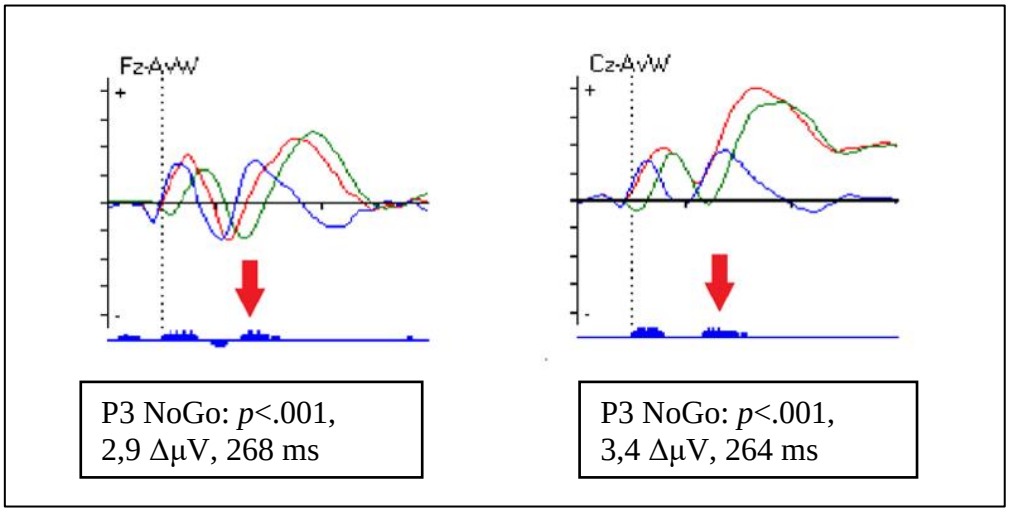


Figure 9: Subjects' grand average of ERP pre-treatment compared to the normative database. The figure illustrates significant deviances in the P3NoGo component with amplitude, latency and significance level for the difference-score. Positive upward deflection for positive potentials.

3.2.2 Initial analysis of treatment group post-treatment vs the normative database

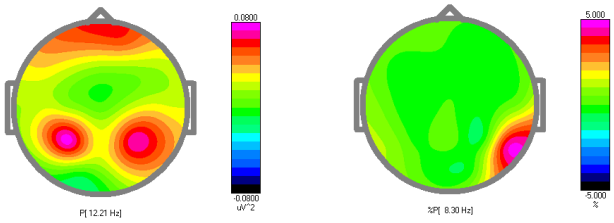
Grand average of power spectra analysis. Comparisons of the EO-condition post-treatment to healthy controls revealed significant differences in the alpha frequency bands at parietal sites (P3) in absolute power and significant differences in the alpha frequency bands at temporal sites (T6) in relative power. Comparisons of the EC-condition post-treatment to healthy controls revealed significant differences in the alpha frequency band at parietal sites (P4, P3) and in the beta frequency band at temporal (T5, T6) sites in absolute power, and significant differences in the alpha frequency band at frontal sites (Fp2, Fp1) in relative power. The significant differences between all conditions post-test compared to healthy controls are presented in Table 2, with a visual representation of topographies in Figure 10 and Figure 11.

Table 2:

Significant differences in grand average of power spectra in all conditions post-treatment compared to the normative database

			Eyes Opened				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
Fp(1)	**P3**	**12,21****	Positive	**T6**	**T6**	**8,3***	Positive
			Eyes Closed				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
Fp(1)	P4, P3	12,21**	Positive	Fp(1)	Fp(1)	12,21*	Positive
Fp(2)	T6, T5	16,6*	Positive	**C3**	**C3**	**16,36***	Positive

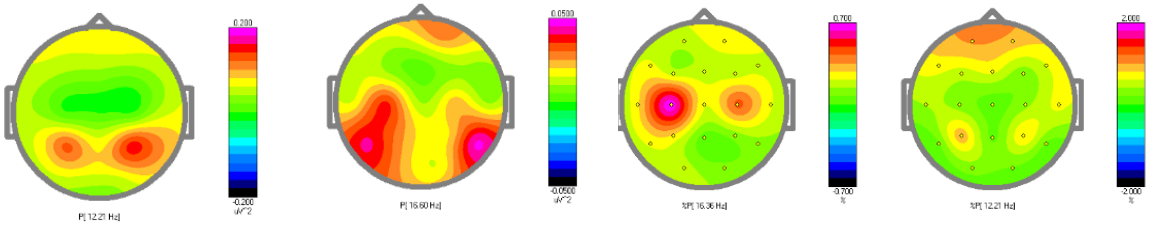
*Note. Source refers to source analysis by WinEEG visually inspected in topographies.. *p<.05, **p<.01*



P3/P4: 12.21 Hz, *p*=.010 in µV

T6: 8,30 Hz, *p*=.013 in %P

Figure 10: Significant differences in grand average of power spectra in Eyes Opened post-treatment compared to the normative database in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.



P3/P4: 12.21 Hz, *p*=.004 in µV

T5/T6: 16.60 Hz, *p*=.025 in µV

C3: 16.36 Hz, *p*=.013 in %P

Fp1: 12.21 Hz, *p*=.023 in %P

Figure 11: Significant differences in grand average of power spectra in Eyes Closed post-treatment compared to the normative database in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.

Grand average of ERP analysis. Analysis of the grand average of the subjects ERP components pre-treatment to the normative database was conducted with WinEEG. The analysis showed significant deviances in all ERP components (P3 NoGo, N1 and CNV) relative to the normative database. Subjects showed significant deviances in N1 amplitude on all relevant sites for the N1 component (O1, O2, T5 and T6), indicating a more powerful negative potential. They also showed significant deviances in CNV amplitude on all relevant sites (Cz and Pz), indicating a more powerful negative potential. Significant deviances in N1 and CNV are presented in Figure 12. Also, the subjects showed significant deviances on all relevant sites for the P3 NoGo component (Cz, Fz), indicating an earlier more powerful positive potential, see Figure 13.

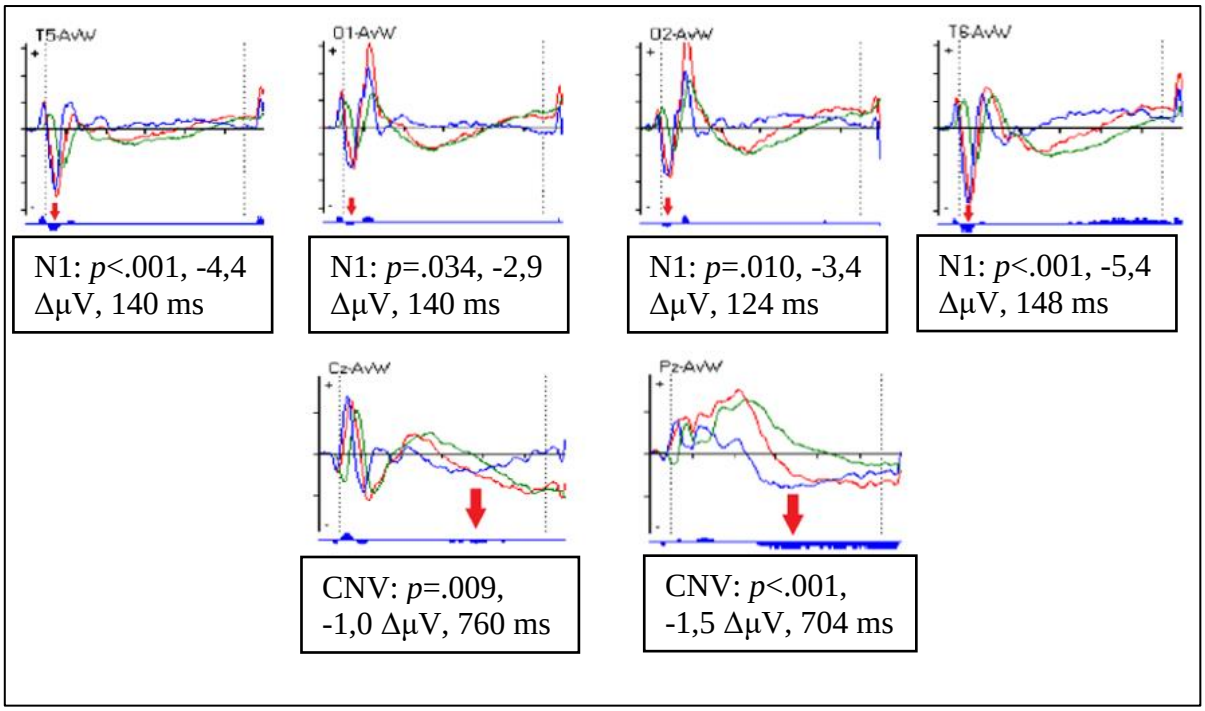


Figure 12: **S**ubjects' grand average of ERP post-treatment compared to the normative database. The figure illustrates significant deviances in the N1 and CNV component with amplitude, latency and significance level for the difference-score. Positive upward deflection for positive potentials.

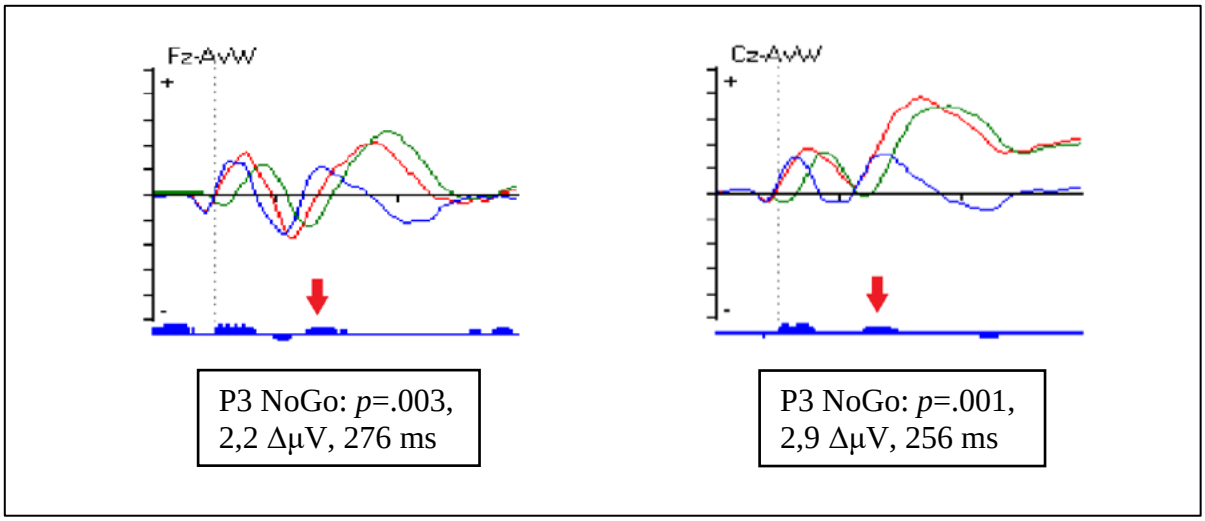


Figure 13: Analysis of subjects' grand average of ERP post-treatment compared to the normative database. The figure illustrates significant deviances in the P3NoGo component with amplitude, latency and significance level for the difference-score. Positive upward deflection for positive potentials.

3.2.3 Secondary analysis of pre-treatment vs post-treatment: effects of treatment condition

Grand average of power spectra analysis. A comparison of the average power post-treatment and pre-treatment revealed significant differences in the EO-condition and the VCPT-condition. No significant differences were found in the EC-condition. Comparisons of the EO-condition post-treatment and pre-treatment revealed significant differences in the alpha frequency bands at parietal sites (P4) in relative power, and in theta frequency bands at frontal sites in absolute power. Significant differences are shown in Table 3, with a visual representation of topographies in Figure 14.

Table 3:

Significant differences in grand average of power spectra in all conditions pre-treatment compared to post-treatment

			Eyes Opened				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
F8	F8	4,64*	Negative	T5	P4	10,01*	Positive
-	-	-	-	O2	O2	4,64*	Negative

*Note. Source refers to source analysis by WinEEG visually inspected in topographies.. *p<.05, **p<.01*

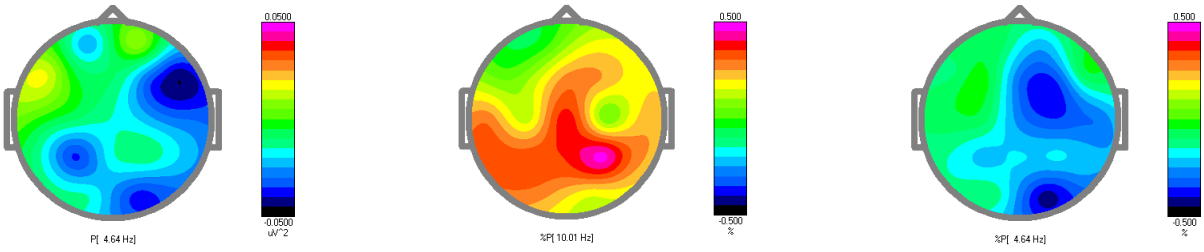


Figure 14: Significant differences in grand average of power spectra in Eyes Closed pre-treatment compared to post-treatment in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.

Grand average of ERP analysis. An analysis of the ERP components pre-treatment to post-treatment was conducted in WinEEG. The analysis showed no significant differences between the groups in the ERP components (P3 NoGo, N1 and CNV).

Behavioural measures. The Wilcoxon Signed-Ranks Test indicated that the post-test ranks (*Mdn* = 355 ms) of the reaction time were significantly lower than the pre-test ranks (*Mdn* = 377 ms) of the reaction time (Z = -2.224, p < .026). The effect size was found to be moderate (r = -.39).

The Wilcoxon Signed-Ranks Test indicated that the post-test ranks (*Mdn* = 9.0) of the reaction time variability were significantly lower than the pre-test ranks (*Mdn* = 8.1) of the reaction time variability (Z = -2.044, p < .041). The effect size was found to be moderate (r = -.36).

3.2.4 Tertiary analysis of best-outcome vs worst-outcome pre-treatment

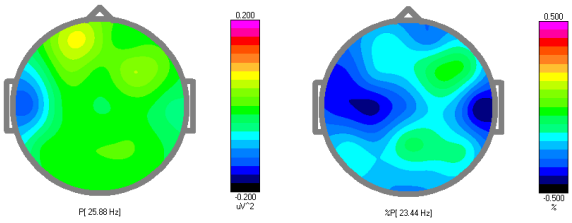
Grand average of power spectra analysis. Comparison of the EO-condition of the best-outcome group (n=5) and the worst-outcome group (n=5) pre-treatment revealed significant differences in the beta frequency bands at temporal sites (T3) in both absolute and relative power. The results indicate significantly less beta in the best-outcome group compared to the worst outcome group at temporal sites pre-treatment. Comparisons of the EC-condition of the best-outcome group and the worst-outcome group pre-treatment revealed significant differences in the beta frequency bands at temporal sites (T3, T4) in absolute power. The results indicate significantly less beta in the best-outcome group compared to the worst outcome group at temporal sites pre-treatment in the EC-condition. Significant differences are shown in Table 4, with a visual representation of topographies in Figure 15 and Figure 16.

Table 4:

Significant differences in the grand average of power spectra in all conditions pre-treatment for the best-outcome group compared to the worst-outcome group

			Eyes Opened				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
T6	T3	25,88*	Negative	O2	T4/C3	23,44*	Negative
			Eyes Closed				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
F3	F3	6,1*	Positive	-	-	-	-
O1	T4, T3	29,54*	Negative	-	-	-	-

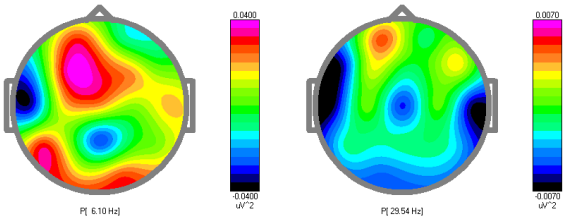
*Note. Source refers to source analysis by WinEEG visually inspected in topographies.. *p<.05, **p<.01*



T3: 25.88 Hz, *p*=.046 in µV

T4/C3: 23.44 Hz, *p*=.035 in %P

Figure 15: Significant differences in grand average of power spectra in Eyes Opened pre-treatment for the best-outcome group compared to the worst-outcome group in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.



F3: 6.1 Hz, *p*=.046 in µV	T3/T4: 29.54 Hz, *p*=.038 in µV

Figure 16: Significant differences in grand average of power spectra in Eyes Closed pre-treatment for the best-outcome group compared to the worst-outcome group in absolute (µV) power, displaying cortical area determined by WinEEG, frequency and level of significance.

Grand average of ERP analysis. An analysis of the ERP components in the best- and worst-outcome groups pre-treatment compared to the normative database was conducted in WinEEG. The analysis showed no significant differences between the groups in the ERP components (P3 NoGo, N1 and CNV).

Behavioural measures. The Mann-Whitney U Test indicated that the pre-test ranks (*Mdn* = 370 ms) of the reaction time in the best-outcome group did not differ significantly from the pre-test ranks (*Mdn* = 339 ms) of the reaction time in the worse-outcome group ($U = 5.0$, $p < .117$). The Mann-Whitney U Test indicated that the pre-test ranks (*Mdn* = 8.1) of the reaction time variability in the best-outcome group did not differ significantly from the pre-test ranks (*Mdn* = 8.4) of the reaction time variability in the worst-outcome group ($U = 10.0$, $p < .602$).

3.2.5 Tertiary analysis of best-outcome vs worst-outcome post-treatment

Grand average of power spectra analysis. Comparisons of the EO-condition of the best-outcome group (n=5) and the worst-outcome group (n=5) post-treatment revealed significant differences in the theta frequency band at temporal sites (T5) and delta frequency band in temporal (T3) and frontal (Fp2) sites in absolute power. In relative power, there were significant differences in the delta frequency band at temporal (T3, T4, T5) and occipital sites (O1), and theta frequency bands at temporal sites (T4). Comparisons of the EC-condition of the best-outcome group and the worst-outcome group post-treatment revealed significant differences in the delta frequency bands at temporal sites (T3) in absolute power, and significant differences in the theta frequency bands at frontal sites (F4, F3) in relative power. The results indicate significantly less delta at temporal sites in absolute power and significantly less theta at frontal sites in relative power in the best-outcome group compared to the worst-outcome group.

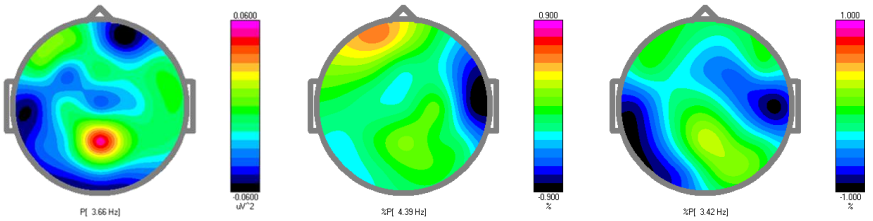
Significant differences are shown in Table 5, with a visual representation of topographies in Figure 17 and Figure 18.

Table 5:

Significant differences in the grand average of power spectra in all conditions post-treatment for the best-outcome group compared to the worst-outcome group

			Eyes Opened				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
C4	T3, Fp2	3,66*	Negative	T4	T4/T3	3,42*	Negative
-	-	-	-	T4	T4	4,39*	Negative
			Eyes Closed				
	Absolute power				Relative power		
Electrode	Source	Frequency	Difference	Electrode	Source	Frequency	Difference
T3	T3	3,91**	Negative	O2	**F4**	**4,88***	Negative

*Note. Source refers to source analysis by WinEEG visually inspected in topographies.. *p<.05, **p<.01*

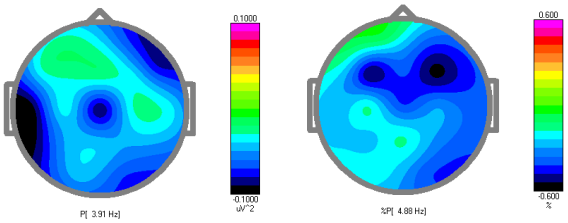


T3/Fp2: 3.66 Hz, *p*=.030 in µV

T4: 4.39 Hz, *p*=.043 in %P

T4/T3: 3.42 Hz, *p*=.049 in %P

Figure 17: Significant differences in grand average of power spectra in Eyes Opened post-treatment for the best-outcome group compared to the worst-outcome group in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.



T3: 3.91 Hz, *p*=.008 in µV	F4: 4.88 Hz, *p*=.013 in %P

Figure 18: Significant differences in grand average of power spectra in Eyes Closed post-treatment for the best-outcome group compared to the worst-outcome group in both absolute (µV) and relative (%P) power, displaying cortical area determined by WinEEG, frequency and level of significance.

Grand average of ERP analysis. An analysis of the ERP components in the best- and worst-outcome groups post-treatment was conducted in WinEEG. The analysis showed no significant differences between the groups in the ERP components (P3 NoGo, N1 and CNV).

***Behavioural measures*.** The Mann-Whitney U Test indicated that the post-test ranks (*Mdn* = 359 ms) of the reaction time in the best-outcome group did not differ significantly from the post-test ranks (*Mdn* = 298 ms) of the reaction time in the worst-outcome group ($U = 4.0$, $p < .076$). The Mann-Whitney U Test indicated that the post-test ranks (*Mdn*= 6.6) of the reaction time variability in the best-outcome group did not differ significantly from the post-test ranks (*Mdn* = 5.5) of the reaction time variability in the worst-outcome group ($U = 9.0$, $p < .465$).

The Mann-Whitney U Test indicated that the difference-score ranks (*Mdn* = 11 ms) of the reaction time in the best-outcome group did not differ significantly from the difference-score ranks (*Mdn* = 16 ms) of the reaction time in the worst-outcome group ($U = 10.0$, $p < .602$). The Mann-Whitney U Test indicated that the difference-score ranks (*Mdn* = 1.5) of the reaction time variability in the best-outcome group did not differ significantly from the difference-score ranks (*Mdn* = -0.5) of the reaction time variability in the worst-outcome group ($U = 6.0$, $p < .175$).

3.3 Follow-up

3.3.1 Fibromyalgia Impact Questionnaire. A Friedman's test showed a significant difference between the FIQ scores of the pre-test, the post-test and the follow-up ($\chi^2_F(2)=9.69$, p=.008). Post-hoc tests using a WRST with a Bonferroni-adjusted alpha level of .017 (0.05/3) showed that the post-test ranks (*Mdn* = 43.5) of the FIQ were significantly lower than the pre-test ranks (*Mdn* = 64.2) ($Z = -3.361$, $p < .001$). The effect size was found to be large ($r = -.59$).

In addition, the follow-up ranks (*Mdn* = 51.0) of the FIQ differed significantly from the pre-test ranks (*Mdn* = 64.2), Z=-2.41, p=.016. The effect size was found to be large (*r* = -.69). The follow-up ranks (*Mdn* = 51.0) of the FIQ did not differ significantly from the post-test ranks (*Mdn* = 43.5), Z=-0.87, p=.382. The effect size was found to be small (*r* = -.24).

3.3.2 American College of Rheumatism: Diagnostic Criteria for Fibromyalgia. The 2010 ACR diagnostic guidelines were evaluated in the follow-up. Before treatment, all subjects met the diagnostic criteria for FM. After treatment, 25% of the subjects (*N*=16) did not meet the diagnostic criteria of the ACR. In the follow-up, 38% of the subjects (*N*=13) did not meet the diagnostic criteria of the ACR. These were the same four subjects that did not meet the criteria post treatment. Yet another subject who met the criteria 7 days post-treatment, did not meet the criteria 3 months after treatment in the follow-up. The development of the number of subjects who met the criteria pre-treatment, 7 days post-treatment and 3 months post-treatment (Follow-up) are visually presented in Figure 19.

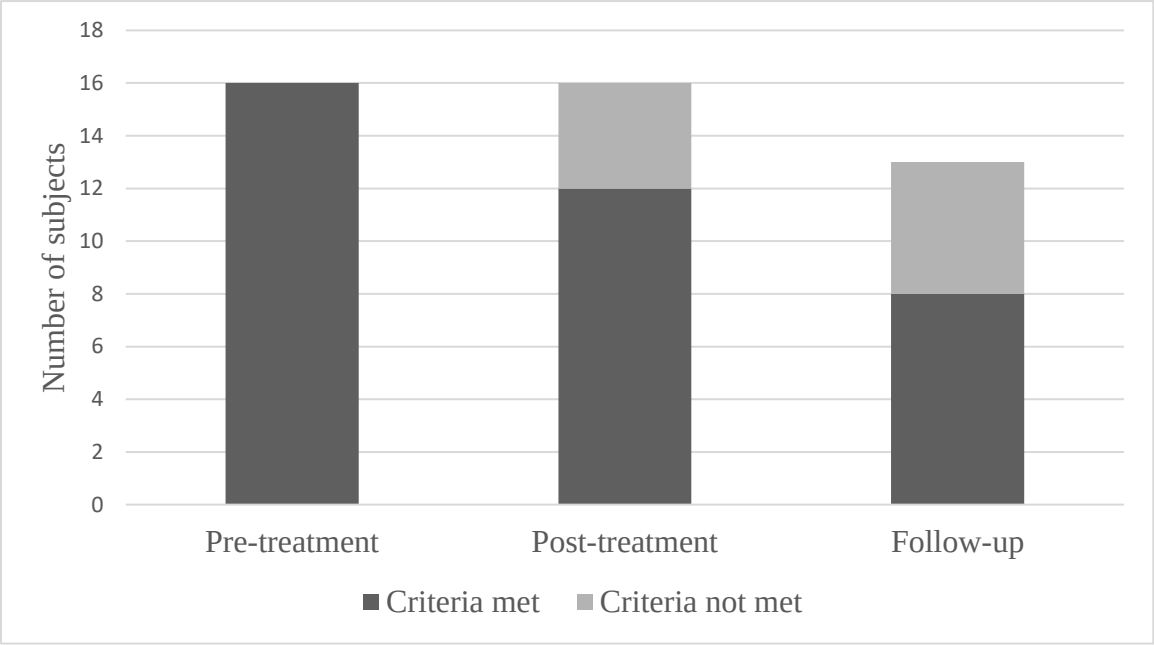


Figure 19: Diagram illustrating the number of subjects who met the criteria for the American College of Rheumatology 2010 diagnostic guidelines pre-treatment, 7 days post-treatment and 3 months post-treatment (Follow-up).

3.4 Adverse effects

Subjects tolerated the tDCS treatments well, with mostly “very mild” or “mild” reported adverse effects. The most frequently reported adverse effects were redness (n=8), itching (n=8), burning sensation (n=5) and numbness (n=4) under electrode during stimulation, in addition to

fatigue (n=6) and headache (n=5) after stimulation. Reported adverse effects are represented in Table 6.

Table 6:

Number of subjects reporting adverse effects after tDCS on a scale from "0=none", "1=very mild", "2=mild", "3=moderate", "4=severe" and "5=very severe".

Adverse effect	Mean	SD
Numbness*	0.31	0.60
Redness*	0.69	0.95
Itching*	0.56	0.81
Burning sensation*	0.44	0.89
Pain*	0.13	0.50
Nausea	0.06	0.25
Fatigue	1.13	1.54
Nervousness	0.00	0.00
Insomnia	0.19	0.54
Headache	0.75	1.18
Difficulty concentrating	0.06	0.25
Acute mood changes	0.13	0.50
Changes in visual perception	0.19	0.54

Note. * = under the electrode during the stimulation; tDCS, transcranial direct current stimulation

4. Discussion

4.1 Symptom reduction

Statistical analysis of the subjective self-report measurements indicate a significant symptom reduction after the treatment condition with tDCS. Comparisons of the FIQ pre-treatment and post-treatment indicated significant symptom reduction with a large effect size. The analysis of the VAS Total showed a significant decrease in average self-report of symptoms. Statistical analyses of the different VASes with Bonferroni correction indicated that change in pain-symptoms seem to be the only significant symptom reduction. However, it is essential to note that a single analysis of any of the individual VAS symptom-measurements would have been evaluated as an indication of significant symptom relief. An individual

measurement would have been assessed differently because the p-value would be satisfactory for a single test ($p < .050$) but not satisfactory for multiple testing with Bonferroni correction ($p < .013$). Because of the non-parametric tests used in this study, it cannot be inferred whether change in the different symptoms (e.g. pain, fibrofog and fatigue) differ significantly from each other. As a result, larger relative changes in pain-symptoms should be treated as an observation for further research. In addition to a significant symptom reduction, twenty-five percent of the subjects did not meet the ACR diagnostic criteria for FM after the treatment condition, further illustrating the clinically significant symptom relief associated with the treatment condition.

It is of great importance to keep in mind that these positive findings are associated with the treatment condition and not the tDCS-treatment alone. This study was executed without a placebo or a no-treatment control group. Thus, the present findings are not differentiated from either the effect of interpersonal contact, placebo or spontaneous recovery. There have been identified correlations between the quantity of social support and pain symptom management and between the quality of social support and psychological well-being (Franks, Cronan & Oliver, 2004). Furthermore, one might argue that FM still is a stigmatised illness. The FM-subjects were met with respect, knowledge about FM and sympathy for the disease, which might further facilitate social support as a confounding variable in the present findings. Further research should aim to differentiate both the impact of placebo and interpersonal contact from treatment-effects through a double-blinded Randomised Controlled Trial design (RCT).

Although no conclusions can be made in the context of this pilot study, the results are in accordance with hypothesis one. Furthermore, the results of the follow-up analysis of the FIQ are indicative of a lasting effect. One can argue that a significant effect with a large effect size which lasts for more than three months are likely not a result of placebo and interpersonal contact alone. Additionally, the subjects who did not meet the ACR criteria for fibromyalgia post-treatment, still did not meet the ACR criteria at follow-up. The lasting effect of the treatment condition strengthens both hypothesis one and hypothesis two.

At follow up, one additional person did not meet the ACR criteria. Care must be taken in inferring meaning into such a potential recovery. One possibility is that further symptom reduction is facilitated by breaking the negative feedback-loop of CS through tDCS. Pain reduction can indirectly promote sleep, and further change fatigue and cognitive symptoms, altering behaviour and further altering neuronal activity leading to further structural change. However, this is one of many possible explanations, and although it is an interesting perspective, it is speculative at best. The possibility of spontaneous recovery is addressed in section 4.5.1.

4.2 qEEG patterns in the FM brain

4.2.1 Power spectra comparisons. Regarding differences in power spectra, the present study identifies few consistent deviances in subjects with FM compared to the normative database, and fewer still in accordance with the literature. In fact, the opposite was identified in the eyes closed condition pre-treatment. The subjects showed significantly increased alpha-power at parietal sites compared to the normative database, contrary to the literature on the dynamic pain connectome. Existing theory hypothesises that chronic pain is associated with decreased parietal alpha and decreased default mode network activation in resting state (Jann et al., 2009). Also, in the eyes closed condition of the pre-treatment test, the analysis showed significantly more beta-power in central areas which is contradictory to the literature on the default mode network.

Deviances in the alpha- and beta-power was also identified post-treatment, with a significant increase compared to the normative database. As stated in hypothesis three, there should be significant deviances which should tend toward normalisation after the treatment-condition. The observed deviances seem to be neither in accordance with the presented literature nor tend toward normalisation post-treatment. Accordingly, the presented findings are not in accordance with hypothesis three.

4.2.2 Power spectra comparisons of FM subjects pre-and post-treatment. Pre-post comparisons identified a significant decrease in frontal theta-power and a significant increase in parietal alpha-power in the eyes opened condition. Frontal theta power is negatively correlated with default mode network activation (Scheeringa et al., 2008). Consequently, a decrease in theta-power may be indicative of increased default mode network activation. A positive change in parietal alpha may also be an indication of an increase in default mode network activation, and increased mind wandering away from pain. Such an increase in oscillatory activity related to default mode network activation strengthens hypothesis three, as the change occur at the same time as significant changes in self reported symptoms.

Although these findings are in accordance with the literature on the default mode network, in accordance with the decrease in subjectively reported symptoms, and in accordance with hypothesis three, its meaning and importance must be interpreted with utmost care. Firstly, the present findings are not identified through both absolute and relative power. Secondly, the deviances are not consistent with the deviances identified in comparisons to the normative database, discussed in section 4.2.1. For the results to be consistent, there should be significantly increased frontal theta-power and decreased parietal alpha-power relative to the normative database pre-treatment. Lastly, these deviances should tend toward normalisation

post-treatment. This is not evident from the present analysis. No significant differences were found on altered theta-power pre-treatment, as would have been expected according to literature. However, it is important to note that a grand average comparison only represents an average of the subjects compared to norm, and is not designed to detect individual differences. Literature on FM and frequency bands suggests an altered theta-power, which implies that an FM patient could have either an elevated or a decreased theta-power. Averaging subjects with altered frequency band power in different directions could zero out their differences. Therefore, the averaging could prevent possible significant findings on abnormalities in theta-power.

As mentioned in section 2.6.5, the individual EEG-properties should be evaluated with caution because of the family-wise error rate. The lack of consistency weakens hypothesis 3, stating that tDCS has a normalising effect on deviances in power spectra in subjects with FM. For future studies, the issue of averaging subjects should be addressed by analysing the individual power spectra, which unfortunately was outside the scope of this study due to time limitations.

4.2.3 ERP component analysis. Consistent with existing literature, the ERP component analysis revealed a significantly increased N1 amplitude in subjects with FM pre-treatment compared to healthy controls. The increased N1 amplitude may indicate an abnormal process of early discrimination of sensory information in the FM population. Results were also consistent within the CNV component, showing a significantly stronger CNV (i.e. more negative) in subjects with FM pre-treatment compared to healthy controls. The stronger CNV amplitude has previously been linked to chronic pain in several studies, which strengthens the hypothesis of the importance of attentional aspects involved in chronic pain. Contrary to existing literature, the P3 NoGo amplitude was not found to be reduced in the FM population compared to healthy controls. Analysis of the P3 NoGo component found an earlier more powerful potential in the FM population. It is important to note that the peak amplitude of the P3 NoGo component in the FM population did not differ significantly from the normative database. The significant deviances in the P3 NoGo component illustrates an earlier latency rather than an increase in peak amplitude. The WinEEG internal engine does not provide the standard deviation for latency, making it difficult to make assumptions about whether or not the observable changes in latency are significant. Research on P3 NoGo latency have shown an increased latency, contrary to our findings.

Significant deviances in the N1 and CNV component in the FM population compared to the normative database are consistent with literature. These findings suggest that ERP components, as suggested by Begleiter et al. (1998), may pose as potential biomarkers for

diseases such as FM. However, it is essential to note that many different disorders show similar deviances in ERP components, which will complicate differential diagnostics using ERP.

According to our hypothesis, ERP deviances should tend toward normalisation after treatment with tDCS. Analysis of the N1 and CNV component in the FM population post-treatment compared to the normative database revealed the same significant deviances as pre-treatment. There were no significant changes between the subjects pre- and post-treatment. The lack of significant change from pre- to post-treatment weakens Hypothesis three, stating that tDCS has a normalising effect on ERP deviances in subjects with FM.

4.2.4 Changes in behavioural measures. Statistical analysis of the behavioural measures shows a significant reduction in both reaction time and reaction time variability after the treatment condition. As previously stated, prolonged reaction times may be related to impaired attentional processes such as impaired automatic processing and direct thinking (Nydén et al., 1999). One could argue that the treatment condition had a normalising effect on a prolonged reaction time related to impaired attentional processes, in accord with Hypothesis three. However, no normative comparisons between the FM-subjects and a normative database were made pre-treatment. The WinEEG software does not provide normative data for the reaction time or the reaction time variability.

4.3 qEEG as an objective measure of treatment-related outcomes

Pre-test comparisons of power spectra revealed significantly decreased beta power in temporal areas in the best-outcome group compared the worst-outcome group, in the eyes opened and eyes closed conditions. Furthermore, in the eyes closed condition, the best-outcome group showed significantly increased frontal theta power compared to the worst-outcome group. Both decreased beta power and increased frontal theta power are associated with reduced default mode network activation. Accordingly, the FM-subjects with the most considerable improvements in self-reported symptoms had less oscillatory correlates with default mode network activation before treatment compared to the worst-outcome group. These findings might suggest that relative to the worst-outcome group, the best-outcome group showed less correlates to default mode network activation and ability to mind-wandering away from pain pre-treatment.

Post-test comparisons identified none of the same deviances found in the pre-test comparisons. Conversely, the best outcome-group showed significantly decreased frontal theta-power in the eyes closed condition compared to the worst-outcome group. In the framework of the dynamic pain connectome, one might argue that the best-outcome group have an observably

different relative change in theta activity, an ocillatory correlate of the default mode network activation, in resting state compared to the worst outcome group.

In summary the analyses show a significantly increased beta power and increased theta power pre-treatment in the best-outcome group. Furthermore, the analyses show significantly less delta and theta power in the best outcome group post-treatment. These findings are in accordance with the presented literature and the results of the pre- and post-treatment analysis of power spectra, which strengthens hypothesis four. With the presented theoretical framework of CS, the dynamic pain connectome, and tDCS, one may hypothesise that such a relationship might be explained by individual differences in neuronal plasticity as reactions to the treatment condition. Furthermore, the best-outcome group is defined by the subjects with the most considerable change in symptom severity, and the groups did not differ in symptom severity pre-treatment. It is in theory plausible to understand such a change in symptom severity as a change in the default mode activation, facilitated by tDCS-treatment. However, the same deviances are not found to significantly and consistently separate the FM-subjects from healthy controls on a group level. Consequently, care must be taken in inferring this theoretical causal relationship from a pilot study, with few consistent findings in oscillatory patterns.

4.4 Adverse effects.

In this study, some adverse effects were reported in the treatment condition, although most of the reported adverse effects were scored as “very mild” or “mild”. Only fatigue had a mean rapport of over 1 (i.e. reported as slightly above “very mild” when averaging the subjects’ rapports).). As previously stated, studies have shown that adverse effects are often minor and uncommon, as well as equally distributed in the active stimulation and sham group (Roizenblatt et al., 2007). In this study, there were no sham group for comparisons, which pose an obvious limitation in determining the actual level of adverse effects in this study of tDCS treatment. Nevertheless, the reported adverse effects in this study were similar to the adverse effects reported by other studies with both an active and sham group (e.g. Fagerlund et al., 2015).

Even though recommendations by Fregni et al. (2015) for the safe use of tDCS to minimise adverse effects were followed, some adverse effects were present. The reported adverse effects must be seen in relation to the big change in daily routine experienced by the subjects. 5 consecutive daily sessions over a week can, for many, pose an additional level of stress in everyday life. Therefore, some increase in levels of fatigue, headaches and sleep difficulties are to be expected. Making tDCS available for home-use could diminish some of the reported adverse effects.

4.5 Limitations

4.5.1 Design. The topics of placebo and interpersonal contact was addressed in section 4.1, but the topic of spontaneous recovery was not mentioned in detail. The likelihood that spontaneous recovery explains a substantial part of the findings is less likely as the diagnostic criteria define FM as a chronic illness (Clauw & Crofford, 2003). However, as the illness is still poorly understood, diagnostic errors may explain wrongly diagnosed individuals, and spontaneous recovery cannot be ruled out as a confounding variable in the present findings. Furthermore, with the addition of the follow-up, the time period of which spontaneous recovery might confound the results are markedly prolonged. The fact that four subjects did not meet the diagnostic criteria of the ACR post-treatment, and five subjects did not meet the criteria at follow-up, might be understood as a result of spontaneous recovery, or as a positive feedback-loop facilitated by the tDCS-treatment. Further research should include a larger sample size, and if possible, even more thorough screening of test subjects, to minimise the effects of wrongly diagnosed patients and spontaneous recovery.

Many of the subjects had other diagnoses such as migraines, fatigue and different forms of rheumatism, in addition to FM. Unfortunately, other diagnoses and ongoing treatment were not properly documented or controlled for. Therefore, the observed changes in self-reported symptoms may have been moderated by individual differences in medication, other diagnoses, or other treatment interventions. However, the subjects were told to report changes in their standard treatment or diagnoses. Subjects were excluded from further analysis if reporting such changes.

4.5.2 Multiple comparisons. Even with the alpha-corrections and care in interpreting single EEG-findings, the issue of the FWER is not completely nullified. This is because the FWER is not controlled across hypotheses. Using Bonferroni-correction across all hypotheses would render the present study with no statistical power. One might argue that a Benjamini-Hochenberg procedure of false discovery rate across all tests would be a better approach. However, a Benjamini-Hocenberg procedure might yield multiple significant findings with individual uncorrected p-values greater than alpha of .05. Furthermore mixing the family of tests on the subjective measures which yielded lower p-values, with that of EEG-analyses which in many cases yielded higher p-values, would greatly reduce the number of significant findings in comparison of datasets with less p-value discrepancy (Ferreira & Zwinderman, 2006). The issue of FWER is widely discussed in the academic community, as multiple studies on the same population is a form of multiple hypotheses testing and correcting for false positives comes at the expense of increased probability of false negatives (Rothman, 1990; Cabin & Mitchell,

2000). Further research should aim at acquiring a sufficient sample size for parametric testing. This might contribute to more flexible ways of correction through Tukey's correction or other approaches. In the current pilot study, it has been chosen to use Bonferroni-correction on the families of variables, rather than across all hypotheses, as not to sacrifice most statistical power, but at the same time correct for alpha-inflation to some extent.

4.5.3 Self-report measurements. The ACR measurement of post-treatment-symptoms is based on the self-reported symptoms from the first week after treatment, whereas the ACR of the pre-treatment-symptoms is based on the-self reported symptoms from a period of three months before treatment. Accordingly, the reduction of subjects meeting the ACR diagnostic criteria post-treatment may be attributed to different periods to experience the symptoms rather than a treatment effect. However, the follow-up ACR showed that the same subjects who did not meet the diagnostic criteria post-treatment, still did not meet the diagnostic criteria at follow up three months later. Accordingly, the time-period to experience the symptoms at follow up was the same as that of the pre-test. One can argue that this result further validates the findings from the post-treatment condition. Thus, the different time-periods are not likely to be a great confounding variable of the post-treatment findings.

4.5.4 EEG. As mentioned, the EEG analysis was run in the internal analysis engine of Mitsar WinEEG 2.129.100, implying little control over the assumptions of the parametric analyses. Furthermore, in the context of ERP-analysis, no estimate of temporal variation is available. Consequently, one cannot differentiate between a significant difference in the average power of an ERP-component peak and a significant difference in time of an ERP-component peak. However, visual inspection of the comparisons and pre-defined time intervals grounded in the literature counteracts obvious mistakes of inferring deviances in average power of ERP-components when, in fact, deviances are a result of the time of ERP-components.

19 channel EEG-recordings have poor spatial resolution compared to hemophysiolgical measurements. The presented literature of default mode network is based on parallel measurements of EEG and fMRI (BOLD), and there is little evidence indicating that the neuronal structures related to the dynamic pain connectome are identifiable by EEG alone (Neuner et al., 2014). Therefore, high reliance on the individual component analysis of source localisation should be avoided.

Due to the family-wise error rate, multiple comparisons must be corrected to infer significance on individual EEG-findings. The small sample size in this study implies a relative loss of statistical power compared to bigger samples. Alpha-correction further reduces the statistical power of analyses. As mentioned in section 2.6.5, the alpha-value of hypothesis 3 is

still satisfactory in this study without alpha-correction of each contrast. Nevertheless, research on individual frequencies and multiple comparisons should aim to increase the statistical power by increasing the sample size, to counteract the loss of power due to alpha-correction.

The healthy controls found in the WinEEG database consists of 40 Russian subjects. Consequently, the results of the EEG-analyses comparing the FM-subjects to the normative database might be related to differences in the populations, or differences in the procedure of artefact correction. More control over norm-data should be an aim for future research. However, Recording, artefact correcting, and analysing EEG-data is resource-demanding. A solution for future research might be to make EEG-recordings of a normative group based on thorough screening, and specific procedures of artefact correction, a research project within itself.

5. Conclusion

The treatment condition has been proven to give a significant decrease in self-reported symptoms in the FM-subjects, which strengthens the hypothesis that neuromodulation of cortical excitability with tDCS will give a reduction in the self-reported perception of pain, fatigue and fibrofog. Because of the limitations, we cannot estimate how much of the treatment-effect can be attributable to the effects of tDCS alone. However, a lasting effect seems to be evident for at least three months, which strengthens the hypothesis of a significant reduction in self-reported symptoms over time due to lasting plastic neuronal changes after treatment with tDCS.

The comparisons of average power spectra pre- and post-treatment are in accordance with literature on oscillatory patterns related to pain inhibition through the dynamic pain connectome. The subjects show a decrease in frontal theta-power and an increase in parietal alpha-power. Care must be taken in interpreting the implications of these findings as the pre-post deviances are not consistent with the deviances identified in comparisons to the norm. It is important to note that because of multiple testing, the actual alpha-level of the pre-post comparisons are far greater than .05. The probability of a type-I error has been controlled to our best ability. However, no such control has been evident in regards of type-II errors. The small sample size leads to an issue of statistical power. Consequently, there might be oscillatory deviances which are not identified.

ERP-analysis show significant deviances in the N1 and CNV-components following previous findings on chronic pain. These findings suggest that ERP components, as indicated by Begleiter et al. (1998), may pose as potential biomarkers for diseases such as FM. However, it is essential to note that many different disorders show similar deviances in ERP components,

which will complicate differential diagnostics using ERP. No significant changes were identified when comparing pre- and post-treatment. Hence, this study does not confirm any change in ERP-components as a result of tDCS.

The explorative comparisons of best- and worst-outcome groups of average power spectra yielded interesting results. The best outcome group were found to have significantly less oscillatory correlates to default mode network activation in resting state compared to the worst outcome group, pre-treatment. The best outcome group were also found to have significantly more oscillatory correlates to default mode network activation in resting-state post-treatment. Although not conclusive, one might suggest that relative change in default mode network activation is related to relative change in self-reported symptoms, which strengthens the hypothesis that there would be significant deviances between the best- and worst-outcome group that possibly could help predict treatment-outcome in future studies.

Further research should aim at investigating the effects of tDCS within the framework of an RCT-design. The research design should include a montage with elliptical electrodes, with the anode covering S1/M1 and an extracephalic cathode. Future research on the effects of tDCS in FM-patients should emphasise the subjective measures, as well as the oscillatory correlates to default mode network presented in the current pilot study. In order to make further advancements on oscillatory correlates for FM, research should include a comparison of both pre- and post-treatment average power spectra as well as individual comparisons of power spectra.

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Appendix

A. Informed consent schema
B. ACR questionnaire (Norwegian version)
C. FIQ questionnaire (Norwegian version)
D. VAS questionnaire for pain, fatigue and fibrofog (in Norwegian)
E. Adverse effects: questionnaire
F. The assumption of symmetry: Boxplots
G. Shapiro Wilk Test of normality: Table
H. Kurtosis and skewness: Table
I. Assumption of equal distribution: Histograms

Appendix A

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

qEEG, Transkraniell Likestrømsstimulering og Nevrofeedback på Fibromyalgipasienter

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

HVA INNEBÆRER PROSJEKTET

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

Videre vil deltagere bli tilfeldig fordelt på to grupper. Man vil få tilbud om enten Nevrofeedback eller tDCS. Nevrofeedback er en treningsmetode som krever minimalt med fysisk innsats, hvor man skal sitte foran en dataskjerm med 3 elektroder på hodet i ca. 30 minutter. Man skal etter instrukser konsentrere seg om bildet på skjermen som er tilbakemelding på egen hjerneaktivitet. Metoden går ut på at hjernen skal trene seg selv opp til ønsket hjerneaktivitet ut i fra resultatene vi får på EEG-målingen gjort i forkant. Denne treningsmetoden er uten ubehag og bivirkninger. I dette prosjektet vil det være ca. 10 økter per deltaker. Det er ingen begrensning på hvor ofte man kan utføre treninger, og hvor raskt vi blir ferdig med alle behandlingene kommer ann på den individuelle tidsplanen vi legger opp. Vi ser for oss ca. 2-3 økter i uka over en periode på ca. 5-6 uker.

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

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

MULIGE FORDELER OG ULEMPER

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

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

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

Hva skjer med informasjonen om deg?

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

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

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

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

Godkjenning

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

Samtykke til deltakelse i prosjektet

Jeg er villig til å delta i prosjektet

_ _

Sted og dato

Deltakers signatur

_ _

Deltakers navn med trykte bokstaver

Appendix B

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

DEL 1: VIDT-SPREDT SMERTE INDEKS

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

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

DEL 2A: SYMPTOMERS ALVORLIGHETSGRAD

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

Fatigue

☐ Ikke noe problem

☐ Litt eller milde problemer; generelt milde eller periodiske

☐ Moderate problemer; betraktelig problemer; ofte til stede og/eller på et moderat nivå

☐ Alvorlig; forstyrrer livskvaliteten

Ikke våkne opplagt

☐ Ikke noe problem

☐ Litt eller milde problemer; generelt milde eller periodiske

☐ Moderate problemer; betraktelig problemer; ofte til stede og/eller på et moderat nivå

☐ Alvorlig; forstyrrer livskvaliteten

Kognitive symptomer

☐ Ikke noe problem

☐ Litt eller milde problemer; generelt milde eller periodiske

☐ Moderate problemer; betraktelig problemer; ofte til stede og/eller på et moderat nivå

☐ Alvorlig; forstyrrer livskvaliteten

DEL 2B: ANDRE SYMPTOMER

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

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

Appendix C

Fibromyalgia Impact Questionnaire (FIQ)

Retningslinjer: For spørsmål 1-11, sett en ring rundt tallet som best beskriver hvordan du totalt 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 D

VISUELL ANALOG SKALA (VAS)

Smerte

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

Ingen smerte _____ **Utholdelig smerte**

Fatigue/trøtthet

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

Ingen fatigue _____ **Kraftig fatigue**

Fibrotåke

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

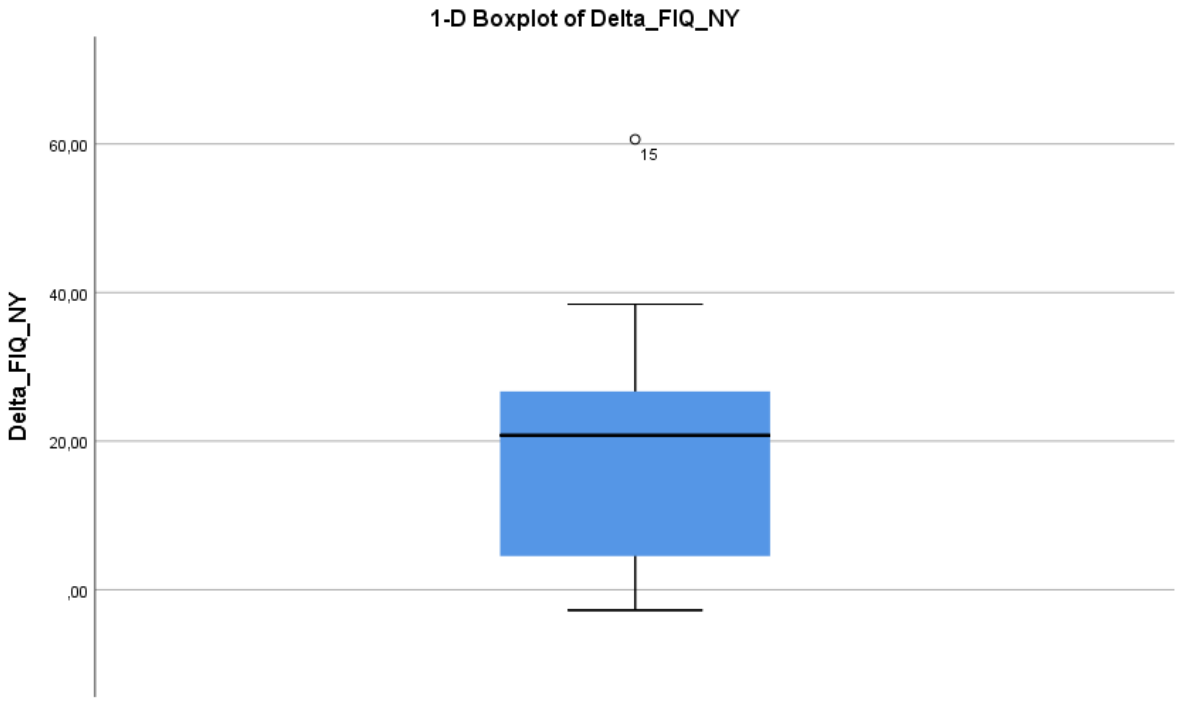
Ingen fibrotåke _____ **Kraftig fibrotåke**

Appendix E

Bivirkninger ved tDCS

Bivirkning	**Ingen**	**Veldig mild**	**Mild**	**Moderat**	**Alvorlig**	**Veldig alvorlig**
Nummenhet under elektrode						
Rødhet under elektrode						
Kløing under elektrode						
Brennende følelse under elektrode						
Smerte under elektrode						
Kvalme						
Fatigue						
Nervøsitet						
Insomnia						
Hodepine						
Konsentrasjonsvansker						
Akutt humørforandring						
Forandringer i visuell persepsjon						

Appendix F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Delta_FIQ_NY
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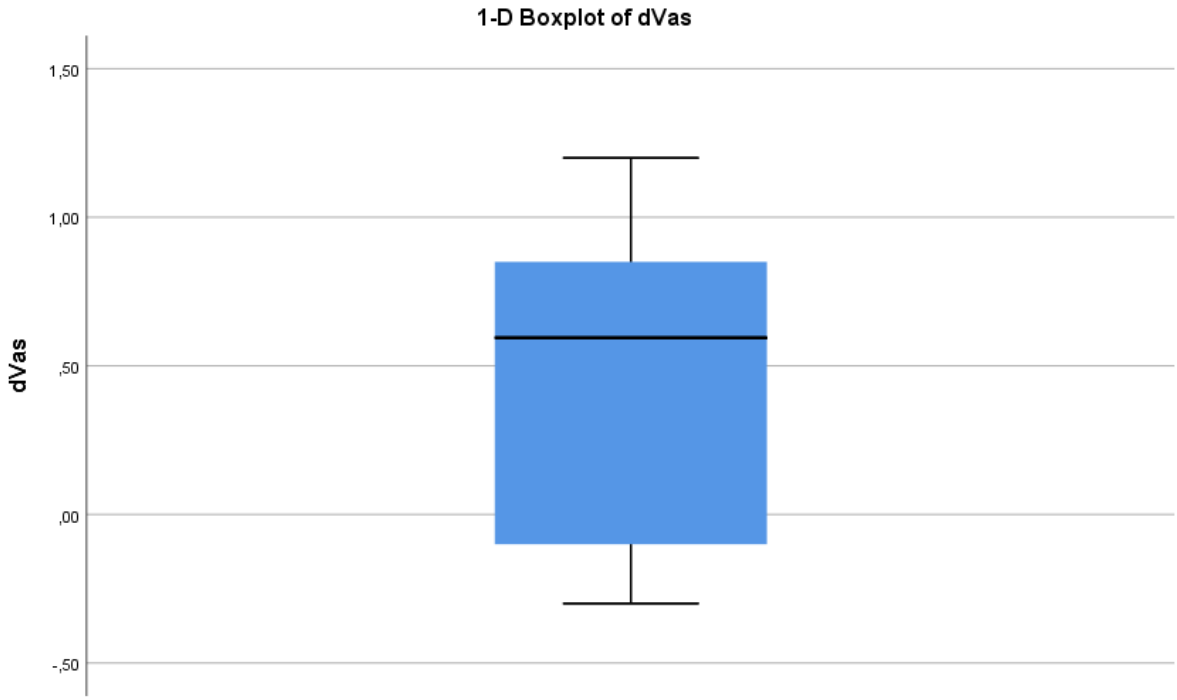
40,00
20,00
,00
15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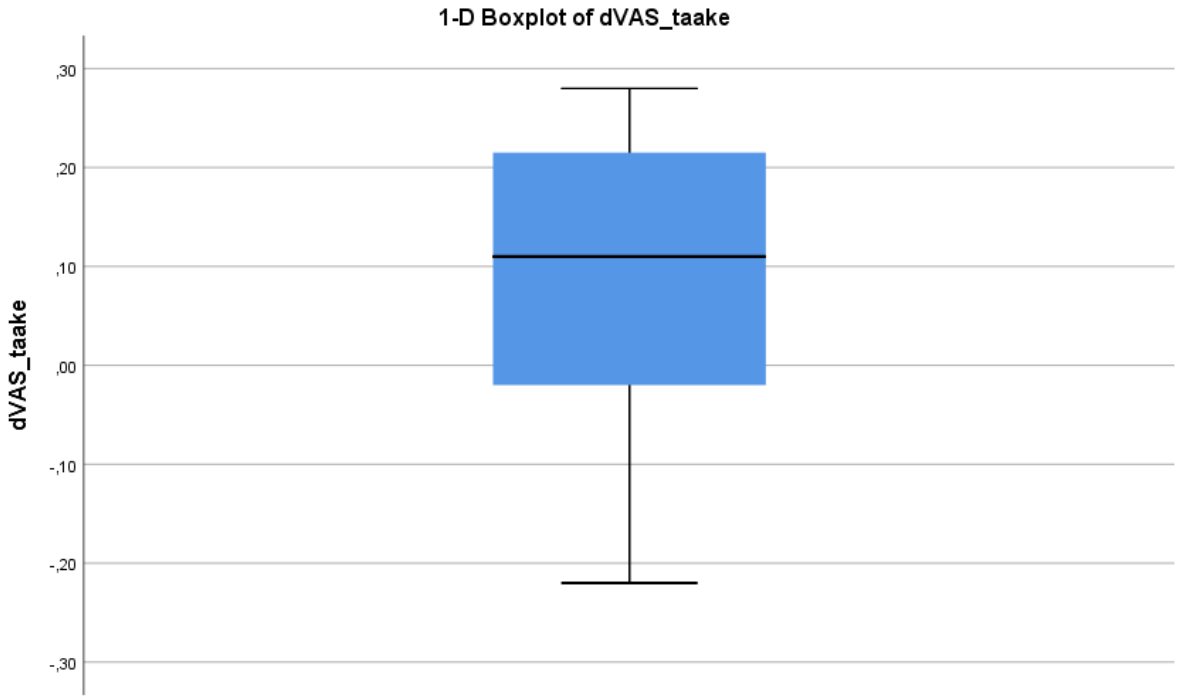
1,00
,50
,00
-,50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dVAS_taake
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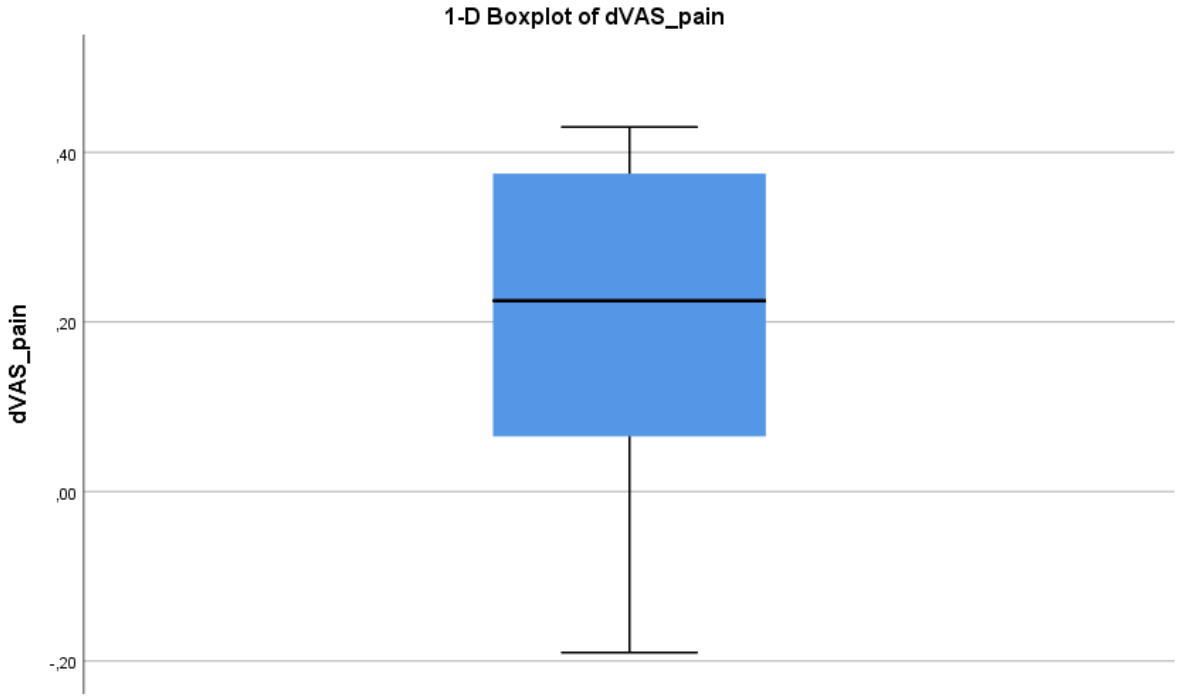
,20
,10
,00
-,10
-,20
-,30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dVAS_pain
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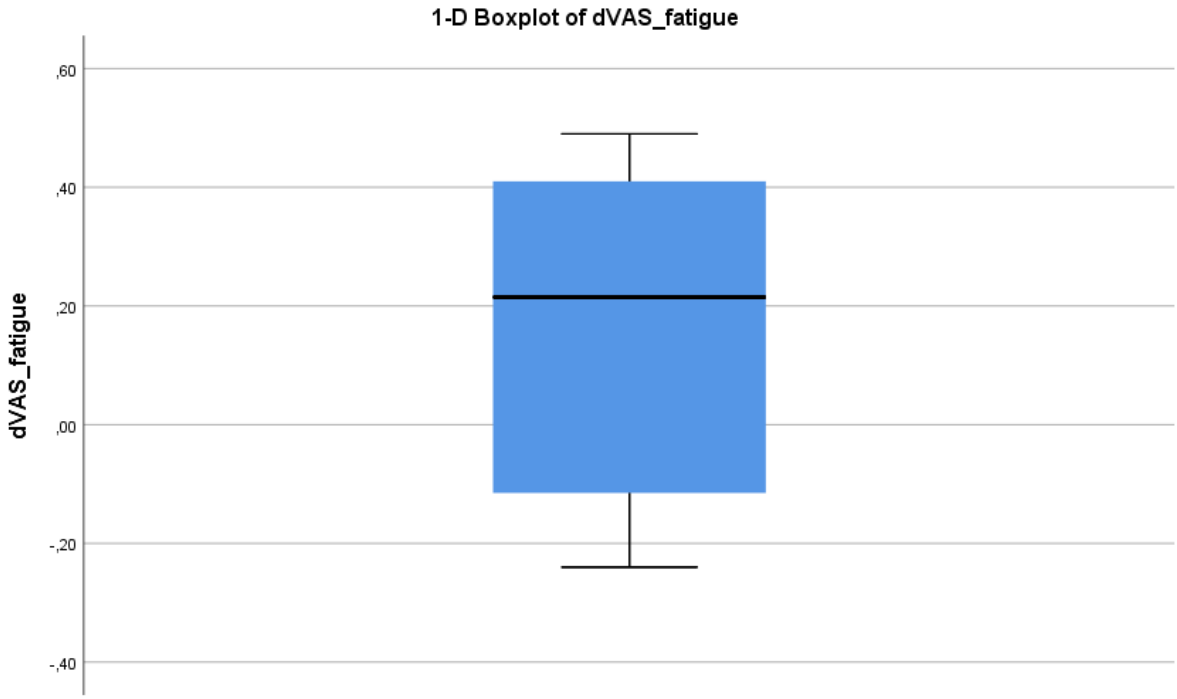
,20
,00
-,20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dVAS_fatigue
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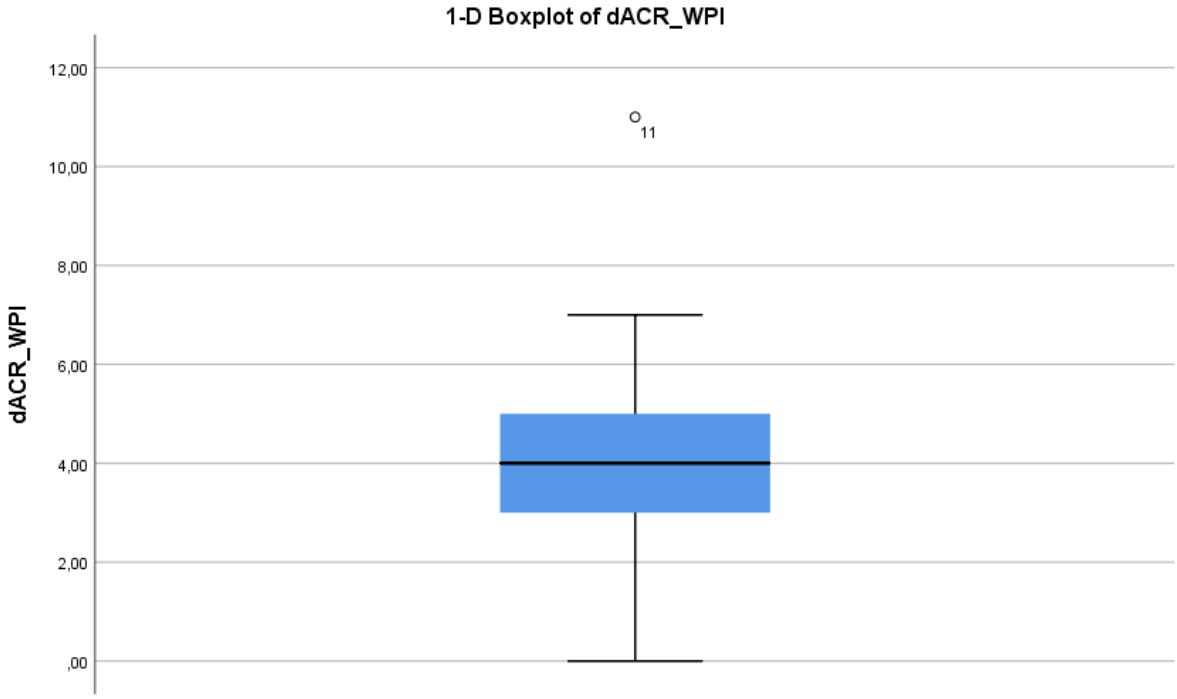
,40
,20
,00
-,20
-,40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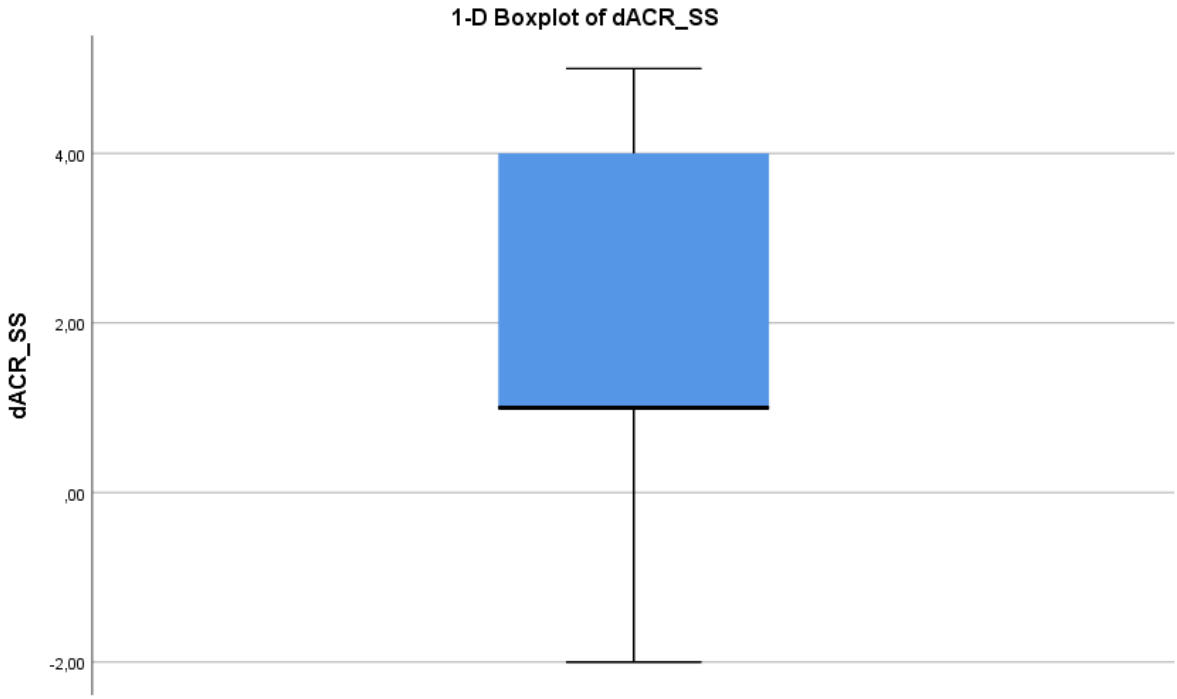
10,00
8,00
6,00
4,00
2,00
,00
11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,00
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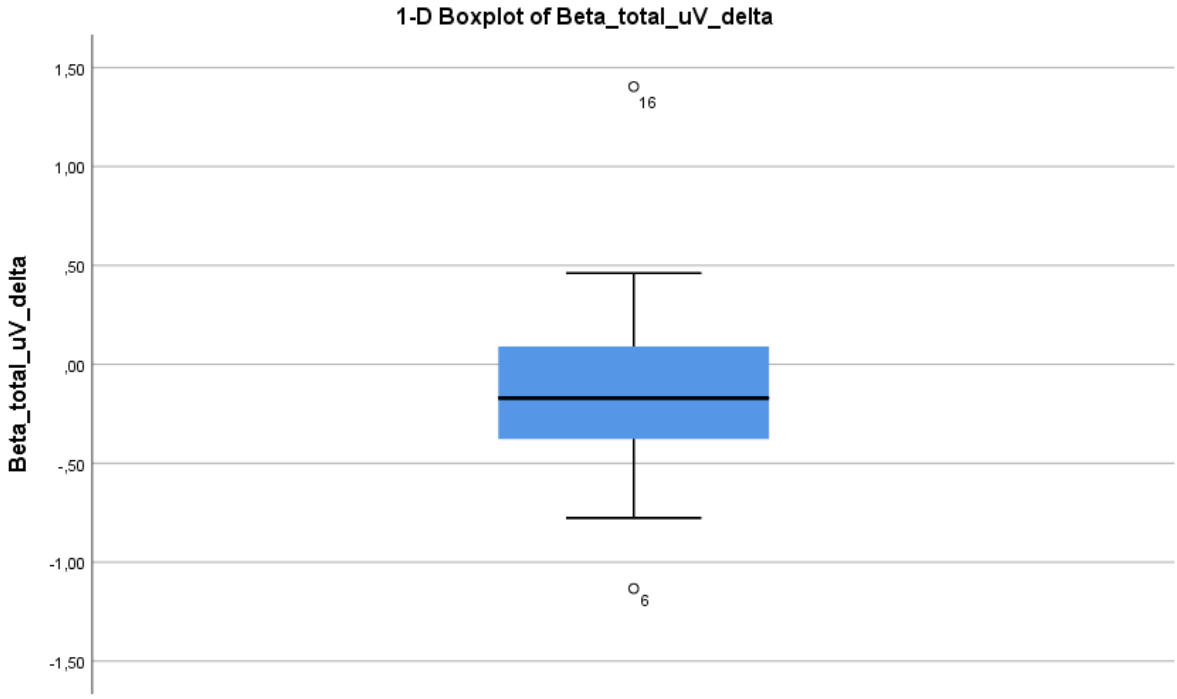
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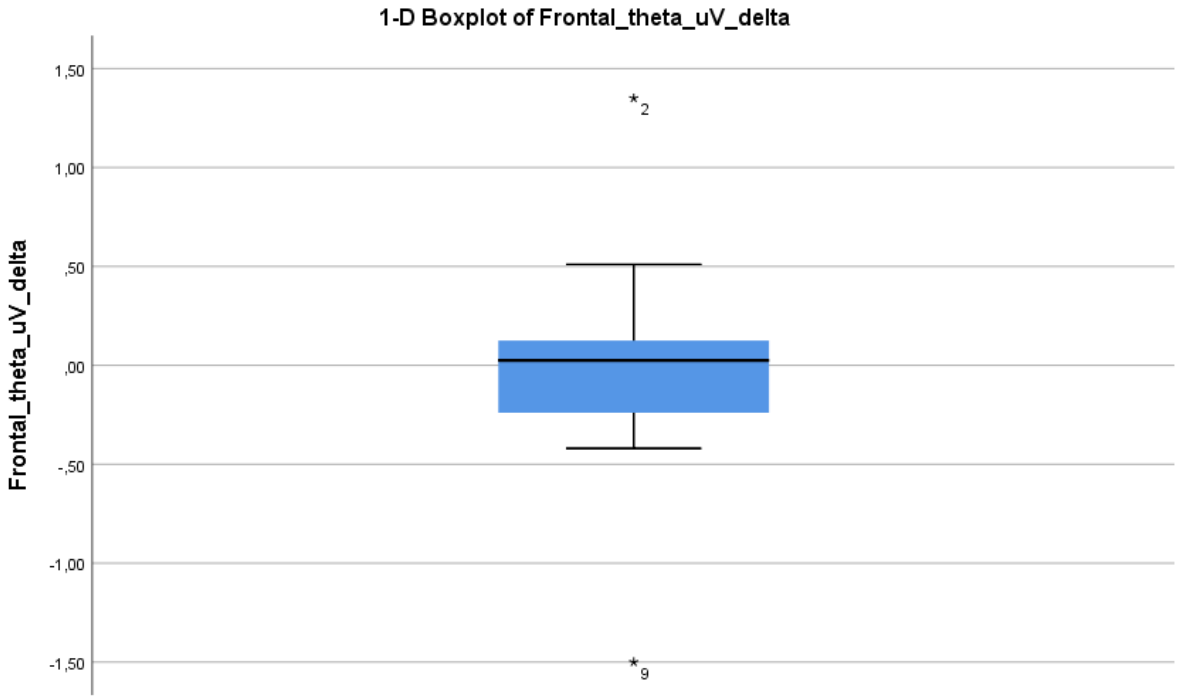
,00
-,50
-1,00
-1,50
16
6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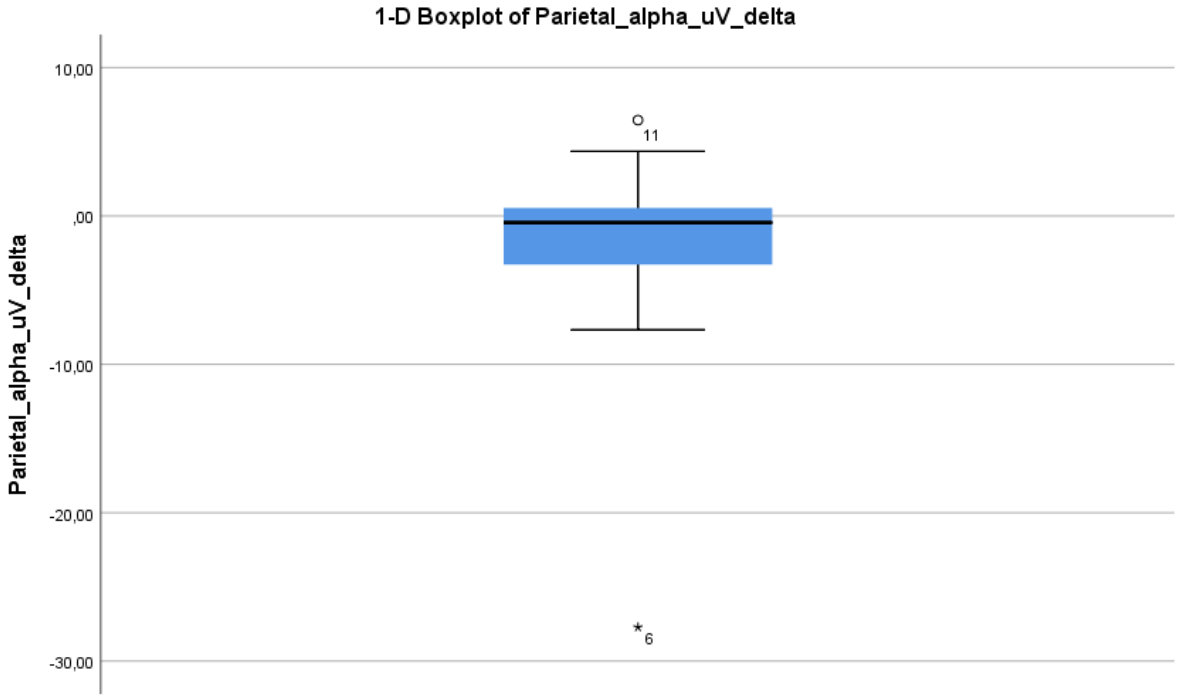
,50
,00
-,50
-1,00
-1,50
2
9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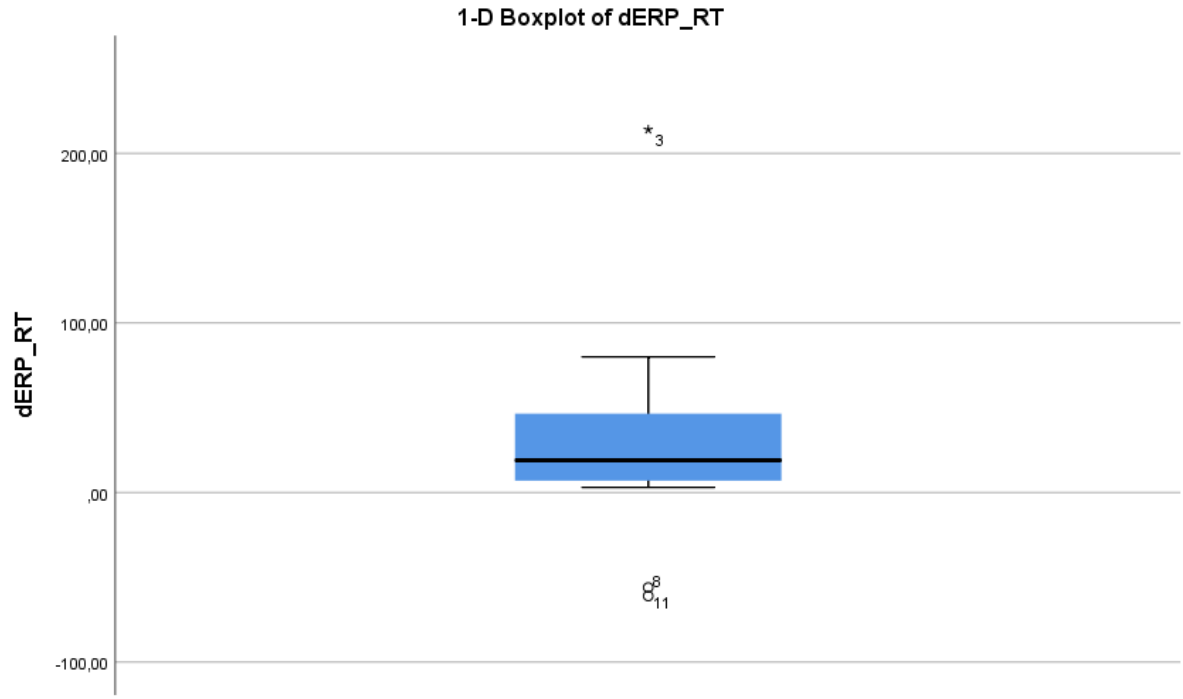
,00
-10,00
-20,00
-30,00
11
6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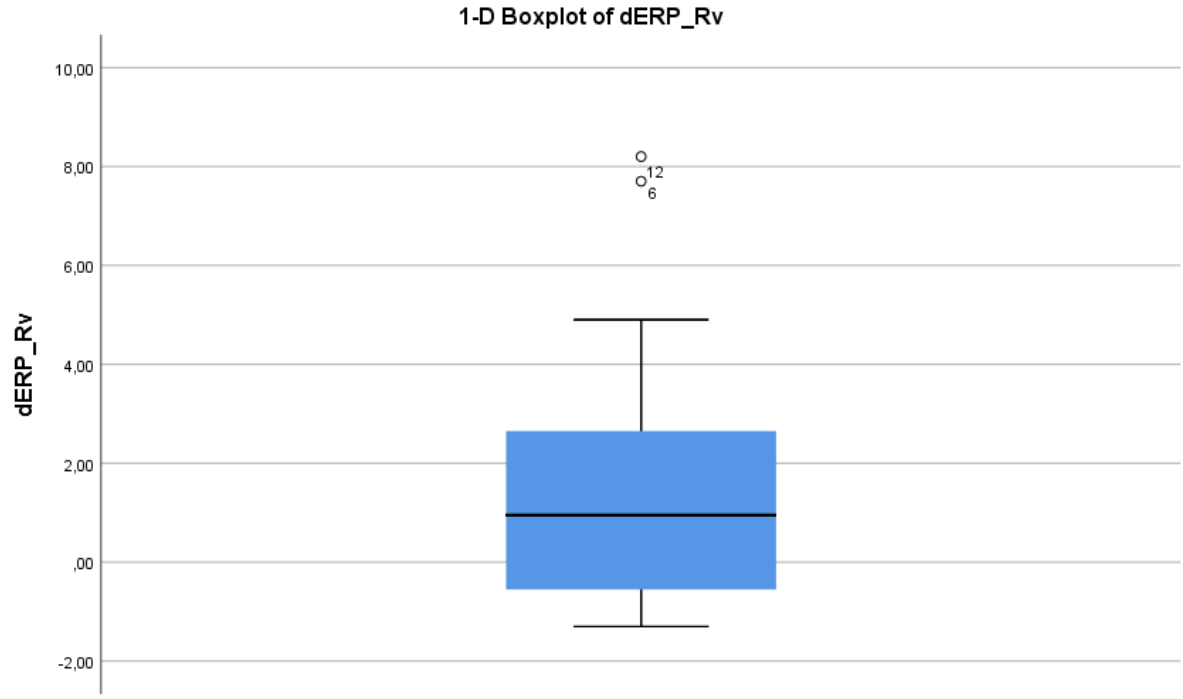
,00
-100,00
3
8
11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dERP_Rv
10,00
8,00
6,00
4,00
2,00
,00
-2,00
12
6

Appendix G

Table G:

Shapiro-Wilk tests of normality for selected variable difference-scores (N=16)

Variable	*W*	*df*	*p-level*
VAS: Total	.90	16	.072
VAS: pain	.92	16	.172
VAS: fatigue	.88	16	.037
VAS: fibrofog	.94	16	.368
FIQ	.92	16	.158
ACR: WPI	.93	16	.235
ACR: SS-score	.90	16	.070
RT	.84	16	.011
RT var	.85	16	.011
Theta-F	.89	16	.049
Alpha-P	.73	16	.000
Beta-Total	.90	16	.094

Note. VAS, Visual Analogue Scale; FIQ, Fibromyalgia Impact Questionnaire; ACR, American College of Rheumatology; WPI, Widespread Pain Index; SS, Symptom Severity; RT, Reaction Time; var, Variability; -F, Frontal; -P, Parietal

Appendix H

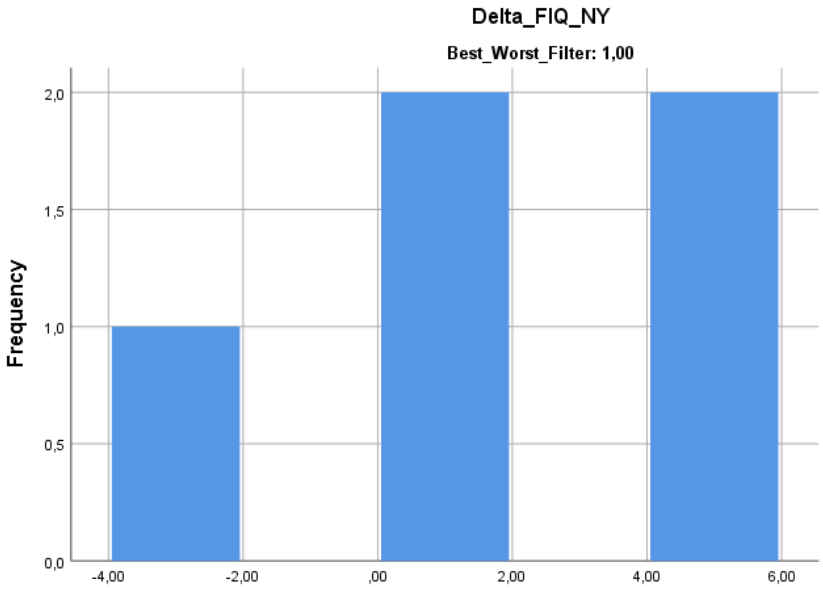
Table H:

Skewness and kurtosis values for selected variables difference-scores (N=16)

Variable	*Skewness*	*Kurtosis*
VAS: Total	-0.23	-1.54
VAS: pain	-0.60	-.075
VAS: fatigue	-0.17	-1.76
VAS: fibrofog	-0.55	-0.39
FIQ	0.94	1.38
ACR: WPI	0.70	1.72
ACR: SS-score	-0.10	-0.34
RT	1.54	4.82
RT var	1.27	0.82
Theta-F	-0.20	3.84
Alpha-P	-2.55	8.31
Beta-Total	1.11	3.50

Note. VAS, Visual Analogue Scale; FIQ, Fibromyalgia Impact Questionnaire; ACR, American College of Rheumatology; WPI, Widespread Pain Index; SS, Symptom Severity; RT, Reaction Time; var, Variability; -F, Frontal; -P, Parietal

Appendix I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0,0
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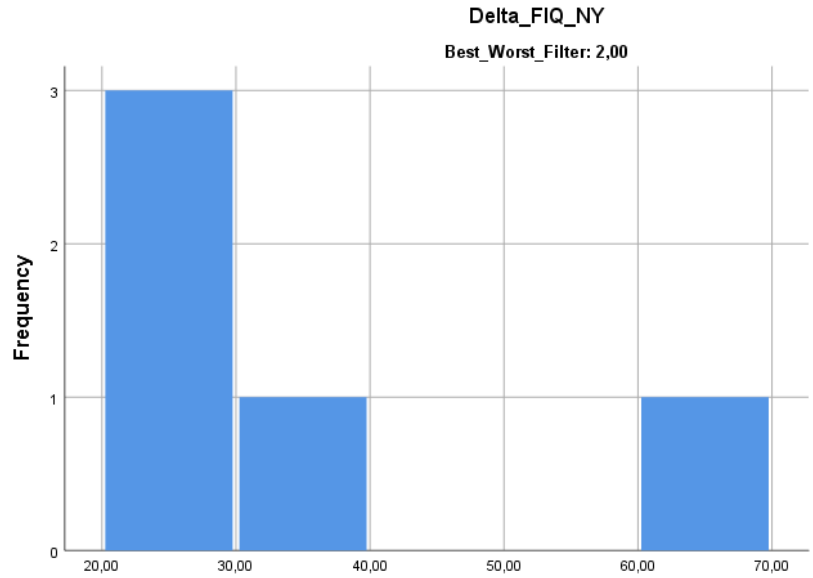
-2,00
,00
2,00
4,00
6,00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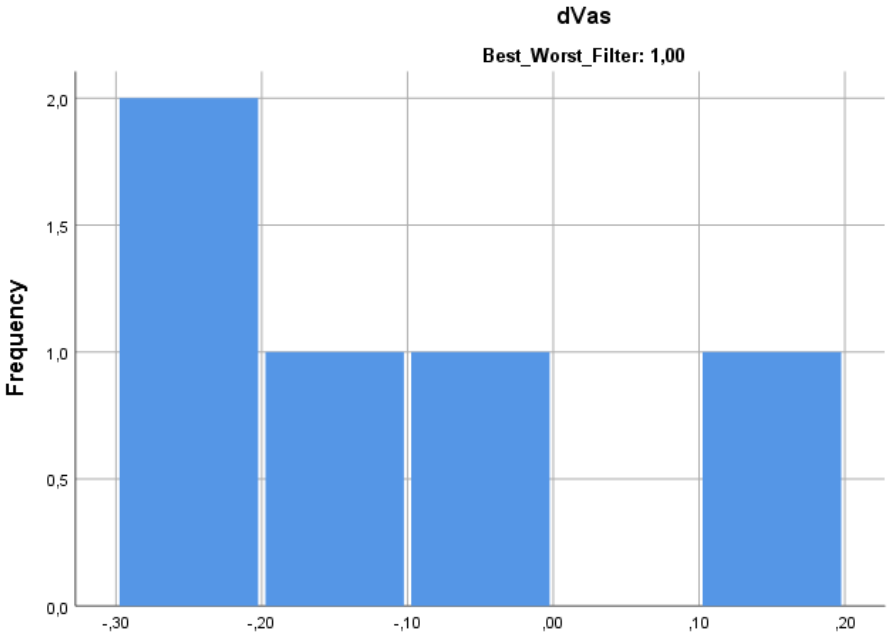
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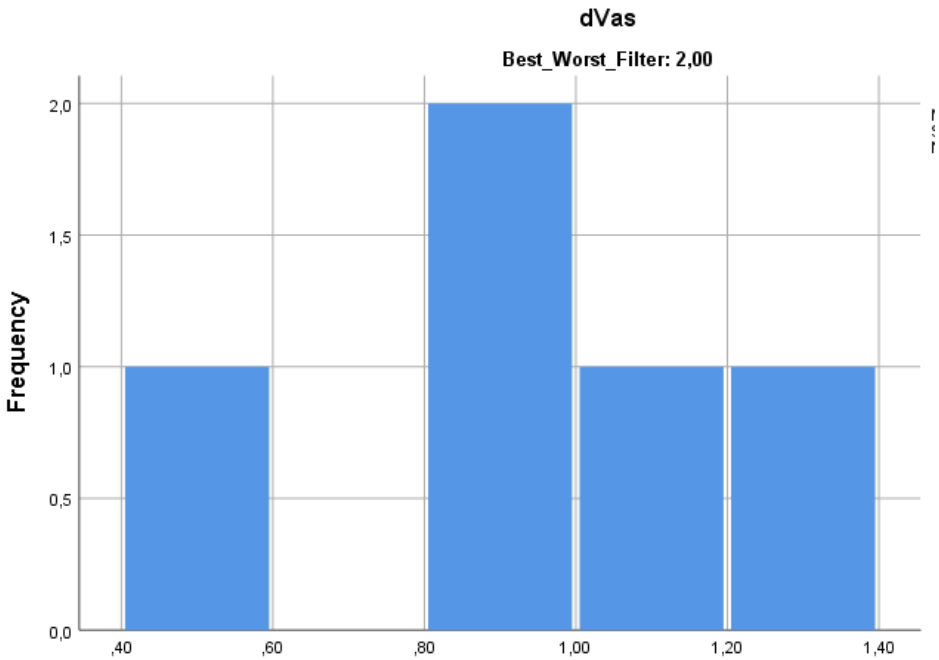
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Kunnskap for en bedre verden