Preface

When I started my studies in clinical psychology at NTNU I did not know exactly what area of psychology I wanted to work in when I was done, but I repeatedly (and quite loudly) swore that child psychology was one of the two areas I would never in a million years even consider. The second was neural psychology and anything remotely associated with biology and the brain. I was quite adamant in my conviction until the mandatory biology-term. During this term we had a course with a mandatory lab exercise with a non-medical treatment method called neurofeedback, which sounded intriguing enough that I volunteered to be a participant. The use of the neurofeedback treatment necessitated a continuous performance test (the very same one as described in this thesis) during an EEG recording. After this test I was allowed to examine the recording of my own brain's activity, with a very patient professor by my side explaining what I was seeing and how my brain worked. From that moment on, I was hooked. The brain and it's many intricacies challenged me enough that I would gladly use most of my extra hours outside of mandatory school activities to read and immerse myself into the available literature. The more I read, the more I felt like I understood human nature and mental conditions in a way I had never been able to before. This, coupled with many hours of discussion with the one who introduced me to the EEG and qEEG, increased my understanding exponentially, and I felt like this was it. This is where I belong. This ever-growing area of research and understanding of the human mind is what I want to continue working with for the rest of my career. Therefore, when I got asked if I wanted to do my main thesis in the lab, there was no need to deliberate my answer, as it was a natural and resounding "yes". As I believe the qEEG is a valuable tool to be used in differential diagnostics it felt natural to investigate hard-to-diagnose conditions of unclear origins as the hope was that I would be able to uncover something that could help the ones afflicted to, if not get better, then at least to get the right diagnosis. This was the start of a journey that has helped me grow as a future psychologist, as well as a person.

Acknowledgements

I would like to thank the person who introduced me to this new world of possibilities, who later on became my supervisor: Stig Hollup. You have showed me a path I did not know I was seeking. I would also like to thank Jan Brunner for giving me the idea to include a second patient group with similar symptomatology into the study. It made for more work, but it was worth it. Additionally, I would like to thank Martin Rasmussen and Kyrre Svarva for taking their time to discuss statistics with me and to give me new understanding and insight into the world of numbers and mathematics, as well as alleviating my concerns regarding methodological choices. And last but not least, my friends and family. You have my sincerest gratitude for your patience with me and for all of your support during this last year. You gave me space when I needed it, all the while looking carefully over my shoulder to make sure I was alright and still breathing. I know I have not been the easiest person to deal with during this period, but I want you to know that I could not have done it without you. It may not always have seemed like it, but your concerns, support and endless patience and understanding made this crazy year possible.

Abstract

Chronic pain and fatigue are two debilitating conditions causing great difficulties in everyday life for the ones afflicted, as well as challenges for mental health professionals. Both conditions are of unknown origin and are difficult to correctly diagnose because of a high degree of symptom overlap, and comorbidities contributing to further complications. Research points towards a possible mechanism of central sensitization underlying both conditions. Indications of such a mechanism should be reflected in the neural activity of the brain, functionally described through ERPs. The aim of this thesis was to investigate the EEG-recordings of a group of patients with chronic pain diagnoses and a group of patients with chronic fatigue diagnoses with each other, as well as compare both groups to a healthy control group to investigate whether there were any differential markers to be found with qEEG. A MANOVA-analysis detected significant differences between these three groups, and a follow-up discriminant analysis revealed that there were two dimensions the groups differed along when combinations of the ERP-components were considered. Along one dimension both patient groups were discriminated from the healthy control group, while the pain group was discriminated from both the healthy control group and the fatigue patient group along another dimension. A Bonferroni-correction resulted in statistical non-significant differences between the groups when comparing single components. However, as some of the components were strongly significant before such corrections were made the results warrant further studies investigating these components. Limitations of this study are discussed.

Contents

Introduction

Central sensitivity and sensitization

There seems to be several different groups of disorders with overlapping symptomatology and with no definitive etiology or explanation for the perceived distress the diagnosed patients experience, including chronic pain syndromes (CPS) and chronic fatigue syndrome (CFS/ME). There seems to be an emerging perspective that the reason for the overlapping clinical features might be because of a shared mechanism of central sensitization underlying these previously "unexplained" syndromes (M. B. Yunus, 2012; Muhammad B. Yunus, 2009).

In general, the sensitization phenomenon is described as an amplified reactivity to stimuli (both sensory and interoceptive stimuli) as well as an amplified reactivity to continual cognitive processes and functioning, and cognitive emotional processes (Eriksen & Ursin, 2004). Central sensitivity is a general phenomenon of sensitization of the central nervous system, but to generate the key symptoms often associated with chronic pain there is a great deal of evidence pointing towards a specific sensitization within the descending pain modulatory network in the brain stem (Tracey & Mantyh, 2007). A possible imbalance of inhibitory and excitatory mechanisms in either the descending inhibitory (Jensen et al., 2009) or facilitatory system might generate or at least moderate the abnormal sensation of pain in chronic pain patients.

Following a physical injury, one often experiences hyperalgesia and allodynia with an after-stimulus of unpleasant pain in the region of injury as the nociceptors expand their receptive fields, and display a prolonged electrophysiological discharge after a stimulus (Kindler, Bennett, & Jones, 2011; Meeus & Nijs, 2007). These characteristics are normal after an acute injury, but after a prolonged period of time, the central nervous system becomes structurally "rewired" to this altered activity of pain transmission (Dickenson, 2007; Woolf & Mannion, 1999; Woolf & Salter, 2000). When these characteristics of pain become wired into the default neural signature of the central nervous system, the system has become chronically sensitized. This is called central sensitivity and is a common denominator of hypersensitivity for different diagnoses characterized by chronic pain (Banic et al., 2004; Coffin, Bouhassira, Sabate, Barbe, & Jian, 2004; Nielsen & Henriksson, 2007). The

prolonged and persistent input of stimuli and consequent chronic activation of nociceptive fibers after an injury could potentially result in central sensitization and thus enhanced pain-related neural activity (Kindler et al., 2011; Meeus & Nijs, 2007; Porreca, Ossipov, & Gebhart, 2002).

A consequence of an acute injury might be a loss of interneurons. The possibility of the consequent constant firing of the disinhibited dorsal horn neurons has been postulated to lower the threshold for neurons to fire in response to subsequent stimuli (Woolf & Mannion, 1999; Woolf & Salter, 2000), as nociceptive disinhibition is a component of the experience of chronic pain (Montoya et al., 2006). Sensitization of a network of neurons and a reduced inhibitory subsystem thus seems to result in an enhanced sensitivity for pain, or a "pathological process of dysregulated nociception" (Kindler et al., 2011). Psychological and emotional factors may also contribute to the neuronal hypersensitivity and the increased experience of pain through deficient modulation of the processing of nonpainful stimuli (Dickenson, 2007; Gracely et al., 2004; Montoya et al., 2006). Disruption of the integration of inputs via bottom-up and top-down mechanisms might thus result in an imbalance of activity represented by an increased sensitivity for pain.

What is chronic pain and chronic pain syndrome?

Nociception is the detection of tissue damage by specialized receptors called nociceptors, attached to Aδ- and C-fibres, which conducts the neuronal signal from the periphery to the central nervous system through the dorsal root ganglion. Pain can occur without objective tissue damage, which is the main challenge when treating chronic pain cases – apart from the dealing with the actual pain itself (Dickenson, 2007). Prolonged exposure to neurotransmitters released when the nociceptors are stimulated, with subsequent changes to the structure and function of synapses, has been suggested to be one of the reasons for sensitization of the central nervous system (Woolf & Mannion, 1999; Woolf & Salter, 2000). Consequently, the intensity of the pain becomes unrelated to the original injury itself or the injured region. Additionally, the intensity and persistence of the pain is experienced as out of proportion to the nature of the original injury (Banic et al., 2004; Porreca et al., 2002; Woolf & Mannion, 1999). Factors of an affective and of a cognitive nature are also thought to

contribute to the development and maintenance of chronic pain (Baliki et al., 2006; Gebhart, 2004; Zusman, 2002) and a dysfunctional endogenous pain management system has also been postulated as a possible explanation (Jensen et al., 2009). The development of altered pain processing in disorders characterized by reduced thresholds for pain and enhanced pain perception seems to be established as a unifying trait for chronic pain disorders (Kindler et al., 2011). However, as other factors modify the perception of pain it is a highly subjective perception and experience, which makes the assessment and diagnosis of these syndromes challenging and as such there is a definitive need for objective diagnostic tools. What seems certain, however, is that the different influencing factors on pain perception and experience are mediated by the central nervous system, including the neuronal activity in the spinal cord (Tracey & Mantyh, 2007).

The International Association for the Study of Pain has defined pain as: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" **(**Merskey & Bogduk, 1994:210**)**. Chronic pain is defined as a persistent ongoing pain, often starting with an acute injury or illness, or during or after some infections, lasting longer than the expected time for the injury to heal, and not necessarily with any obvious relationship between the degree of pain and the extent of tissue damage (Bennett, 1999). The distinction between acute and chronic pain is often arbitrary and may range from less than one month to more than six months. Often three months is used as a point of distinction when dealing with non-malignant pain, but in research six months is often preferred (Merskey & Bogduk, 1994). Common symptoms of chronic pain include hyperalgesia (increased pain response to normally noxious stimuli) and allodynia (sensation of pain elicited by stimuli not normally painful) (Woolf & Mannion, 1999). The term "chronic pain syndromes" is a constellation of poorly understood syndromes ("a group of symptoms which consistently occur together" – Oxford English Dictionary) characterized by either localized or diffuse pain, or both, and difficult to treat with traditional medical models. These syndromes include, but are not limited to, fibromyalgia syndrome (Nielsen & Henriksson, 2007), whiplash injury (Banic et al., 2004), irritable bowel syndrome (Coffin et al., 2004), phantom pain (Flor, Nikolajsen, & Staehelin Jensen, 2006), temporomandibular joint disorder, chronic low back pain and headaches (Kindler et al., 2011), all with considerable symptom overlap (Aaron

& Buchwald, 2001). As the classification criteria often are unspecific, and most of the underlying pathophysiological mechanisms are unknown, these conditions are defined as syndromes of chronic pain, if not without some controversy surrounding definitions and distinctions between the different syndromes (Carette, 1996; Merskey & Bogduk, 1994).

With an unclear aetiology and poor response to therapy and treatment, chronic pain syndromes are a major challenge for health-care personnel as the symptoms are difficult to explain, and are often associated with repeated visits in general medical practice. A poor response to therapy has resulted in a stigmatization of chronic pain patients, as this often results in assumptions of malingering or the use of mental illnesses as an explanation for the constant pain. In addition, chronic pain patients become additionally burdened by a seemingly never-ending back-and-forth between mental health personnel and medical doctors, often resulting in long-term sickness compensation and an inability to work, as well as dealing with associated problems like comorbid anxiety and depression (Eriksen & Ursin, 2004; Meeus & Nijs, 2007) that doesn't necessarily improve after treatment (Thomsen, Sørensen, Sjøgren, & Eriksen, 2002).

In Europe, the prevalence for chronic pain is approximately 20% for the adult population (van Hecke, Torrance, & Smith, 2013) with a point prevalence of 17,1% of general chronic pain during the past month (Reid et al., 2011), where a lower socio-economic status, older age and being female are associated with higher prevalence. Anxiety and depression are associated with different chronic pain states and a poorer prognosis. The directionality and relationship between these illnesses are unclear, but anxiety and depression seems to augment the pain experience and become a part of the chronic pain condition. Other risk factors include sleep problems and an accumulation of stressful life events. There also seems to be evidence of a combination of genetic effects that, to an extent, determines one's sensitivity to pain and the potential development and following degree of severity of chronic pain. To date, however, there are no consistent findings regarding risk factors (van Hecke et al., 2013).

Pain neuromatrix

The pain neuromatrix (connected neuronal networks activated in a close temporal manner) consists of an extensive cortical network consistently reported to be activated by pain and related to varying degrees of pain sensation in clinical and healthy populations. This neuromatrix traditionally includes the thalamus, the somatosensory and cingulate areas, as well as prefrontal cortex, parietal and insular areas (Bennett, 1999; Gracely et al., 2004; Legrain, Iannetti, Plaghki, & Mouraux, 2011; Peyron, Laurent, & García-Larrea, 2000; Price, 2000; Rainville, 2002). Activity in these areas has been shown to be associated with differences in the reports of pain level for patient groups compared to healthy control subjects (Bennett, 1999; Gracely, Petzke, Wolf, & Clauw, 2002), and the medial prefrontal cortex (mPFC), rostral anterior cingulate has shown increased activity during sustained high pain (Baliki et al., 2006).

However, studies are not always in agreement with each other in regards to which areas should be included, as well as disagreements about the pain matrix actually constituting the neural representation of pain in the brain. Some studies emphasize that the insula is the crucial structure for the experience of pain (Isnard, Magnin, Jung, Mauguiere, & Garcia-Larrea, 2011); that the ACC may be related to processing the attentional, evaluative and affective components of pain, as well as coordinating input between different cortical areas (Gracely et al., 2004; Legrain et al., 2011; Price, 2000); somatosensory cortex might be related to the localization of the stimuli on the body, instead of the pain per se (like a multimodal body map) or related to coordination of perception and action (Legrain et al., 2011), or also related motor/behavioural functions (Price, 2000). There seems to be evidence that the activity observed in the "pain neuromatrix" is, in fact, possible to evoke by both non-nociceptive and non-painful stimuli. The magnitude of elicited brain responses and other physiological measures seems strongly influenced by other factors not related to the intensity of the nociceptive stimulus, like attention, contextual information and the predictability of stimuli. It also seems that the operculo-insular and the cingulate areas respond to the novelty aspects of stimuli, independent of the sensory modality carrying the information. (Legrain et al., 2011). In addition, the activation pattern of the brain in response to painful stimulation overlaps in part with activity patterns for attention networks (Gracely et al., 2004). This makes sense, as pain is intrinsically salient, and captures one's attention quite thoroughly, and it has been shown that

distraction from the pain attenuates activation in areas associated with the pain system (Kucyi & Davis, 2015).

It seems thus that the sensation of pain and observed brain activity is not exclusively tied to the experience of the painful stimulus, but also to orienting (Legrain et al., 2011), future and emotional appraisal of the stimuli (Gracely et al., 2004; Price, 2000), memory encoding and recall of the pain sensation (Yi & Zhang, 2011) and anticipation of and attention to the stimuli (Gracely et al., 2004; Zusman, 2002). Some of the observed neural activity might also be a reflection of the top-down/bottom-up interaction of the inhibitory or facilitatory mechanisms related to the descending modulation of nociceptive processing (Gebhart, 2004; Porreca et al., 2002). Current findings regarding neural responses and mechanisms of pain are thus equivocal as some of the responses are not specific for painful stimuli, and different cortical and subcortical structures appears to be involved and responsible for different features and dimensions of the pain experience as other cognitive and behavioural mechanisms also seems to be involved (Bennett, 1999; Price, 2000).

It is as such argued that the interaction and patterned activity between these areas are important for the emergence of the pain experience in its entirety, including emotional, cognitive and contextual factors (Tracey & Mantyh, 2007). As will be further explained in a later section, the temporal sequence of interaction between the relevant cerebral structures during processing is just as important as the traditional focus on topographic cortical activation. There are different degrees of cerebral receptiveness to stimuli dependent on the interplay between spatiotemporal activation and different constellations of interactions in the brain. This may be a necessity for the integration of information from different brain regions. A part of this modulation is due to intrinsic spontaneous fluctuations, and it has been shown that the neural activity preceding a painful stimulus influences the following pain response (Kucyi & Davis, 2015). The fluctuating baseline state of the cerebral networks determine what level and intensity of pain will be perceived, and whether it will be perceived as painful or not (dependent of the temporal match or mismatch between the nociceptive signal and the fluctuating network). In other words, the balance and interaction between bottom-up and top-down processing could be viewed as a determinant for pain perception.

Chronic fatigue syndrome (CFS)

An illness which shares symptoms with chronic pain syndrome and similar challenges regarding credibility from the mental health profession is chronic fatigue syndrome (CFS), a condition associated with significant dysfunction and disability in daily life (Stubhaug, 2008). Patients with CFS share the heterogeneity of chronic pain syndrome, with a reported higher level of subjective health complaints than a general patient population (Stubhaug, Tveito, Eriksen, & Ursin, 2005), but with a primary emphasis on fatigue to a severely debilitating degree lasting for at least six months. Differences and difficulties regarding the definition of CFS complicates prevalence estimates greatly, as well as disputes regarding etiology and the heterogeneity of the diagnosed population (Tiersky, Johnson, Lange, Natelson, & DeLuca, 1997). CFS and ME is often used interchangeably in research, often referred to as CFS/ME, but this case definition hasn't been acknowledged for clinical use (Stubhaug, 2008). In the International CD-10 Chronic fatigue syndrome is given the same code as benign myalgic encephalomyelitis, found under Postviral fatigue syndrome (G 93.3) (World Health Organization, 1993), however earlier versions of the ICD-10 differentiated between Chronic Fatigue Syndrome NOS (Not Otherwise Specified) and benign myalgic encephalomyelitis both by name and with different codes. Based on the heterogeneity of the illness, it is thought that different pathophysiological disturbances manifest with similar symptoms, as it seems unlikely that it is caused and maintained by a single cause. However, a majority of patients diagnosed with CFS by practitioners seem to have been exposed to some kind of virus infections premorbidly, despite the lack of consistent results regarding immune and endocrine function (Afari & Buchwald, 2003). The Norwegian Directorate of Health has chosen to use the term CFS/ME in official documents as a compromise (Helsedirektoratet, 2014), and will as such be the preferred term in this thesis except for when discussing specific diagnostic criteria for CFS.

Fatigue is often simply referred to as "being tired" but fatigue seems to be quite comorbidly prevalent in some capacity or other in primary care and hospitals, disregarding the chronicity of the fatigue itself. There seems to be an arbitrary distinction between "common" fatigue, chronic fatigue and chronic fatigue syndrome, and as such the prevalence for chronic fatigue syndrome ranges from 0.007% to 2.6% in community and primary care settings, dependent upon which criteria is being used.

If limited to the most widely used CDC-1994 definition (Fukuda et al., 1994), the prevalence ranges from 0.2% to 2.6% according to studies from the United Kingdoms and USA (Ranjith, 2005). In the general population in Europe, Australia and USA the prevalence of CFS/ME seems to be estimated between 0.2% and 0.7%, with an increase to 2.5% when including psychiatric comorbidity (Stubhaug, 2008). Epidemiologically, there seems to be a higher prevalence rate of CFS/ME found in women and in lower socio-economic classes (Ranjith, 2005).

What characterizes this syndrome is fatigue frequently accompanied by somatic and neuropsychological symptoms that are not resolved by rest or sleep, and is further exacerbated by physical activity. These are included as symptom criteria for CFS, as guidelines delineated by Fukuda and colleagues (1994) for research and clinical diagnoses. A major symptom is unexplained persistent or relapsing fatigue of new or definite onset that results in a substantial reduction of previous levels of functioning. Minor symptoms include myalgia, sore throat, sleep disturbances, neuropsychologic complaints, headaches of a new type, arthralgia, tender lymph nodes and postexertional fatigue. The major criteria has to be fulfilled along with four minor symptoms, all of which must have been recurring or persisted during at least 6 months (but not predating the fatigue) to receive the diagnosis of CFS. However, receiving the diagnosis is mainly done through exclusion of other etiologic possibilities that could explain the symptoms. Cognitive disturbances like impairments in concentration and short-term memory are also reported (Fukuda et al., 1994). This operationalized definition is the most widely used in both research and clinical practice, but as the minor symptoms include manifestations of pain the overlap found between CFS and CPS complicates differential diagnostics. Especially as there is a high degree of comorbidity of both somatic pain disorders and psychiatric disorders (like depression, anxiety, if to a lesser degree, and personality disorders) in CFS/ME (Stubhaug, 2008).

It seems that the most common brain areas of interest in CFS/ME are the frontal cortex (hypometabolism and reduced activation compared with controls in frontal lobes, including the ACC), lateral temporal cortex, and basal ganglia (Johnson & DeLuca, 2005). There also seems to be a more diffuse and widespread activation in prefrontal, anterior cingulate and inferior parietal regions during challenging cognitive

tasks, which might indicate a compensatory mechanism through greater recruitment-needs in order to perform such tasks. One of the most consistent findings seems to be abnormalities in cerebral white matter. But the structural and functional abnormalities are also found in healthy controls and in patients with depression, and is as such considered inconclusive (Afari & Buchwald, 2003).

There seems to be indications of abnormalities in both sympathetic and parasympathetic systems in subjects with CFS/ME. However, even if stress and a dysfunctional HPA-axis has been proposed and investigated in relation to chronic fatigue syndrome, there seems to be no evidence of a specific HPA-axis dysfunction uniform across patients. Almost all of the findings pertaining to changes in the HPA-axis in response to different experimental challenges seem to be in the direction of diminished cortisol and ACTH responses, and these could just as easily be reflective of different corollaries of the condition (Sisto et al., 1995; Tiersky et al., 1997; Cleare, 2003).

Understanding both the symptoms and the etiology of CFS/ME, as well as CPS, warrants an integration of mental and medical health professions, as both these illnesses seem to be complex disturbances that touch upon both domains, and is confounded by the difficulty of separating them from each other and additional illnesses. High degrees of comorbidity and disagreements regarding causality complicate the matter further as the criteria for the diagnosis is quite vague, and at times the distinctions between CFS/ME and other similar diagnoses are arbitrary. As CFS/ME is a severe illness plagued by a wide spectrum of severe and debilitating symptoms, in addition to comorbidity as a confounding cause or consequence, makes clinical diagnosis and comparison across studies difficult (Stubhaug, 2008). A step in this direction would be to find definitive biomarkers that differ between these patient groups and other disorders with overlapping symptoms without the diagnosis of CFS/ME, as simple comparisons with healthy controls are inadequate for specificity (Fukuda et al., 1994).

There is a considerably greater degree of research and theories concerning the processing and developing of chronic pain conditions than there are for CFS/ME. As a consequence of this, the theories and information relevant for this thesis has been

given appropriate space. As genetics and the immune system is beyond the scope of this thesis, the introductory segment for CFS/ME is considerably shorter than the one regarding chronic pain.

How neural signals work

The signalling between neurons is not simply about the propagation of action potentials through axons, where one only needs enough excitatory drive for an action potential to be propagated from one neuron to another. The temporal timing between the activity of the pyramidal neurons and the activity of inhibitory interneurons is crucial for successful signal propagation. The constant influx and outflux of ions across the membrane of a pyramidal cell gives rise to a fluctuating charge often illustrated as a sine wave, with peaks representative of particular points in time when the neuron is in a probabilistic state of higher excitability and troughs as times were there is less excitability and consequently less probability of signal propagation. If action potential(s) arrive at the pyramidal neuron at the exact time of a peak, the signal will continue to be propagated along to other neurons downstream. If the presynaptic action potential(s) arrive at the time of a trough, the probability of the signal being propagated further reduces dramatically. If, however, the signal is powerful enough, it might overcome the less excitable baseline of the pyramidal neuron and "force" its signal along. These rhythms can be entrained to both endogenous and exogenous factors, and interneurons play a crucial part as regulators of neural rhythms as their inhibitory functions contribute to determine the firing probability of neurons (Buzsaki, 2006). When the sine rhythm of several thousands of neurons are synchronized it enables communication between those networks that are on, in a sense, the same "wavelength". This means that the firing patterns of specific neurons are phase-locked to the observed oscillations of distinct frequencies across different brain areas. As different rhythms on different frequencies are to a greater degree phase-locked to similar (or functionally complementary) rhythms, this might indicate that they provide a mechanism for temporal segregation of the propagation of information from potentially interfering sources (Colgin et al., 2009). The different rhythms might thus function as facilitative (and necessary) for signal propagation, while simultaneously retaining an inhibitory function if the neural signal is "off-rhythm". The different phases of neural firing seems thus to carry different temporal codes. In a matter of top-down versus bottom-up processing, this is then explained by

the bottom-up signals arriving at a point in time when the brains rhythms are in a more excitable point in a cycle and are thus propagated further, which often is the case as external stimuli is capable of entraining the rhythms in a fashion where the possibility of precise timing is greatly improved. However, if the firing patterns (the temporal codes) of the neurons are, for whatever reason, inflexible and phase-locked into a specific top-down rhythm, the bottom-up signals are unable to time their signals to a favourable time point for propagation, and is consequently inhibited and denied further impact on the neural communication (Fries, 2005).

Pain connectome

What has traditionally been perceived as the structural and spatially confined seat of pain in the brain – the "pain neuromatrix" – instead seems to be an inter-connected, dynamic representation of the entire experience of the pain sensation. This includes other cognitive processes not tied to the pain itself, but rather to the context and the characteristics surrounding the stimuli, as well as pain-unrelated processes. The neural communication across the network of the brain is not a static point-to-point, node-based communication network, but rather a dynamic, constantly fluctuating network where the spatiotemporal aspects of neural activity (organized patterns of action potentials time-locked to the neural rhythms) are fundamental for the integration of perception (Hutchison et al., 2013). Specific spontaneous fluctuations in brain activity have been found associated with different encodings of subjective pain intensity (Baliki et al., 2006) Pain has thus not a distinct "pain area", but more of a spatiotemporal neural signature – termed the pain connectome. It is the timing of activation of neural networks that predict how stimuli are perceived and integrated into our consciousness, as well as the trial-to-trial variations in prestimulus brain states (Kucyi & Davis, 2015).

Kucyi & Davis propose three networks as crucial components of the pain connectome that contribute to different aspects of the dynamics of pain perception. These networks are the salience network, the default mode network, and the antinociceptive (descending pain modulatory) system. The salience network is thought to scan or "track the degree to which external stimuli intrinsically capture attention". The default mode network is active when one's attention and thoughts are not related to the present sensory world, and as such has the opposite function of the salience network.

We will return to the default mode network in more detail later. The antinociceptive system is associated with pain modulation, and is characterized by an increased functional connectivity between the default mode network and PAG during mind-wandering away from pain. PAG is rich in opiates and is suggested to be heavily involved with the attentional modulation of pain. It is thus proposed that dynamic communication between the antinociceptive system and the default mode network are at least partly responsible for the spontaneous fluctuations observed in attention to pain (Kucyi & Davis, 2015). The descending modulatory pain system can also enhance pain, so that the dynamic connectivity between PAG and DMN could, when dysfunctional, be increased and instead lead to increased levels of pain perception (Tracey & Mantyh, 2007).

Regarding the default mode network, the antinociceptive system and the salience network, there has been identified structural abnormalities in regions of the three networks/systems in multiple populations characterized by chronic pain (Kucyi & Davis, 2015). The spontaneous fluctuation activity observed during rest is argued to possibly be a reflection of the processes operating below our awareness – traditionally thought of as our unconsciousness – as it continually scans our surrounding environment and situational contexts and processes information not salient enough to grab our conscious attention. This activity within different functional-anatomic networks could reflect a constant consolidation of information that coordinates activity between neuronal ensembles and anticipates future neural activity and information processing (Buckner & Vincent, 2007).

The exact spatiotemporal signature of the brain network communications that constitutes the dynamic pain connectome are not yet precisely delineated, and it is thus warranted more research into describing exactly the mechanisms of the pain connectome.

Default Mode Network

The Default Mode Network was proposed by Raichle and colleagues (2001) as a baseline state of brain activity, an organized default state of decreased fluctuating cortical activity in the absence of task-related activity to the point of equilibrium between neuronal activity and metabolic requirements. In short, when resting, the

brain switches its activity to default processes that become suspended during task-conditions or otherwise actively engaged in cognitive goal-oriented processes. The default mode network was defined as the level of activity (the equilibrium between neuronal activity and metabolic requirements) in the brain during an eyes closed resting state. This means that when a subject is engaged in a specific task, activity in specific brain areas independent of the task-specific behaviour will be attenuated. The default mode network is thus suppressed in a goal directed state, and returns to baseline activity ("reactivates", if you will) when returning to the resting state, i.e. not engaged in cognitive task-processes (Kucyi & Davis, 2015). Following this observation, there has been an increased interest in regards to the default mode network, both relating to how one is able to measure this network, and most importantly what it actually does.

The regions often referred to as the default mode network includes the precuneus and the anterior and posterior cingulate cortex, the medial prefrontal cortex (mPFC), inferior and medial temporal lobes, parahippocampal gyrus, lateral parietal and cerebellar regions. Of these, Raichle and colleagues (2001) posited that the precuneus and posterior cingulate cortex is continuously "scanning" and gathering information about both the external and the internal world. The default mode system also includes multiple subsystems of the default mode network within specific neuro-anatomical systems, several of which encompasses sensory areas (Fox & Raichle, 2007), where at least three subsystems could be relevant in the experience of pain as there has been found abnormal and disrupted resting-state functional connectivity between areas within these networks in chronic pain patients. The mPFC has been shown to play a mediating role in pain intensity, with individual differences in pain perception correlating with the functional connectivity between mPFC and default mode network in chronic low back pain, and functional connectivity between mPFC and insula in multiple chronic pain conditions (Kucyi & Davis, 2015).

Functional connectivity is a term used for describing networks of brain regions with a high degree of dynamic synchronous activity with correlated, synchronous spontaneous fluctuations both within and between networks, which suggests coordinated activity (neuronal synchrony changes) during – and coordinated shifts between – different vigilance and cognitive states (Kucyi & Davis, 2015).

The observed spontaneous neuronal activity in the default network represents intrinsically generated neuronal activity in the brain, not attributable to specific inputs or outputs (Fox & Raichle, 2007). This kind of spontaneous temporal dynamics within and between networks seems to be found in many brain systems, as studies have identified an assembly of functionally connected cortical areas ("nodes") independent of the traditionally conceived default mode network, some with anticorrelated activity. The dynamic spontaneous activity is usually measured as correlations in slow (<0.1 Hz) spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal, as increases of neuronal activity increases the metabolic demand for glucose and oxygen, which is supplied by an increase in the cerebral blood flow to the active region of the brain. This activity has been shown to be both correlated within networks, as well as anticorrelated between networks in an amplification/attenuation dichotomy during engagement to and disengagement from a task, irrespective of visual fixation, or eyes opened or closed conditions. By obtaining the BOLD time course from a region of interest, one can correlate this signal with the time course of all other brain voxels to determine the temporal correlations between networks, and thus examine inter-regional correlations in neuronal variability (Fox & Raichle, 2007). Kucyi & Davis argue that this could reflect an increased adaptability/flexibility/efficiency of the networks, as they summarize findings that indicate less flexible communication and weaker connections between the antinociceptive system and the default mode network in individuals with difficulties with ignoring pain. The networks' high degrees of rigidity regarding their capabilities of adapting neural rhythms, and thus impede optimal inter-network communication, are thus postulated to be a characteristic of different disorders.

The character of the default mode network is more in-line with a network that "activates" (is anticorrelated with the task-activated network) during task-disengagement/rest and various aspects of self-referential processing when no external events demand attention (Fox et al., 2005; Fransson, 2005). Fluctuations in the default network might still be present during attention demanding tasks, if in a more attenuated capacity. This is postulated to be a reflection of our neuronal representation of the "self", as this default network is modulated, instead of being completely abolished, by task performance and is thus constantly active (Fransson, 2006). Disturbances in the correlation structure of spontaneous activity has been

reported for several pathological conditions and possibly to differentiate between healthy and patient populations (Fox & Raichle, 2007).

EEG

An approach to the study of mental disorders is the recording and examination of the brain's bioelectrical activity by either intracranial or extracranial methods. The EEG is such an extracranial approach by using electrodes placed on the subject's scalp to record the rapid fluctuations in brain activity with a temporal resolution of a few milliseconds (Otten & Rugg, 2005). As such, it is a non-invasive procedure highly sensitive to manipulation of an experimental context. The high temporal resolution makes it possible to record the electric fields created due to neural activity, and correlate activity patterns with different experimental conditions and manipulations. Because the electrodes used in EEG are separated from the signal source by head tissue like cerebrospinal fluid, skull and scalp, the spatial resolution is in reality quite poor (ranging from 10-20 mm) (A. K. Liu, Dale, & Belliveau, 2002) compared to the fMRI (2-4mm) (Yoo, Talos, Golby, Black, & Panych, 2004) and PET (~2mm)(Pichler, Wehrl, Kolb, & Judenhofer, 2008). This results from the conductivity, permittivity and membrane boundaries of the tissue that distorts the signal of the electrical fields summated on the scalp (Hutchison et al., 2013). Despite the poor spatial resolution of the EEG, its temporal resolution as near as instantaneous is only matched by the far more expensive and cumbersome magnetoencephalogram (MEG) that measures the magnetic fields in the brain. Combined with the ability to record simultaneous activities in all parts of the cortex and the flexibility and ease of use where the subjects does not have to be behaviourally confined to a rigid position (like with the fMRI or MEG), as well as its portability and low-cost, the EEG displays some unique advantages compared to it's contemporaries (Onton, Westerfield, Townsend, & Makeig, 2006).

The EEG signal is to a large degree a summation of multiple post-synaptic potentials of cortical neurons – IPSPs and EPSPs – generated synchronously and thus strong enough to be picked up through the tissue by the electrodes on the scalp. The PSPs create an active current density (the density of the bioelectrical field) with an assumed dipolar nature. The orientation of the neurons (perpendicular to the cortical surface)

and their neighbours might cancel out each others' observable local field activities if oriented unfavourably, unless there is the aforementioned local area synchrony, which enables local field potentials of sufficient strength to be detected by the electrodes on the scalp (Onton et al., 2006). The summation of neuronal activity in an area results in the poor spatial resolution, as the summation of multiple sources of activity has to occur for the signal to gain the necessary strength. Currently, there is no way to accurately separate these sources, to pinpoint a single source location and with certainty establish the number of sources. In addition, the number of signal sources is largely unknown. This is known as the inverse problem.

The inverse problem is best explained with an example. Imagine two cortical areas are synchronously active, but the areas are physically opposing each other – e.g. on opposite sides of a sulcus – so they might thus cancel each other's signals and their combined activity would not reach the electrodes on the scalp. If at the same time there was a third simultaneously active cortical area there would be no way to determine from the scalp data if the observed activity was evoked from the third source alone, from the shared activity of all three sources, or a number of different activity patterns and combinations with even more self-cancelling sources which summed activity match the recorded scalp activity of the assumed single third area (Onton et al., 2006). In short, the observed activity distribution of potentials and fields on the scalp can be explained by multiple different distributions and configurations. The inverse problem is then to figure out which of the signal generators is the correct one.

QEEG

A qEEG (Quantitative Electroencephalography) is a quantification of the raw EEG-recording, where the averaging of ERPs allows the aforementioned quantification and subsequent analysis of the EEG with more objectivity and specificity focused on the activity time-locked to the event under examination. The waveform of the ERP is made up of a time series where the neural activity reflected in scalp electrical fields is plotted over time in milliseconds. By averaging the event related brain activity, the dynamics that are consistently time-locked to an event will be possible to discern, and all other activity not time-locked to the same event will be cancelled by their cycle-

phases as part of the random "background noise". This is one of several methods to analyse brain activity (Handy, 2005).

The most common approach to analyse ERP data is by way of a temporal analysis, where the focus is on how the recorded waveforms vary of time and across conditions at the individual electrode sites. The amplitude and latency of the ERPs are quantified as a function of the specific experimental condition in the form of positive or negative deflections in the ERP waveform, and the scalp distribution is indicative of underlying neuroanatomical activity as it provides the pattern of voltage gradients of the component pattern over time (Friedman, Cycowicz, & Gaeta, 2001). When analysing and interpreting ERPs, inferences are being made about the timing, degree of engagement and functional equivalence of the underlying cognitive processes. Differences in the time course, amplitude and scalp distribution of the ERPs are the aspects these inferences rely on (Otten & Rugg, 2005) and are consequently what is used in ERP-based studies and are correlated with clinical findings (Hruby & Marsalek, 2003). It is also possible to transform time-data into frequency-data, and thereby use a Spectral analysis, but as this is not pertinent to this thesis it will not be explained further. The following ERP-components are the components relevant for this study, but is not a complete list of all known components.

What is an ERP?

An event-related potential (ERP) is defined by Otten & Rugg (2005) as a small change in the brain's electrical activity, brought on by an internal or external event, and recorded on the scalp. This change is thus accredited to being evoked by the event, hence the name. The neuronal populations in different parts of the brain generate fields of bioelectric activity, which is summated and picked up by electrodes placed on the scalp during any given temporal window. This produces time-varying scalp fields that EEG software is capable of presenting visually and numerically. The scalp fields could be a reflection of the activity of multiple, anatomically distributed neuronal populations, or they might be generated by the event-related, time-locked activity of a single, anatomically circumscribed neuronal population (Otten & Rugg, 2005).

The waveforms of the ERPs consist of either positive or negative voltage fluctuations, which result in a waveform with either a positive or negative deflection representing the voltage difference between electrodes. Based on the chosen electrode montage, this difference might be between a reference and a recording electrode (as in a global average montage), or it might be the voltage difference between two separate recording electrodes (as in a bipolar montage). The positive or negative deflection is relative to the pre-stimulus period and results in the labelling of either a P-component or a N-component, respectively. The amplitude is measured in microvolts (μV) and defined as "the difference between the mean pre-stimulus baseline voltage and the largest positive-going peak of the ERP waveform within a time window." (Polich, 2007). The approximate peak latency, which traditionally is the measured time in milliseconds (ms) from stimulus-onset to peak amplitude (the point of maximum amplitude of the component) is denoted by an indexing component number, which resulted in for example the labelling of the P300-component, or P3. "P" is for the positive deflection of the waveform, and the "300" is because the average latency of the component is empirically observed to peak around 300 ms.

Relative to the seemingly random waveforms that constitute the background activity of the EEG during events, the ERPs are quite small (1-30 microvolts). This necessitates an averaging of multiple trials that evokes ERPs to be able to delineate a component, as the background "noise" of the EEG activity would otherwise obscure the ERPs. To be able to successfully delineate a component the amplitude of the component has to be greater than the background noise, and is as such a function of the signal-to-noise ratio. This is considerably influenced by the number of experimental trials able to elicit an averaged waveform, the amplitude of the component relative to the background activity and the degree of artifacts (eye blinks, high muscle tone, movement, etc.) in the original dataset (Friedman et al., 2001). In general, at least 70 trials is needed for a sufficient signal-to-noise ratio when averaging results (Kiesel, Miller, Jolicoeur, & Brisson, 2008) to obtain reliable data.

By way of an experimental design, one can measure how the brain reacts to different stimuli by using strict protocols where as much as possible of potentially disturbing stimuli are eliminated or controlled for. This results in ERPs being products of the

protocol, as the protocols used determines which potentials will be evoked. By definition, protocols evoke potentials by being designed in such a way that the subjects are challenged with tasks known to be relevant for the evocation of the potential one desires to examine.

The simplest type of interpretation in regards to ERP protocols would be to compare the ERP waveforms (or other characteristics) in two different conditions (ignore or press button, for example) and examine how they differ. Different scalp distribution between the two conditions (the distribution of activity across the scalp, recorded differently at different electrode placements) suggests different patterns of neural activity. Operating on the assumption that different cognitive processes have different neural patterns of activity, one can assume that a reliable ERP difference between two experimental conditions implies that the cognitive processes associated with the conditions differ. If the amplitude of the component were greater in the experimental condition compared to the control condition, this would suggest a greater degree of neuronal resources reflected in greater synchronous activity as a result of the experimental condition (Otten & Rugg, 2005). The latency of the component is assumed to reflect the time required to detect and process the stimulus (Polich, 2007). Based on this, ERPs can be used to provide information about central nervous system functions through the assessment of cognitive processes.

The interpretations of ERP data are based on underlying a priori assumptions, or based on interpreting the temporal information versus the spatial information. Many studies that have examined and decomposed the sequences of positive and negative waveforms that constitute an ERP, and spatial and temporal associations, have found some particular ERP features as correlated markers for cognitive processes. These particular features are called components (Otten & Rugg, 2005) and some of these components have clinical established utility by reflecting different neurocognitive processes (Brunner et al., 2015; Duncan et al., 2009).

P3

In existing literature the third wave after a stimulus, the class of P3 components collectively labelled as the P300-complex, are the most prominent and most researched ERP components for assessing the integrity of the neural networks

underlying attention and working memory. However, it is not known exactly how and why the brain produces this component (Polich, 2007). The component is obtained using a protocol where the subject is instructed to discriminate infrequent target stimuli from more frequent, standard stimuli by noting a target stimulus, often by pressing a button as fast as possible or counting the occurrences mentally (Polich, 2007). The specific protocol used determines what kind of P3-component is generated. This experimental paradigm where one has to discriminate rare deviant stimuli from a series of regular stimuli is known as the oddball-paradigm. This positive component appears between 250 and 500 ms after a stimulus in normal young adults, depending on whether the stimulus is visual or auditory, with an average peak latency of 300 ms and 400 ms for auditory and visual stimuli, respectively (Polich & Criado, 2006). The P3 is also possible to elicit with somato-sensory, olfactory and taste stimuli, with different wave shape and latency for each modality (Hruby & Marsalek, 2003). It is found to be maximal over midline scalp sites, with a centro-parietal scalp distribution independent of modality (Duncan et al., 2009).

The P3 is perceived as an index of mental effort (the degree of mobilization of activity) as it seems to be reflective of the allocation of attentional resources, and is made up of several different subcomponents each with their own neuropsychological correlates (Linden, 2005). The amplitude of the P3 is sensitive to task demands and is interpreted as an index for attentional resources and the updating of mental representations (Polich, 2007), and the latency is thought to reflect the speed of stimulus classification and evaluation (Polich & Criado, 2006). The greater the difficulty of the task, the greater the reduction in amplitude and lengthened peak latency of the components as a consequence of the demands made of memory processes. Conversely, superior cognitive performance (the speed of allocation of attentional resources) is correlated with shorter latency (Polich, 2007), and both shorter latency and larger amplitudes have been found to correlate with intelligence (T. Liu, Xiao, Shi, & Zhao, 2011). The amplitude of the P3-component also seems to be associated with vigilance and selective attention (Van Damme, Crombez, Eccleston, & Roelofs, 2004), and is affected by the time between stimuli, expectancy effects related to the sequence of stimuli and the informational salience of the stimulus (affective significance or reward value) (Duncan et al., 2009).

A prominent hypothesis for the P3 is that after initial sensory processing of incoming stimuli, the representation of the previous event in working memory is evaluated by an attention-driven process of comparison. If this comparison detects an attribute change in the stimulus that does not correspond to the existing mental representation, attentional processes manage the update of the representation concomitant with P3 generation (Polich, 2007). Thus, the P3 seems to be a reflection of both attention and working memory as underlying mechanisms for the generation of this ERP (Linden, 2005). This makes the P3 a global component in regards to the executive processes of task setting, energization and monitoring, with the different subcomponents being more specific and sensitive for different neuropsychological parameters of cognition and behaviour. Task setting is a process of organising and forming criterions of how to respond to a defined target and complete a particular task. Energization refers to the voluntary attentional process that boosts and facilitates processes necessary for the instigation and maintenance of optimal response patterns necessary for making decisions and goal-directed behaviour. Monitoring is thought to be a process of assessing task performance and outcome over time, which is necessary for being able to adjust ones behaviour appropriately. These processes are correlated with the P3-Nogo-component (Brunner et al., 2015), which will be further elucidated shortly. It is also suggested that the P3 has an overarching theoretical mechanism of neuroinhibition, as it might be a neural reflection of the rapid neural inhibition of brain activity occurring concomitantly with important stimulus events and task demands, with the objective of maximizing attentional focus and promote memory operations for relevant target stimuli in an effort to facilitate transmission of relevant information (Polich, 2007).

Because of these aspects of the P3, it is no surprise that it has been investigated in multiple studies of different patient populations, as it seems to be indicative of the neural networks' integrity, which is important for normal function. This is exemplified by the consistent decreased amplitude and increased latency found in different patient populations (Duncan et al., 2009; Linden, 2005). However, these P3 alterations are unspecific and general across patient populations, which means that alterations in the P3 is indicative of a disturbance of *something*, but it is not yet well enough understood to have any specific diagnostic merit as a singular biomarker. In

conjunction with other tools it is useful for explorative examinations and differential diagnosis, and might thus have a potential role as an endophenotype for mental disorders (Linden, 2005; Polich, 2007).

It is possible to record the P3 from multiple brain regions, including but not restricted to the hippocampus, ventrolateral prefrontal cortex, thalamus and amygdala simultaneously and with a relatively uniform latency. Intracranial recording studies implicate the potential for multiple cortical and subcortical generators for the P3, or it might be a reflection of a widespread neuronal system with a variety of connections throughout the brain. The fact remains that there probably is not one sole P3 generator, but rather a complex cortical and subcortical system that in conjunction generates the P3 component (Duncan et al., 2009).

P3a

A subcomponent of the P3 called the "P3a" is elicited over the frontal/central areas when infrequent stimuli (such as a high tone or the picture of an animal) are presented within a series of more standard stimuli (such as pictures of plants) that interrupts the attention and focus required for the principal discrimination task. The latency is observed from 250 to 400 ms, reaching peak latency earlier than the regular P3. The P3a has been interpreted as mainly reflecting frontal lobe function (which is indirectly related to the activity of the subcortical hippocampus) because of its frontal/central scalp distribution, quick amplitude habituation to repeated stimuli presentations and relatively short peak latency (Comerchero & Polich, 1999; Friedman et al., 2001). This seems to be corroborated by dipole locations (Debener, Makeig, Delorme, & Engel, 2005), lesion and hemodynamic studies and intracranial ERP recordings, irrespective of modality (Friedman et al., 2001).

This subcomponent is suggested to index the operation of frontal automatic attention networks that respond to stimulus deviance, including unexpected novel stimuli (Polich & Criado, 2006). It seems the P3a is evoked when infrequent stimuli interrupts ongoing information processing, and thus attentional resources are allocated to this interruption by means of frontal lobe engagement, assumed to govern the generation of the P3a component. This would not be the case if discrimination between target and standard stimuli was easy, as the stimulus context would not

demand a greater degree of intense attention. Instead, it would facilitate a more automatic processing of the non-target information (Comerchero & Polich, 1999). P3a thus seems to have an orienting function as a result of salient stimuli that lacks a neural representation during a continuous process of comparing representations to incoming information (Friedman et al., 2001). In short, to elicit the P3a the discrimination difficulty between target and standard stimuli has to be great enough to demand frontal system engagement to redirect the attentional focus (Friedman et al., 2001; Polich & Criado, 2006) and increased perceptual discrimination difficulty seems to increase the amplitude of the P3a component (Hagen, Gatherwright, Lopez, & Polich, 2006).

P3b

The central/parietal subcomponent – with a latency between 300 and 600 ms (Friedman et al., 2001) – of the generated P3-component is called "P3b" (b because of a later peak latency than the P3a) and is thought to originate when mechanisms in the temporal-parietal areas process the relevant stimulus information for memory comparison, updating and storage (Polich & Criado, 2006). If the subject discriminates target stimuli from standard stimuli, the P3b is generated and the neural representation of the stimulus context is updated. As such, where the P3a reflects the attentional mechanisms generating the P3-component, the P3b reflects the aspects of working memory. To elicit the P3b, it seems that the evoking events have to be task-relevant and attended to, or demand a decision (to press or not to press a button) in regards to infrequently occurring events. This is in agreement with the assumption that this posterior aspect is assumed to reflect a process of stimuli categorization in accordance with a working memory template (Friedman et al., 2001). The P3b is thus central in determining whether to execute (P3-Go) or inhibit (P3-Nogo – another aspect of the P3-component, which will be described shortly) a motor response. Other studies argue that both target and non-target deviant stimuli are capable of eliciting the P3b (Debener et al., 2005). It seems that the amplitude of the P3b is reduced and peak latency is increased when there is an increase in the demand of attentional resources in a perceptual discrimination task. In other words, when the discrimination task is too difficult, the P3b is less efficiently generated (Hagen et al., 2006). Lesion studies implicate the temporo-parietal junction as a main contributor to the scalp-recorded ERP response at the central and posterior scalp sites (Friedman et al., 2001).

P3a and P3b connections

It has been demonstrated that the generation of the P3a and P3b is context-dependent, as the magnitude of the perceptual difference between the target and nontarget stimuli affects the generation of the P300, and the modality dependent scalp distribution. It seems like the strength of the difference might be dependent on an interaction between the distinctiveness and the modality of the stimuli, this effect being strongest in an auditory condition (Comerchero & Polich, 1998). Small differences between target and standard stimulus demands a greater degree of processing compared to large differences (Comerchero & Polich, 1999). The spatiotemporal overlap of ERP components makes it difficult to unequivocally delineate certain subcomponents, especially the P3a and P3b as they often appear to be one waveform. This is corroborated by a study with single-trial data that showed that the greater amplitude of the P3a during an oddball task (in response to attended novel stimuli) was due to, at least partly, overlapping P3b-related processes (Debener et al., 2005).

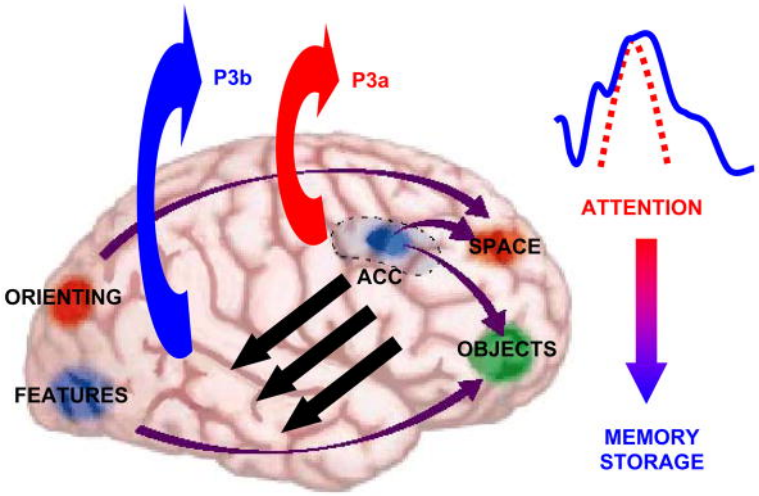

Figure 1: From Polich (2007) after Gazzaniga et al., (2000)

The P3 seems thus to be comprised by a spatiotemporal overlap of P3a and P3b activities, with the P3a latency most often peaking earlier than the P3b. As studies have implicated major cortical sources for the generation of the components of the P3, they have also shown other, related cortical contributors, and as such there is a whole network of cortical activity that together generates the P3 in its entirety (Friedman et al., 2001). However, in cases of the two peaks being observable the P3b is often assumed to reflect the true P3-component (Hruby & Marsalek, 2003).The generation of P3a is proposed caused by the activation pattern of the anterior cingulate and related structures when attention is disrupted by sensory input like the detection of a target or distractor stimulus. Cellular recording studies indicate that the attention-driven neural signal might propagate to temporal-parietal areas where the P3b is generated as memory-related operations are engaged in context updating for future stimulus presentations (Polich, 2007).

P3-Nogo

In response to infrequent non-target stimuli a P3-component with maximal deflection (amplitude) over the central/parietal areas is often referred to as a P3-Nogo or nogo-P3 because the subjects are instructed not to respond to these targets (Comerchero & Polich, 1999; Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984). The subcomponent is also observable with a fronto-central distribution (Brunner et al., 2013). The subcomponent has been related to response inhibition mechanisms (Polich, 2007), but there are arguments being made for the P3-Nogo to be a reflection of multiple control processes of both suppression of incorrect responses as well as the facilitation of correct responses by replacing initial prepotent response tendencies (Brunner et al., 2015).

The P3-Nogo waveform has been shown to be amenable to decomposition into two independent components (early and late) with different topographies and latencies, as well as reflective of different processes. The late P3-Nogo seems to always come after the early P3-Nogo, and in a study done by Brunner and colleagues (2015), it was shown that the early P3-Nogo had a peak latency of 330 ms with a central distribution, and the late P3-Nogo had a peak latency of about 380 ms and showed a fronto-central distribution. The window of interest for the entire wave was 230-480 ms. It seems like energization correlates with the amplitude of the early P3-Nogo

component and monitoring with the amplitude of the late P3-Nogo component. The amplitude of the early P3-Nogo has a strong positive correlation with reaction time, as well as correlating significantly with Full Scale IQ, and the late component correlated with a Working Memory Index score (Brunner et al., 2013; Brunner et al., 2015).

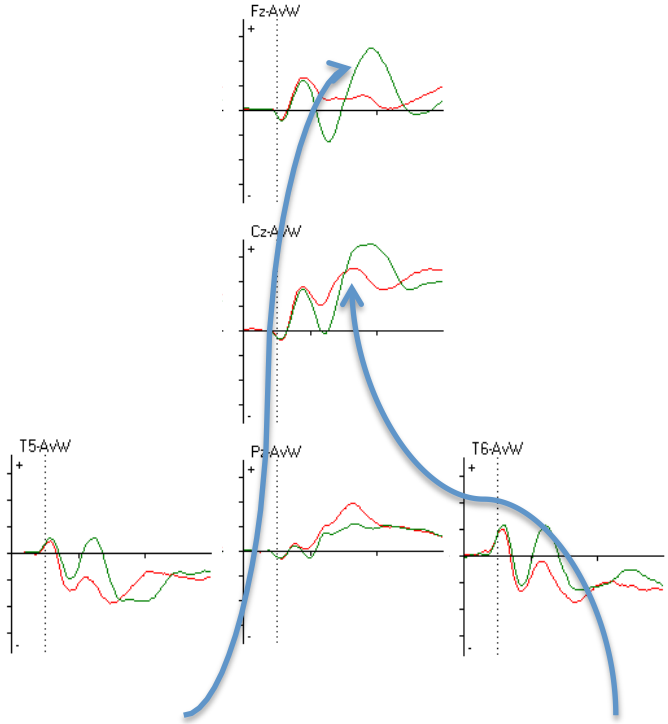

Figure 2: Green line is P3-Nogo, clearly distinct from P3b in red. Data taken from the VCPT-protocol

CueP3

As previously mentioned, the protocols employed determine what ERPs are evoked, and the cueP3 is such a parietal P3 component elicited in cued trials where the first stimulus acts as a cue for the second stimulus, which one assumes contributes to activate proactive processes reflected in the cueP3 component. CueP3 precedes the P3 component in such a cued attention task, and its latency is assumed tied to the main P3 component(s) and is thus empirically found between 200-600 ms after the first stimulus (the cue), whereas the target-P3 is elicited by the second stimulus. The component seems to have posterior sources, and might be a specific index of attentional preparation and orienting to targets (Brandeis et al., 2002; van Leeuwen et

al., 1998). It is thus argued that the cueP3 reflects the involvement of a general posterior attention system, as the same source was found for ADD and control groups both, rather than prefrontal deficits characterizing ADD. Brandeis and colleagues argue that the modulation of the posterior attention by the prefrontal areas were not affected, but rather that there was an underactivation of the posterior attention system it self.

Research indicates that both the anterior and posterior attentional systems are implicated in orienting (Petersen & Posner, 2012) and the anterior attention system might bias and enhance sensory input processing by modulating the top-down functions of posterior cortical areas and consequently modulates the posterior attention system (Sarter, Givens, & Bruno, 2001) where the cueP3 seems to be generated. The cueP3 is a component mainly investigated through studies of attention-deficit/hyperactivity disorder, and results indicate that cueP3 reflects a degree of processes related to (in)attention and attention orienting to potential targets and to cognitive preparation and resource allocation (Banaschewski et al., 2003; Brandeis et al., 2002; Kratz et al., 2011; McLoughlin et al., 2010).

Accordingly, an increase in Go-expectancy is accompanied by an increase in the amplitude of the cueP3, and is argued to involve attention rather than bias. An increase in the amplitude of the cueP3 is suggested to be related to an increase in Go probability and thus expectancy (Jonkman, 2006). The amplitude of the cueP3 could thus be a reflection of the initial evaluation of the predictive relevance of the cue for upcoming events; in other words its informational and imperative salience (Bekker, Kenemans, & Verbaten, 2004). As such, it might be an index of early allocation of attentional resources along the lines of a neural facilitator in preparation for the information processing and context updating indexed by the target-P3.

According to Gratton and colleagues (1990) the amount of information the cueP3 provides regarding the upcoming stimulus in a cued Go/Nogo task is proportional to the amplitude of the component. It is argued that the cueP3 is an index of the amount of information extracted from the cue stimulus. The latency of the cueP3 covaried with the cueP3 amplitude in this study, and was argued to indicate that the more extracted information from the cue stimulus, the longer processing time was required.

The expectancy effect is argued to facilitate the recognition and encoding of the target stimulus, in other words, a priming of perceptual processing. This is in accordance with the "context updating" hypothesis of the P3, as the amplitude of the component elicited when one needs to modify ones operating sets of assumptions about the environment, is proportional to the degree the existing context model will be modified (Gratton et al., 1990).

Based on these studies, it could be argued that the cueP3 is an index of sensitivity. The preparatory state elicited by orienting to a cue stimulus is indexed by the cueP3 and relates to cue evaluation processing, Go-expectancy and the allocation of attention. However, more studies regarding this component are warranted.

CNV

The fronto-central distributed component known as CNV (Contingent Negative Variation) is considered an attention-system related index of effortful performance of response-related processes in a cued task, often requiring a motor response for elicitation of the wave. It is seen as a negative slow wave with a gradual increase in negative amplitude after the first stimulus, up until the second task-relevant stimulus where it returns to baseline (Falkenstein, Hoormann, Hohnsbein, & Kleinsorge, 2003; Tecce, 1972). The observed scalp negativity reflects depolarization of the apical dendrites of pyramidal neurons, interpreted as increased activation.

The peak of the complete CNV component seems to be reflective of a time-based decision making mechanism preceding the actual motor response, and it is thus argued that the decomposition of the component results in an early and a late wave, in addition to reflecting other aspects when measured as a whole component (Macar & Vidal, 2004)**.** The early wave is believed to be related to orienting and timing processes, and the late wave is thought related to motor preparation. There may also be a relationship between the early CNV with arousal processes, while the late wave might be related to a facilitation of attention to the second stimulus. The component, with mainly ACC and prefrontal sources, has an onset time after 400ms in the inter-stimulus interval, but empirically it is often observable during a Visual Continuous Performance Test protocol from around 600ms. It also draws from activity in

posterior sources, as well as subcortical structures like the brainstem reticular formation and thalamo-cortical circuits (Gómez, Marco, & Grau, 2003; Tecce, 1972).

The component seems thus to reflect different mechanisms associated with the identification of the first stimulus, anticipation and motor preparation for the upcoming second stimulus in cued Go/Nogo-tasks, where the amount of attention paid to the task might moderate the amplitude of the CNV. The CNV seems to be a reflection of trial-by-trial shifts in performance and resource allocation, externally and internally induced, and the amplitude seems related to preparatory mechanisms and inversely related to reaction time in some subjects, possibly reflecting the intention to execute a stimulus-timed response, instead of a general preparedness to respond (Falkenstein et al., 2003; Hillyard, 1969). There are several hypotheses and equivocal findings in the research literature regarding the exact origins and functionality of the CNV (van Rijn, Kononowicz, Meck, Ng, & Penney, 2011). Macar & Vidal (2004) argue that the CNV reflects an innate time processing capability at the CNS-level. There are also indications that the CNV amplitude might be related to a greater degree of attentiveness and alertness to expected stimuli and has been found to be associated with the P3-component (Brunner et al., 2015; Tecce, 1972), which makes this a component necessary to investigate from a sensitization hypothesis and for its relationship with aspects of attention.

Previous findings for chronic pain

A study used pressure stimulation and a sub-maximal exercise test to correlate sensory amplification with scores relating to fatigue and pain. In a group comprised of patients with these complaints it was found that the sensory amplification only had a significant association with pain, but not with fatigue. The authors argue that this supports a hypothesis of generally modality-unspecific altered central sensory processing mechanisms as characteristic of fibromyalgia (Geisser et al., 2008).

Regarding event-related potentials and pain, a review paper showed that except for one study, a reduced amplitude of P3-component compared to controls was a consistent finding, while results regarding the latency of the component are inconsistent (Glass, 2006). Based on neuropsychological findings they argue that pain and pain-related information may interfere with attentional systems in fibromyalgia

patients, as well as suffering from dysfunctions in memory, learning and working memory. The same attenuation of the P3, possibly moderated because of the attentional resources demanded by pain, is found using auditory oddball tasks (Van Damme et al., 2004). As the experience of pain is thought to have a moderating function upon the link between available resources and performance in attention demanding tasks, pain might very well be the explaining factor for attenuated P3 components. It might be that the attenuated P3 is a reflection of the moderating effects of pain on neural synchrony in a task-relevant setting where said synchrony is required for optimal performance. As such, the attentional system might not be compromised per se, but it is rather the constant experience of pain that moderates the availability of attentional resources thus reflected in an attenuated P3 and consequent behavioural performance.

A meta-analysis and review by Berryman and colleagues (2013) investigated possible working memory deficits in a variety of chronic pain studies. The general consensus was worse performance on tasks supposed to measure attention and working memory by way of both number of correct responses and reaction time. However, the physiological outcomes associated with EEG-recordings (latency and amplitude) found no significant results between chronic pain groups and controls for auditory working memory and expectancy/orientation and selective attention. They did however report one study where enhanced P3 amplitudes were found in the chronic pain group for running memory – a measurement of working memory capacity. No significant differences in latency were found for the patient and control group (Veldhuijzen et al., 2006). These results were interpreted as indicative of deficits in the allocation of attention, not deficits in attentional capacity, and indicative of deficits in disengagement of attention. This allocation impairment is thought to be associated with a hypervigilance to pain (Crombez, Van Damme, & Eccleston, 2005). Berryman and colleagues also reported BOLD/fMRI findings for decreased activation in dorsolateral prefrontal cortex, supplementary motor area, right parietal cortex and the ventrolateral prefrontal cortex during an n-back working memory task. Some of these studies were criticized on the grounds of failing to screen for a psychiatric disorder, and most did not control for sleep or medication use, which is known to affect working memory performance (Berryman et al., 2013).

A second meta-analysis and review by Berryman et al. (2014) investigated possible impairment of executive functions in people with chronic pain. Their analyses indicated that chronic pain was associated with decreased Complex Executive Function (an umbrella component which includes planning, visuo-construction, abstract thought, problem solving, sustained attention and decision making) and poorer Set Shifting (considered to constitute psychological flexibility, as it describes the ability to shift back and forth between tasks, like the Wisconsin Card Sorting Test and Trail Making Test, where one has to connect a set of dots as fast and accurate as possible) based on the correct responses on tests measuring these cognitive components. Regarding response time, they found that chronic pain was associated with impairments in Response Inhibition (Stroop Test), poorer Complex Executive Function and Set Shifting. All impairment effects where small to moderate.

A study by Demirci & Savas (2002) using auditory ERPs found no significant differences in P3 amplitude and latency between healthy controls and two pain groups (chronic lower back and episodic tension-type headache), but they did find reduced habituation in the chronic pain group. This is in line with the findings of Montoya et al. (2005; 2006) using both auditory and somatosensory stimulation, which might indicate a general habituation or sensory gating deficit in chronic pain patients; at the very least an altered sensation processing of some kind. However, the Demirci & Savasonly study averaged 30 responses, which is lower than the minimum recommended 70 trials (Kiesel et al., 2008). This could partly explain why other studies have found conflicting evidence with reduced P3 amplitudes and prolonged latencies in chronic pain populations (Alanoglu et al., 2005). However, a minimum of 36 trials has also been argued to suffice for a reliable measure of the P3 (Duncan et al., 2009).

Previous findings for CFS/ME

There has been found indications of reduced serotonin transporter (5-HTT) density in the rostral anterior cingulate in patients diagnosed with chronic fatigue syndrome (Yamamoto et al., 2004), as per Fukuda's and the CDC's criteria. This part of the anterior cingulate cortex is thought to be involved with processing of emotional and pain related information (Rainville, 2002). This is peculiar, as one of the most robust findings from neuroendrocrine studies is the up-regulation and increased serotonin

neurotransmission in chronic fatigue syndrome patients (Afari & Buchwald, 2003; Michiels & Cluydts, 2001). It does seem that the serotonin function in chronic fatigue is of abnormal character, but is as of yet meaningfully unclear.

ERP-findings suggest deficits in auditory information processing and attention in patient groups with CFS/ME, as reflected in abnormal latency (significantly delayed) or amplitude (greatly diminished, sometimes almost absent) in the P3 component compared to healthy controls (Prasher, Smith, & Findley, 1990). The sensory evoked potentials were found to be normal, which argues against sensory sensitivity, contrary to findings for chronic pain syndrome. The same study also identified low correlations between reaction times and P3 for the CFS/ME group. Results from neuropsychological functioning corroborate these findings with significant impairments in auditory information processing abilities related to CFS/ME (DeLuca, Johnson, Beldowicz, & Natelson, 1995), which seems to be the area where one finds the most consistent neuropsychological impairments, with a few exceptions (Tiersky et al., 1997). However, two earlier studies found no difference in P3 latency or amplitude between control groups and CFS/ME groups (Polich, Moore & Wiederhold, 1995, Scheffers et al., 1992), which they ascribed to indicate that the cognitive disturbances that CFS/ME patients often self-report or indicated by neuropsychological tests – perceptual, attentional and short-term memory process deficits – are not of a CNS origin. However, in the study by Scheffers and colleagues, there was a substantially prolonged reaction time in the patient groups, which they took to indicate possible impairments in information processing related to response-related processes.

Indeed, visual attention tasks and related information processing seems not to be impaired, and neither is sustained attention in continuous performance tasks in this patient group. But impaired working memory, poor learning of information and slowed processing speed seems to be general cognitive dysfunctions in patients with CFS/ME (Michiels & Cluydts, 2001). Discrepant and conflicting findings with both slower and no impairment in reaction times compared to controls are also reported, and the general verdict regarding neuropsychological functioning is thus that CFS/ME subjects perform within the normal limits comparable to control groups. However, Thomas & Smith (2009) responded to all earlier methodological problems with a

massive study with appropriately diagnosed and matched groups, and in this study it was found impairments on all neuropsychological performance tests compared to the control group.

In a study by Tomoda et al. (2007) on Japanese children diagnosed with childhood chronic fatigue syndrome (CCFS) they found subgroups based on differences in the latencies and amplitudes of the P3 component; one with low amplitude and prolonged target latency and another with short target latency and high non-target amplitude, and a third group not reaching abnormalities above 2 SD threshold. Earlier ERP-findings for this patient group are thus equivocal, and support the growing argument of subgroups in the CFS diagnosis as an explanation for the variable findings, especially as it has been established that one distinct subgroup of CFS suffers from chronic widespread pain (Meeus, Nijs, & Meirleir, 2007).

Importance of this study

The impact of chronic pain on a patients' life has been shown to interfere significantly with ones daily life and personal economy, quality of life, social interactions and relationship with others, as well as being associated with depressive symptoms and anxiety (Reid et al., 2011). There is an extensive overlap between Chronic Fatigue Syndrome/Myalgic encephalomyelitis (CFS/ME) and different chronic pain syndromes, as both patient groups suffer from sleep disturbances, headaches, severe fatigue, diffuse and localized pain, as well as different symptoms of a neurocognitive and neuropsychiatric character (Meeus et al., 2007; Tiersky et al., 1997), which greatly complicates a differential diagnosis. Additionally, routine laboratory tests on both fibromyalgia and CFS/ME individuals are often found to be normal (Aaron & Buchwald, 2001). If this study is capable of establishing differential markers between the two patient groups, this will strengthen the argument of CFS/ME and chronic pain as two distinct illnesses. In addition, by possibly differentiating between the two patients groups and a control group, this will also strengthen the legitimacy of these two conditions as clinical diagnoses.

Aims of the thesis

By comparing these two patient groups with each other and a control group of healthy individuals, we aim to uncover possible markers that might differentiate between the

three groups. Simultaneously, there should be found significant differences between the control group and the two patient groups. During an initial routine examination of the EEG-data for the pain group, the cueP3 component was found to be highly significantly different from the clinical norm database at a p-level of < .001. As this was done using the internal statistical system of the WinEEG-program, and because the norm database only compares age-matched averages without any information about standard deviations or any additional information, it was necessary to attempt a more thorough examination with SPSS. It was additionally necessary to contrast with a second patient group with similar symptoms to investigate if this was indeed a specific biomarker for chronic pain conditions. To determine how these groups differ from a normal population, a control group was deemed necessary. The intent of the following study is largely exploratory, and as such we have examined a large number of variables that are theoretically plausible as being reflective of potential dysfunctions in the two patient populations. The main aim is to replicate the significant finding of an enhanced cueP3 in the patient group characterized by chronic pain syndromes, and secondary to examine which components, if at all, evidenced significant differences between chronic pain states and chronic fatigue.

As the cueP3 was the initial finding instigating this extended investigation, we operate with the main hypothesis that central sensitization might be a common underlying feature of both chronic fatigue and chronic pain conditions, as this component might be an index of sensitivity. If central sensitization truly is an underlying mechanism for both development and maintenance of chronic pain states and chronic fatigue conditions, then the altered signal-transmissions of the CNS should be reflected in altered ERP-components, as they index the physiological functioning of the attentional system inextricable from the functioning of the CNS.

Based on previous findings, we expect to find attenuated amplitudes of the P3-component in the chronic pain group, as the experience of pain is thought to have an interfering effect on the attentional system, which the P3 indexes. As impaired response inhibition has also been associated with chronic pain states, we expect to find reduced P3-Nogo components compared to both the CFS/ME and control group.

As both Chronic Pain and CFS/ME have overlapping symptomatology, especially considering a CFS/ME subgroup characterized by chronic widespread pain, we expect to find some overlap, but also some differentiating ERP components between CFS/ME and Chronic pain groups. As such, due to the possibility of central sensitization being an underlying mechanism for both the chronic state of fatigue and chronic pain, we also expect to replicate the enhanced cueP3 identified earlier for Chronic Pain as similarly different between CFS/ME and the control group. We also expect to find significantly reduced amplitude of the CNV-component compared to both the control group and chronic pain, as the CNV is thought to reflect motor preparation in a response-dependent continuous performance task. As ERPs index the integrity of a greater neural system, deviances in the components might indicate a general dysfunction of the default mode network. The null hypothesis would be that there are no differences to be found on any components between these three groups.

Method

Participants

This study was done by analysing archived EEG-files from three different groups, which had already been approved by the Norwegian Regional Ethics Committee (REK) and the Norwegian Data Services for Social Science (NSD) for use in earlier studies.

Participants undergoing assessment at the Hospital Traunstein, Pain day-unit, Traunstein (Germany) were offered a qEEG investigation from Dieter Göhrman in addition to the assessment they received from the hospital. 11 patients from the pain group were excluded due to age (20 or younger and older than 60, because of curvilinear age related P3-effects on amplitude and latency are found for visual ERPs (Mullis, Holcomb, Diner, & Dykman, 1985) and another 2 patients were excluded due to reaction times of more than 2 SD from the rest of the patient group to reduce possible confounding factors reflected in behavioural measures like reaction time. There does not seem to be a consensus in the literature regarding the exact relationship between reaction times and P3-components, which might be related to varying emphasis in the instructions from the experimenters to the subjects, as there seems to be some correlation if it is demanded of the participants to react as quickly as possible (Brunner et al., 2013). Because of this uncertainty, the reaction times within the three groups were controlled in an effort to better the between-comparability. This left a group of 32 pain patients to include in the analysis.

The patients were diagnosed with different kinds of pain conditions, which included myofascial neck, shoulder and back pain, chronic headache, migraine, lumbalgia, fibromyalgia, gluteal pain with ischialgia, polyarthrosis, lumbal ischialgia, gonarthrosis, osteoporosis, atypical face pain, and somatoform pain. Patients were also on different pain medication at the time of the recordings. Unfortunately, this is an incomplete list, as we do not have the complete documents for all patients regarding diagnosis and possible pain medication.

42 patients for the chronic fatigue group recruited from the Pain Care Unit at St. Olav Hospital in Trondheim during the time period of 2009 to 2012. All patients suffered

from a form of unexplained chronic fatigue, they did not however fulfil all of the CDC-1994 criteria for CFS/ME (Fukuda et al., 1994), but were still accepted as suffering from idiopathic fatigue. Of these patients 3 were excluded from the chronic fatigue group based on reaction times, and 4 were excluded because of the age cut-off (20 or younger and older than 60). We were left with 26 viable EEG-recordings after an exclusion of subjects with less than 70 trials in each relevant condition, as this is a recommended minimum for detecting latency differences for the P3 components (Kiesel et al., 2008). There were no records of any of these patients being on medication at the EEG-recordings.

The control group was comprised of 40 psychology students and faculty staff that volunteered for different unrelated lab exercises related to a psychology course at NTNU in Trondheim between 2005 and 2008. 1 subject was excluded from the control group based on reaction times, and 3 were excluded because of age (20 or younger), which left the control group with 36 subjects. To our knowledge, none of the participants were on any medication or had any diagnosed mental illnesses.

Apparatus

EEGs of chronic fatigue syndrome patients and controls were recorded using a 19-channel digital EEG amplifier from Mitsar (St. Petersburg, Russia) with electrode caps of tin (Sn) from Electro-Cap (Electrocap International Inc) fillied with conductive gel and the WinEEG vs. 2.82 software package (Mitsar, St. Petersburg, Russia). The participants in the pain group were recorded with the same type of hardware and software. All electrodes were distributed according to the 10-20 international standard (Klem, Lüders, Jasper, & Elger, 1999). Reference electrodes were placed at the ear lobes and the ground electrode was situated at FPz, which on the below picture would be situated in the middle of Fz, Fp1 and Fp2. The ERP signal for analysis was recorded from midline electrodes; Fz, Cz and Pz. Impedance was kept below 10 kOhm. Data was digitized and stored on a computer for off-line analysis. Exclusion threshold for the signal in general was set to 100 microvolts. The high pass filter for slow waves was set to 0.53Hz; low pass for fast waves was set to above 50Hz. Prestimulus baseline was 50 ms and the presentation of each picture was 100 ms. The notch filter was on (45-55Hz) during the trials in order to reduce electric noise. All of the recordings were inspected visually to ensure their quality. The

majority of the recordings' sampling rates were 250Hz, and in instances where the recordings were 500Hz they were compressed to 250Hz for ERP analysis. Input impedance for the amplifiers was 200MOhm and A/D was of 14 bit precision.

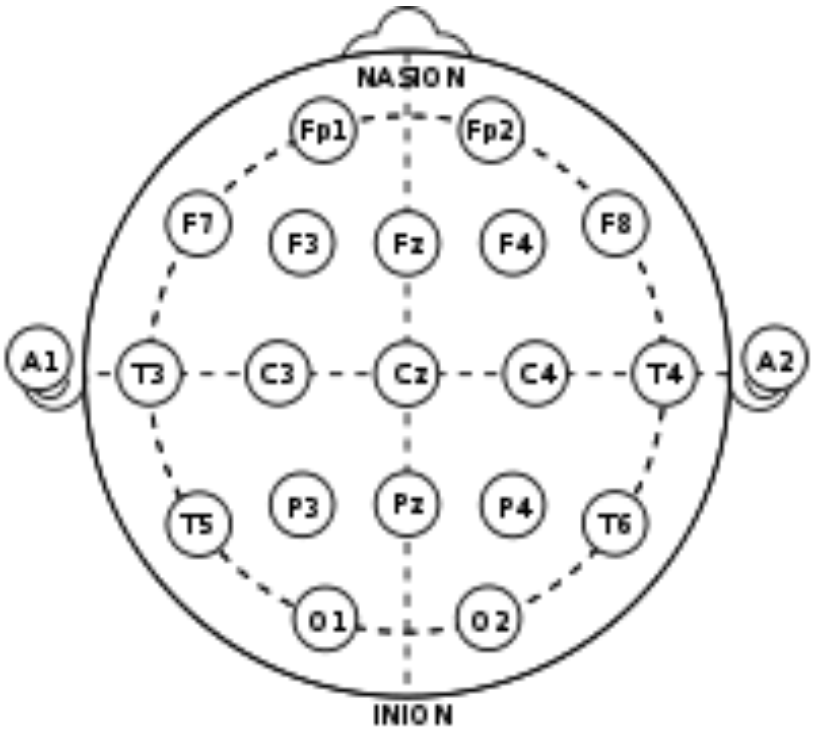

Figure 3: The standard arrangement of the 10-20 international system where Fp denotes frontal poles, F denotes frontal electrodes, T denotes temporal electrodes, C denotes central electrodes, P denotes parietal electrodes, O denotes occipital electrodes and A denotes auricular electrodes, as these are the linked earlobe reference electrodes. Even numbers are found on the right, while uneven number are distributed on the left. Fpz is not shown on this picture, but is located centrally between Fp1, Fp2 and Fz.

Stimuli and procedure

The protocol used was a resting condition (three minutes of eyes opened followed by three minutes of eyes closed) and an active condition (Visual Continuous

Performance Task), which lasted 20 minutes and with a short break every 5 minutes to promote a continuous good performance and counteract task-related weariness. Eyes open and eyes closed conditions were utilized to obtain each participant's resting EEG. The participants were seated in a comfortable chair 100 cm from a 22" screen, with a resulting visual angle for the images of 5 degrees in a sound isolated room. Sound pressure level for the sound condition was 60 db.

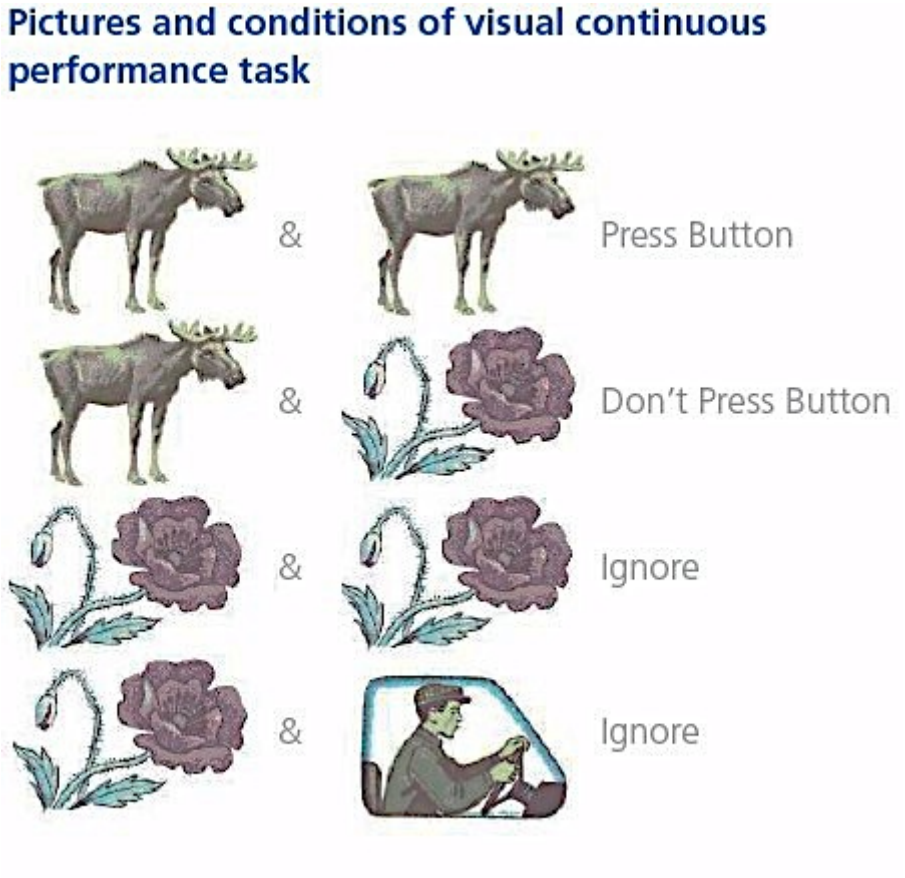

Figure 4: The instruction screen at the start of the VCPT

The visual continuous performance test (VCPT) used in this study is a visually cued Go/Nogo task designed for the study of ERPs (Kropotov & Ponomarev, 2009). For reliably assessing the P3 wave, it has been recommended to average more than 70 trials (Kiesel et al., 2008). This Go/Nogo task provides 400 trials in total, divided on four conditions termed a-a (animal-animal), a-p (animal-plant), p-p (plant-plant), and p-h (plant-human) with 100 trials in each. After every 100 trials (approximately 5 minutes) a short break is initiated, which amounts to 3 short breaks during the main

recording session and four blocks of testing. The four conditions are made up of three categories of visual stimuli: 20 different images of animals, 20 different images of plants, and 20 different images of humans. Each condition is composed of picture-pairings with an inter-stimulus interval of 1000 ms and a 3 second interval between pairings. In the p-h condition, the human picture is presented simultaneously with a "novel" sound. In the a-a and p-p trials, the two pictures presented were identical. In each block, there was an equal probability of each condition being presented. The subjects were instructed to press a button as fast as possible with their right index finger to the second image in the a-a conditions (Go-condition), to withhold a response to the second image in the a-p conditions (Nogo-condition) and to ignore the two other conditions, p-p and p-h. It is assumed that all trials with an animal picture as the first stimulus (found in a-a and a-p conditions) activates proactive responses, and are thus referred to as "cues".

Artefact correction

Artefacts from eye movements as well as muscle artefacts and electrical disturbances were removed using independent component analysis (ICA) and spatial filtering. The rejection threshold of artefacts for slow waves (0-1Hz) and fast waves (above 30Hz) was 50 microvolts. Lastly, all recordings were visually inspected to ensure adequate removal of artefacts.

Analysis

The different components were identified by visual inspection of the averaged ERPs of each subject and examined with the WinEEG's internal statistics engine to an age-matched Norwegian database and another normative database (the Human Brain Index reference base) with means from an appropriate age-matched reference group. These are used to calculate if there are significant differences between the observed ERPs of the recording and ERPs of healthy controls by way of a t-test. The cueP3 was found to be highly significant in the recordings of pain patients, but as the HBI database is a clinical tool that serves to aid clinicians in differential diagnosis and potential treatment planning, the parameters of the program are not specified (http://www.hbimed.com/en/qeeg/hbi-database/why-biomarkers.html). Such a comparison is thus a single point-estimate, and without any information about standard deviations or any other information about the controls that comprise the two

databases, we followed up this clinical finding with our own controls and more stringent analyses through SPSS.

A relative criterion version of the fractional area technique was used to measure the latency of the ERP components (Brunner et al., 2013; Kiesel et al., 2008). In this approach, the onset of the component is defined as the time point where the amplitude first exceeds 50% of the maximum peak-to-peak amplitude of the waveform (before the peak), and the offset is defined as the time point where the amplitude reaches the same level as onset (after the peak). The latency is then set as the median between 50% onset and offset according to the max amplitude of the waveform. The latencies according to the relative criterion were calculated manually, and the max amplitudes were operationalized as peak amplitudes. Where there were complex waveforms where the values of the onset amplitudes did not match the value at the offset point, the time point with the closest amplitude value within the span of max peak to the end of the pre-specified time window was chosen as the offset time for latency calculations. If the relative criterion was not reached before the end of the time window, the end of the time window was chosen as the latency, and if the relative criterion has been fulfilled (or exceeded) before or at the start of the time window, the start of the time window was chosen as the latency used for computation. Some waveforms did not lend themselves able to be calculated using the relative criterion at all (like the CNV), and in such instances they were computed using peak latency and peak amplitude, as the use of several methods to analyse differences between ERPs should be unproblematic as the level of Type I errors for each of these procedures are low (Kiesel et al., 2008).

The relevant time frames of interest was decided based on existing literature for the different components: P3: largest positive peak occurring 200-600ms after the presentation of the target stimulus, cueP3: 265-550ms, P3-Nogo: 250-600. Only the peak amplitude was computed and used in statistical analysis for the CNV. As we were only interested in examining whether there were any differences between the groups regarding the amount of preparatory resources allocated to the task and not the speed of allocation, the latency of the CNV-component was not included in these analyses.

The most commonly used measure of amplitude and latency of ERP waves is the method of measuring the peak amplitude and peak latency of each component. However, it is assumed that especially for ERPs without a clear peak and latencies that are difficult to pinpoint, sometimes a large temporal extension and not always a clear onset – like the P3 and its subcomponents – the FA approach might be better (Kiesel et al., 2008).

All analyses were performed with SPSS version 21 on Mac with an alpha-level of $p < 0.05$ accepted as significant. ANOVA was used to analyse the potential differences in reaction time (RT) between groups (Control, Pain and Chronic Fatigue). As the components under investigation are neurobiological concepts originating in the same systems and they are all evoked by the same task, they are being considered together and we thus ran a MANOVA to examine whether there were any significant differences between the groups on a linear combination of these variables, i.e. if there are significant differences to be found when these components are interacting.

Considering that ERPs are only partial reflections of major underlying processes in the brain, and as the central nervous system is not a simple, compartmentalized system, the probability of a single class of ERPs being capable of unequivocally discriminating between patient and healthy populations is unlikely, at least with a certain degree of specificity. As such, the choice for analysis fell on the MANOVA, as this method of analysis investigates the effects of interactions, as well as being capable of investigating single factors.

For the MANOVA the independent variable was Groups (Control, Pain and Chronic Fatigue) and the dependent variables were P3Go latency, P3Go amplitude, P3Nogo latency, P3Nogo amplitude, cueP3 latency, cueP3 amplitude and CNV peak amplitude. A Bonferroni-correction was utilized where multiple analyses were performed to ensure this statistical threshold was maintained. Partial eta squared (η^2) is a measurement of effect size representing the proportion of variance in the dependent variable explained by the independent variable. Effect size is a measurement of the magnitude of the differences between groups, thus denoting whether the potential significant differences are negligible or whether they are

genuine differences of clinical relevance (Pallant, 2013). According to Cohen (1988), a small effect size is $\eta^2 = .01$, medium is $\eta^2 = .06$, and large is $\eta^2 = .14$.

Results

Behavioural data

A one-way between-groups analysis of variance was conducted to explore potential differences in reaction time between the three groups Control, Pain and Chronic Fatigue. As Levene's Test was significant, this indicated that the reaction time variances within each group were unequal ($p = .005$), and a follow-up with Welch F was conducted. The equality of means showed significant results ($p < .001$), and it was thus deemed appropriate to continue with the analysis. There was a statistical significant difference at the $p < .001$ level for the three groups: $F\ (2, 91) = 12.384$, $p < .001$. The effect size, calculated using eta squared, was .21, which in Cohen's terms is considered a large effect (Field, 2013). Post-hoc comparisons using the Games-Howell test indicated that the mean score for the control group ($M = 348.42$, $SD = 52.09$, *95% CI* = 330.79 to 366.04) was significantly different from the pain group ($M = 435.06$, $SD = 93.52$, *95% CI* = 401.34 to 468.78) and the chronic fatigue group ($M = 385.54$, $SD = 63.91$, *95% CI* = 359.72 to 411.35) at the .05 level. The reaction times between pain and chronic fatigue did not differ significantly ($p = .053$).

ERPs

Preliminary assumption testing for a MANOVA-analysis was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no serious violations noted.

All variables were first analysed for multicollinearity. A bias corrected accelerated bootstrapped correlational analysis showed significant correlations between several of the components, to varying degrees, but none strong enough to violate the assumption of multicollinearity (all below 0.8). A visual inspection of the scatter plots for all variables showed no signs of non-linearity, which means the assumption of linearity between dependent variables for each group were met.

P-P plots indicated that all variables were somewhat normally distributed, but with slight skewness. This was confirmed by a significant Shapiro-Wilk test. However, by calculating Mahalanobis' Distance for each case, we discovered that none exceeded critical values at a critical alpha level of .001 (df = 7, critical value = 24.32, our

highest value was 21.83). There was therefore deemed that there were no critical outliers and none too extreme scores in our data set, which established the normality of the distribution of the scores. Thus, we continued the analysis with a MANOVA. MANOVA is reasonably robust to modest violations of normality with our current groups sizes and is able tolerate a few outliers if they aren't too extreme (Pallant, 2013).

The variances for all variables, except cueP3 amplitude, were equal for all groups (at the .05 level); P3Go amplitude ($F(2, 91) = .980$, $p = .379$), P3Go latency ($F(2, 91) = .166$, $p = .848$), P3Nogo amplitude ($F(2, 91) = .173$, $p = .842$), P3Nogo latency ($F(2, 91) = 2.384$, $p = .098$), cueP3 amplitude ($F(2, 91) = 3.122$, $p = .049$), cueP3 latency ($F(2, 91) = .231$, $p = .794$) and CNV peak amplitude ($F(2, 91) = .082$, $p = .922$). A follow-up with Welch F-test on the equality of means of the cueP3 amplitude showed non-significance ($F(2, 58.445) = 1.277$, $p = .287$), which means that this component violates the homogeneity of variance and is thus not viable to use in this analysis at a conventional .05 alpha level. It is suggested that in these instances, the alpha level is set to a more conservative value for this variable in the following F-tests (Pallant, 2013).

As Box's Test of Equality of Covariance Matrices was non-significant, the covariance matrices of the three groups are assumed to be the same (homogeneity of covariance).

The MANOVA was significant for all test statistics. Hotelling's T^2 is used when there are two groups, and is thus not applicable to this study design. Wilks' Lambda might be chosen because we have three groups in this analysis, as it is commonly used when the independent variable has more than two groups. Pillai's Trace is however considered more robust and is thus a good choice if there is a violation of homogeneity of covariance (or other assumptions are violated), or the sample sizes are unequal, but it is also the also the most conservative of the test statistics. Roy's Largest Root is the more liberal of the tests, but it only uses the variance from the one dimension that separates the groups the most, and thus looses it's power if the differences lie along more than one dimension. Usually, there is one dimension the differences are found along (in practice), and Roy's is thus more powerful in such a case if homogeneity of covariance assumption is met. As we have no reason to

speculate in along how many dimensions the groups differ, and because there was some uncertainty regarding the normality of the samples (even if the tests are oversensitive when the samples are small (Field, 2013)), and because we have unequal N values and we want to reduce the probability of committing a Type I error, we opt for the more conservative test statistic; Pillai's Trace.

Using Pillai's Trace, there was a statistically significant difference between Pain-groups, Chronic Fatigue-group and Control-group on the combined dependent variables ($V = .389$, $F = 2.968$, $p < .001$, Partial eta squared = .195). The actual means and standard deviations are found in table 1.

Table 1: Descriptive Statistics

Means and standard deviations of each component within each group

Component	*Group*	*Mean*	*Std. Deviation*
P3Go amplitude	Control	10.237	2.7597
	Pain	8.399	3.3756
	Chronic Fatigue	9.041	3.4016
P3Go latency	Control	360.69	46.39
	Pain	362.78	54.32
	Chronic Fatigue	350.42	52.01
P3Nogo amplitude*	Control	13.094	4.9072
	Pain	10.387	5.0238
	Chronic Fatigue	10.520	4.4321
P3Nogo latency*	Control	364.81	29.20
	Pain	393.78	44.25
	Chronic Fatigue	379.35	37.35
cueP3 amplitude	Control	4.408	2.0764
	Pain	3.694	1.6170
	Chronic Fatigue	4.078	1.8055
cueP3 latency*	Control	416.89	56.79
	Pain	444.41	64.88
	Chronic Fatigue	405.08	57.46
CNV peak amplitude	Control	3.431	1.5327
	Pain	3.621	1.5698
	Chronic Fatigue	3.955	1.2552

** = Statistical significant differences found between groups before Bonferroni-correction*

The univariate analysis indicated that there were significant differences between the groups in P3Nogo amplitude ($F(2, 91) = 3.352$, $p = .039$, Partial Eta Squared = .069), P3Nogo latency ($F(2,91) = 5.165$, $p = .008$, Partial Eta Squared = .102) and cueP3 latency ($F(2,91) = 3.401$, $p = .038$, Partial Eta Squared = .070), and a trend towards significance between the groups in P3Go amplitude ($F(2,91) = 2.968$, $p = .056$, Partial Eta Squared = .061). However, after a correction of the alpha-value for the multiple

ANOVAs being run, the acceptable statistical significance was $p > .007$. This resulted in no statistical significant effects between groups when the variables were considered separately. Since the MANOVA was significant on the combined dependent variables, we followed up with a discriminant function analysis.

Because the corrected non-significance of the univariate analyses precludes a post-hoc analysis, but we still want to examine how the dependent variables separate these groups, another possible follow-up analysis to a significant MANOVA is a discriminant analysis (Field, 2013). A discrimination analysis breaks down the linear combinations of the outcome variables that the MANOVA examines, to see how several predictors can best discriminate between these three groups. In short, the discriminant analysis attempts to predict one or more grouping variables from a set of outcome variables – it predicts group membership based on a combination of the dependent variables. The linear variates the MANOVA identified are thus used as functions in a discriminant analysis (Field, 2013). In short, we have found a significant difference between the three groups, and now we will try to identify along what dimension(s) these groups differ.

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 81.5% of the variance, canonical $R^2 = .30$, whereas the second function explained only 18.5%, canonical $R^2 = .09$. In combination these discriminant functions significantly differentiated the three groups, $\Lambda = 0.64$, $\chi^2(14) = 36.61$, $p < .001$, but removing the first function indicated that the second function did not significantly differentiate the groups, $\Lambda = .91$, $\chi^2(6) = 8.17$, $p = .226$. Thus, the group differences we found in the MANOVA can be explained in terms of two underlying dimensions in combination. In order to determine which of the variables contributed to the differences between the three groups, the standardized discriminant function coefficients and the structure coefficients were examined. The correlations between outcomes and the discriminant functions revealed that P3Nogo amplitude loaded higher on the first function ($r = .41$) than on the second ($r = -.07$), as did the P3Go amplitude ($r = .37$ and $r = -.29$, respectively). The cueP3 latency loaded heavier on the second function ($r = .85$) than on the first (r -.11), as did P3Nogo latency ($r = .53$ on the second and $r = -.45$ on the first), P3Go latency ($r = .31$ on the

second and r = .06 on the first), cueP3 amplitude (r = -.28 on the second and r = .216 on the first) and CNV peak amplitude (r = .28 on the second and r = .18 on the first). These results are also shown in Table 3.

Table 2 shows which variables contribute to the discrimination between the groups; the larger the standardized coefficient, the greater the respective variable contributes uniquely (partly, without overlap) to the discrimination between the three groups (along the functions). As such, P3Nogo amplitude and the CNV amplitude contribute strongly to the discrimination along the first dimension, and cueP3 latency and P3Nogo amplitude to the second dimension. However, as the different polarities show, the P3Go amplitude contributes moderately uniquely to both functions, but in different directions.

Table 2: Standardized Canonical Discriminant Function Coefficients.
The value for each function denotes how much each variable contributes uniquely to the discrimination of the groups along the two functions.

Component	*Function 1*	*Function 2*
P3Go amplitude	.343	-.426
P3Go latency	.224	-.132
P3Nogo amplitude	.963	.756
P3Nogo latency	-.492	.289
cueP3 amplitude	.154	-.012
cueP3 latency	.074	.826
CNV peak amplitude	-1.225	-.413

This is also shown in the structure matrix (table 3) that denotes the simple (not unique) correlations between the variables and the different functions and identifies which variables help cause the discrimination between the groups. Here we see that the P3Go amplitude and the P3Nogo amplitude in combination contribute most to the discrimination along the first dimension. At this point, it isn't possible to determine which groups the functions discriminate between.

Table 3: Structure Matrix.

Exact correlations between each variable and each underlying function.

Component	*Function 1*	*Function 2*
P3Nogo amplitude	.413*	-.068
P3Go amplitude	.365*	-.287
cueP3 latency	-.110	.846*
P3Nogo latency	-.448	.530*
P3Go latency	.057	.306*
cueP3 amplitude	.216	-.280*
CNV peak amplitude	-.179	-.275*
** = Greater contribution to the discriminative qualities of the respective function*		

The Group Centroids (table 4) are the means for the significant discrimination functions across groups. These centroids (or means) show locations along which dimensions the groups differ, as the values are akin to coordinates in a multivariate space where the further away from zero the mean is, the more discriminative is the respective function. The closer the value is to zero, the less discriminative the function between groups. According to this, function one discriminates between Control and the patient groups, while Function 2 discriminates between Pain and the two other groups. The group centroids indicates the ability of the constellation of combined variables to discriminate between the three groups, as function 1 discriminates strongly between the healthy controls and the two patient groups, as evidenced by the different polarities and high values. Function 2 also discriminates between the Pain group and the other two, but not as strongly as the first function.

Table 4: Functions at Group Centroids.

The mean of each group along the two functions in a multivariate space.

Group	*Function 1*	*Function 2*
Control	.818	-.014
Pain	-.480	.361
Chronic Fatigue Syndrome	-.542	-.424

The discriminant function plot showed that the first function discriminated the control group from the patient groups of pain and chronic fatigue, while the second function differentiated the pain group from the chronic fatigue and control group. This classification is based on computing how close the individual cases are to each group centroid in the multivariate space. The individual case would thus be classified into the group it is closest too; in other words the cases are classified according to where the distances are smallest to each group mean. Classification statistics indicated that 61.7 % of originally grouped cases were correctly classified by the seven variables. 80.6 % of the subjects in the control group were correctly classified, while 56.3% and 42.3% of the subjects were correctly classified into the Pain group and the Chronic Fatigue group, respectively.

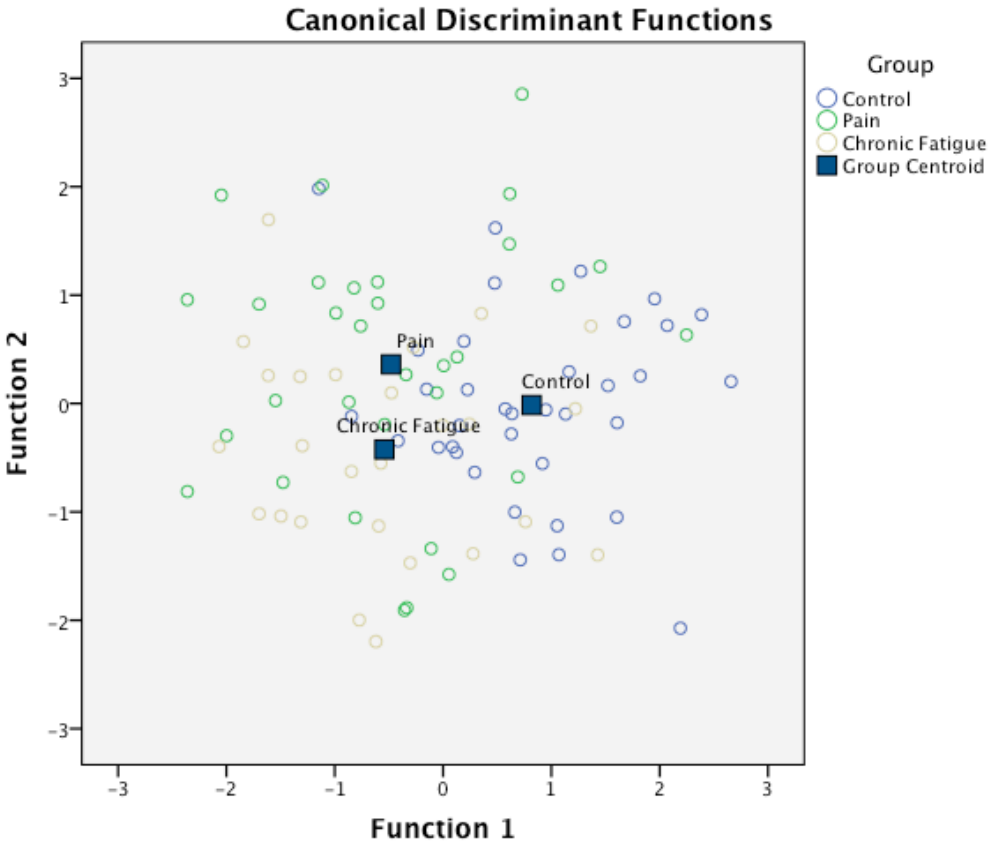

Figure 5: This is the multivariate space where the mean of each group is denoted with a dark box. Each circle is a single participant, and their placements are computed along both functions (function 1 horizontally, function 2 vertically). Function 1 discriminates between patient groups and the control group, and function 2 discriminates between the CFS/ME group and the Chronic pain group, with negligible discriminative impact with regards to the control group.

Discussion

Behavioural data

Reaction time is an overt indicator of information processing, and these results show that the group with pain patients responded slower than the two other groups, but only significantly slower than the control group. The standard deviation of the pain group was also found to be higher than either of the two other groups, which means that there also were greater differences between the reaction times of each individual. The means indicate that the chronic fatigue group was faster than the pain group, almost reaching statistical significance. However, they were significantly slower than the control group, and with a greater standard deviation, if not by much. These results indicate that there might have been a greater degree of processing disruption in the time between the presentation of the stimuli and the following motor response in the patient groups than in the healthy controls. This could have been explained by a difference in energization and the preparation of motor responses (Brunner et al., 2015), however, the CNV-component did not trend towards statistically significantly different between the groups even before the Bonferroni correction was executed, and as such this is not an adequate explanation for these behavioural deviances. This indicates that there might be some kind of disruption of processes in other systems.

ERPs

The results of both the MANOVA and the discriminant analysis indicate that *in combination*, the P3-components and the CNV permits a differentiation between chronic pain, chronic fatigue syndrome and healthy controls. The heterogeneity of both pain and fatigue conditions reduces the possibility of locating a single differential diagnostic marker. The possible existence of subgroups within the different patient populations and the high degree of symptomatic overlap complicates such a matter greatly. It is thus more likely that one will find several singular markers denoting these subgroups, rather than one single marker for each patient population as a whole. One of the more interesting findings in this study is the lack of significant differences between the control group and the chronic fatigue patients along one dimension, and the lack of significant differences between pain and chronic fatigue along another. This might be explained by the symptom overlap between the two patient populations in general (fatigue, pain, cognitive disturbances, etc.). This was

corroborated by the discriminant analysis where only 42.3% of the chronic fatigue and 56.3% of the chronic pain cases were correctly classified, compared to 80.6% of the control group cases. As such, the classification of chronic fatigue and chronic pain was above chance, but based on the variables examined in this study, it was definitely not enough to discriminate correctly approximately half of the patient cases.

Function 1 identified from the discriminant analysis might be interpreted as belonging to the dimension of experienced pain, as this is often found to be a shared symptom among pain and fatigue patients (Stubhaug, 2008) and it has shown to affect attention (Legrain et al., 2009). It could also be interpreted as a dimension of a shared sensitization mechanism. Function 2 might be an unknown underlying mechanism that differentiates between the patient groups, but which chronic fatigue patients have in common with healthy controls. As the second function discriminates between pain and the two other groups, one could speculate that the underlying mechanism might be that the attentional systems of chronic fatigue patients are functioning more equal to healthy controls than to a condition with similar core symptoms. If this were the case, this is relevant for the interpretation of the results as the Shapiro-Wilk normality test actually showed that the CFS/ME group was more normally distributed than the control group. This null-finding for the CFS/ME group could be explained due to the visual nature of the Go/Nogo task used in this study, as the reported impairments regarding information processing are more pronounced in the auditory domain (Tiersky et al., 1997). In visual information processing tasks CFS/ME subjects usually were found to perform within normal limits comparable to control groups (Scheffers et al., 1992).

The lack of significant differences found for the CNV can not explain the differences in RT. It has been shown that the amplitude of the CNV is increases when the participants are instructed to concentrate hard and respond very quickly with a button press, thus investing more effort. This correlates with reaction time and is thought of as an energization process, possibly a reflection of both selective attentional and arousal processes (Brunner et al., 2015; Tecce, 1972). As there were no indications of CNV being affected in the univariate analysis, and considering the reaction times were significantly different for both groups compared to a control group, it is reasonable to assume that the disruption of response related processes do not lie with

the mobilization of efforts. The theory of the amplitude of the CNV as an Index of a temporal accumulator, reflected in motor timing to a stimulus, suggests that if there was a dysfunction in behavioural timing and prediction as a function of attention in relation to motor preparation, the amplitude of the CNV (the amount of synchronously activated neurons) should be attenuated. It thus seems like the symptoms found in Chronic Fatigue patients are not due to disrupted processes related to motor responses or time-based decision making, at least those related to the press of a button with one's finger. The CNV is postulated to be associated with the degree of attention paid to the stimuli (selective attention), as the subjective perception of timing seems to be determining for the CNV amplitude (Macar & Vidal, 2004).

The context updating hypothesis of the P3 is also thought related to the aspects of temporal memory (attentional and working memory processes) reflected in the CNV, as there has to be some kind of memory trace to be able to predict an upcoming stimulus (Macar & Vidal, 2004). As there were found no significant differences for neither component's amplitudes, they support a relatively intact and functional attention and working memory system as well as available neuronal resources to both task-relevant stimuli and motor preparations. At the very least, it supports the notion that the patients are able to mobilize the attentional system adequately when necessary, during the test.

The results from this study could also reflect a difference in etiology between chronic pain and chronic fatigue. Both might share the mechanism of sensitization, and according to the literature and findings it is plausible that chronic pain syndrome started with central sensitization mechanisms. Over time this may have resulted in a modification of default networks that consequently increased vigilance to potentially harmful stimuli. Among other things, this could be reflected in reduced amplitude in the P3-components, as the system is unable to disengage from this hypervigilance and allocate attentional resources towards a cognitive non-sensory modality task (Van Damme et al., 2004).

Phrased differently, the system may have been altered with an overpowering top-down neural activity that gives precedence to stimuli and cues in the environment that could signal threat to one self. A hypervigilance which biases somatosensory brain

activity in such a way that the attentional capture of pain, modulated by top-down processes, is reflected in an attenuated P3 is in accordance with behavioural and neuroimaging evidence of a neurocognitive model of attention to pain (Legrain et al., 2009). Such a model attempts to explain the effect of pain on attention through a balance between top-down and bottom-up influences, conceptualized in regards to functionally connected neuronal networks as temporally synchronous activity (Fries, 2005). A system-wide shift in the dynamics of the network could thus result in a neural filter highly vigilant for potentially threatening stimuli, but disrupts the transmission of information associated with attentional task-related processes. As the discriminant analysis showed, the two variables strongest correlated to discriminate the patient groups from the control group along the first dimension (function1) were P3Go-amplitude and P3Nogo-amplitude. These attenuated components could possibly reflect a less synchronized system. It is however uncertain from this study if the less effective synchronization reflected in these P3-components is due to an increased attention to pain and fatigue symptoms in the two groups, or if it is due to a more general system modification which results in the attenuation of the components as a reflection of ineffective dynamics between networks.

At a central nervous system level in chronic fatigue, one could speculate that there might have been a different functional activation of the brain's default networks, which might have resulted in the non-significant findings and results when compared to a healthy control group. It might have started with and facilitated the development of the illness through central sensitization, which perhaps resulted in abnormal parasympathetic functioning (as reflected in diminished vagal activity) which might have resulted in an excessive energy usage during situations requiring efforts, with the expenditure of energy becoming out of proportion to the requirements of the situation, leading to a low threshold for the feeling of fatigue (Sisto et al., 1995). It is however important to note that the vagus nerve influences multiple organs in different ways, and conclusions from such studies should remain tentative. Other reported abnormalities in the HPA axis reflected in hypocortisolism, which is linked to lethargy and fatigue that might be due to a deficit in the corticotropin-releasing hormone and indicates an altered physiological response to stress. Increased serotonin neurotransmissions are also reported (Michiels & Cluydts, 2001). Abnormalities in

sympathetic and parasympathetic systems might be a consequence of system sensitization in CFS/ME.

Sensitization processes may thus underlie the range of problems comprising chronic fatigue syndrome. Sensitization may develop on several different levels, not just centrally or peripherally, but also at cognitive and immune-system levels (Jones, 2008). In CFS/ME, the initial preoccupation with somatic sensations, especially after an infection or a period of high stress, might result in a constant activation of neural networks responsible for communicating interoceptive sensations. Following this, sensitization mechanisms and neural plasticity in central nervous loops would later on result in normal physiological processes (like stress, exercise-related arousal, drowsiness during the day, etc.) to be perceived by some people as intolerable (Eriksen & Ursin, 2004). This might be the result of increased activity of noradrenergic neurons coupled with less neurotransmitter release per firing as well as depleted noradrenergic stores. As the early stages of stress are marked by increases in adrenergic, serotonergic and noradrenergic activity, these changes are characteristic of an apparent exhaustion of physiological systems after prolonged stress (Otto, Yeo, & Dougher, 1987).

James F. Jones reviews this kind of evidence in a thought-provoking essay that proposes the possibility that, like the memory of pain, the brain also monitors, records, and processes sensations, consequences (cognitive, affective and autonomic) and biological events of past infections through interoception, such that it, in essence, creates and remembers an "infection-memory". This memory is reflected in alterations in cell surface proteins that are produced during an infection, and consequently induces changes at multiple brain levels (also autonomic nervous system levels). The integration of all these sensations and alterations, combined and coordinated with ones memory, perceptions and situational needs, results in an altered self that fails to change and adapt back to a different illness-free state of being. He considers this A self ("the Altered self") that has strayed from the healthy baseline. Because of disturbed recognition or evocation of biological signals this Altered self is unable to regain this previously illness-free baseline as a "functional self" capable of adapting and responding to current and future events and challenges (Jones, 2008). Some consistent findings of immune system abnormalities in chronic fatigue

syndrome patients might serve to strengthen such a hypothesis. However, as there are no consistent evidence of a single infectious agent causing chronic fatigue, it is more probable that such an "infection-memory" – if so is the case – would be the result of a heterogeneous group of infections (Afari & Buchwald, 2003). The thought of alterations to the nervous system on several levels is compatible with the conception of alterations to default networks that consequently maintain the chronicity of the illness via inflexible and overpowering top-down activity that outmatches and disrupts the bottom-up processing of actual somatosensory signals. A possible result of infection or immunological processes could be a sensitization of the nervous system, where the increased reactivity and amplification of several symptomatically central systems could present as a sustained arousal and activation of physiological and cognitive systems. This could partly explain the excessive fatigue reactions found in CFS/ME; as an amplification of interoceptive sensations, which in most people are perceived as normal physiological processes (Eriksen & Ursin, 2004; Stubhaug, 2008). This could tentatively be explained by a rewiring and over-activated default network chronically augmenting and oriented towards internal sensations, expressed as a chronic mode of preparedness and alertness (Fransson, 2005) reflected in inflexible and ineffective functional connectivity.

Even if our findings did not reach statistical significance, the differences found in the means might be a tentative indicator of support for such a theory. The mean cueP3 latency for the Chronic Fatigue group was the shortest off all three groups, meaning that this patient group processed early cued information faster than the two other groups, which argues for a sensitive and alert system. As the latency and amplitude of the cueP3 component has been shown to covary (Gratton et al., 1990) a shorter latency would also predict an attenuated amplitude, which is in accordance with our findings when compared to the control group. This could argue to be reflective a highly alert system which initiates a process of stimuli-evaluation very quickly, but as the external stimuli was not deemed salient enough to warrant greater processing, less attentional resources allocated to the stimuli. This could be explained by a biased top-down modulation of the attentional systems prioritizing greater resource allocation towards the processing (and consequent enhancement) of internal sensations (Sarter et al., 2001) over external sensations. The fact that the mean amplitude of all P3-components were attenuated in the Chronic Fatigue group compared to the control

group supports the theory of less available attentional resources to process the externally presented stimuli because of a strong top-down focus reflective of an inflexible system (Engel & Fries, 2010). This seems to negate our earlier expectations of finding an enhanced cueP3-amplitude as an indicator for sensitivity in the Chronic Fatigue group. We assumed that the cueP3 would show enhanced amplitudes regardless of whether the system was sensitive towards internal or external stimuli, but because a post-hoc test was prohibited in this study, this is not testable with our current data. Based on the findings of previous studies and the theories presented here, one could assume that such an internal/external distinction could be reflected by the cueP3-component in a similar study with more participants.

Something similar has been proposed regarding pain: a neuronal template of pain. Loeser & Melzack formulated the theory of a neuromatrix as a pattern-generating mechanism based on sensory inputs in conjunction with affective and cognitive information from other areas of the brain. This was thought to generate an output, which resulted in the perception of pain, based on genetics and memories of past experience. As such, stress, learned experiences and expectations were thought capable of interfering with the interactions between the peripheral stimuli and the neuromatrix (Loeser & Melzack, 1999). The idea of a neuromatrix for pain, more commonly known as the pain matrix, has now evolved into a perception of a pain connectome (Kucyi & Davis, 2015).

With a consistent activation of this connectome, the output pattern may become a learned pain template, and the brain may thus generate the perception of pain even in the absence of actual noxious stimuli. As previously mentioned, there doesn't necessarily have to be actual tissue damage for pain to be perceived as real, and the individual's personal experience of the stimulus is thus important for the experience of pain. If the bottom-up processing of noxious stimuli is strong or persistent over a long period of time, the pain matrix might develop a template for pain. In other words, the reorganization of parts of the nervous system following long-lasting noxious input could permanently alter neural circuits at central levels, which affects the processing of input and eventually might be activated as an implicit somatosensory memory of pain in response to benign sensory processing (Flor et al., 2006; Yi & Zhang, 2011). These functional circuits could thus work as a kind of memory trace, courtesy of the

established template, as inflexible and recurring spontaneous communication "loops" within default networks, like the traditional default mode network and the antinociceptive system, as well as disturbed connectivity between networks. This repeating dynamic may thus be both detrimental for the structural and functional integrity of the systems, consequently entraining and reshaping the functional organization of key networks within the pain connectome towards abnormal sensory processing (Kucyi & Davis, 2015). It has been shown that reduced intrinsic connectivity in the default mode network correlates with reduced self-reported spontaneous pain (Napadow, Kim, Clauw, & Harris, 2012).

Even though the analysis yielded no clearly interpretable results, our data contributes tentative support for such persistent and repetitive communication loops in inflexible neural networks, as this type of activity is in accordance with a strong top-down modulation of attentional systems along the same lines as our findings for the Chronic Fatigue group. Similarly, the mean amplitudes of all P3-components were found to be attenuated for the Pain group when compared to the control group, but they were also attenuated when compared to the Chronic Fatigue group. As such, this could indicate that the attentional systems of the subjects in the Pain group allocated the least resources to the processing of the presented stimuli in the VCPT. In contrast to the Chronic Fatigue group and the control group, the latency of all P3-components were the longest for the Pain group, indicating that their attentional systems initiated stimulus processing later than the two other groups. This could be a disruptive effect of the experience of pain, as pain has been argued to interfere with attentional systems (Glass, 2006), but it could also reflect an inflexible system, as well as disturbed connectivity between networks, which would also result in a delayed processing of stimuli. The finding of attenuated amplitudes of the P3-Go and P3-Nogo components are as expected, with the exception of the attenuation of the cueP3-component. Based on preliminary simplified analysis that indicated an enhanced cueP3 we expected to replicate these results. Not only did we not accomplish this, but the amplitude of the cueP3-component in the Pain group is the most attenuated of all three groups. This is, however, in accordance with a theory of a constantly reiterating pain memory disrupting the orienting functions of the attentional systems the cueP3 is assumed to index, but is nevertheless confounding. Such contradictory findings strongly indicate

a need for further studies of the functionality of the cueP3-component, as well as more EEG-studies of chronic pain syndromes.

Ever since Raichle and colleagues coined the term "default mode network", interest in this underlying intrinsic system has only increased, and more and more evidence seems to indicate that these spontaneous fluctuations modulate all other brain activity, and it is found to be attenuated or disrupted in several psychiatric disorders, pain included (Tracey & Bushnell, 2009). These same brain activity fluctuations seem to be predictive of somatosensory perception, as the timing between neural baseline activity preceding processing of stimuli determines the perception of nociceptive stimulation (Boly et al., 2007). It is argued that dysfunctional attenuation of a vigilant network that mainly is preoccupied with the external world results in heightened vigilance and awareness towards the external somatosensory stimuli. A network anticorrelated to the default mode network is oriented towards changes in the internal environment and introspective processes (Fransson, 2005). Contrasting this with chronic fatigue where there seems to be a self-reported heightened awareness and perception of the interoceptive sensations (Stubhaug, 2008), it would be highly interesting to examine if similar decoupling dysfunctions were found in the default network associated with these processes. Following this, there seems to be reason to believe that it isn't the attentional system per se that is affected in both patient groups, but rather that the attentional disruptions might be symptoms or consequences of the underlying default mode network having become altered, thus not modulating the neural activity needed for a cognitive demandingly task good enough (balanced top-down/bottom-up interaction and efficient coupling/decoupling between networks). When examining each participant's individual P3-components, an overwhelmingly large portion of the patient populations had drawn out and hard to define waveforms, which could reflect that the coordination between networks needed for effective and well-synchronized neural activity is delayed and disrupted. The same impact of spontaneous fluctuations on attention has been postulated to be found reflected in reaction times (Weissman, Warner, & Woldorff, 2009) as a result of the dynamics between anticorrelated default mode networks.

On a more local level, dysfunctional descending inhibition and facilitation mechanisms maintains and exacerbates the centrally sensitized state of chronic pain

patients, which could present as a functional disturbance between bottom-up and top-down processing (Montoya et al., 2005; Montoya et al., 2006). Following increased top-down activity, a resulting specific oscillatory rhythm where the timing of the peaks and troughs allows more irrelevant information through than in healthy individuals, might thus give a different sensory gating neural rhythm (Fries, 2005). It is hypothesized that oscillations within the beta band subserves the maintenance of a status quo of neural activity, meaning that increased activity and connectivity in the beta band is a reflection of a strong top-down modulation of the brain to reduce the impact of irrelevant and possibly disruptive stimuli to the active behavioural or sensory neural template (Engel & Fries, 2010). Studies of ERPs are not sufficient to further investigate such assumptions, but spectra-analysis of the activity in different oscillation bands should be able to contribute further on this subject. An earlier unpublished study did indeed find unspecified beta-disruptions in areas related to pain processing (Wiik, 2009), indicating that this area warrants further research.

Anticorrelated networks could thus subserve the attentional shifts observed during experimental tasks, where a lack of attention results in poorer task-performance, and vica versa. Earlier explanations have conceptualized the allocation of attentional resources as a competition of processing resources, but Fox et al. (2005) argues instead that the spontaneous and intrinsic anticorrelated fluctuations in the human brain better explains this phenomenon. As such, ERPs may be indexes of how well synchronized and correlated these networks are during an attention demanding task. Good performance reflected in higher amplitude and shorter latencies, one could then postulate, reflects the magnitude of functional activation of a task-positive network, while simultaneously being effective in attenuating the default mode network. Abnormal ERPs could then reflect a poorer correlated interaction and shift between these networks, as the default mode network would be more difficult to suppress or modulate (by sensory information) and would thus interfere with the activity of the task-positive network, resulting in reduced attention to the task. As continuous spontaneous activity and task-evoked neuronal activity (measured with BOLD) are proposed to be linearly superimposed (Fox & Raichle, 2007), and the spontaneous fluctuations of that default mode network contributes to inter-trial variability in tasks (Fox, Snyder, Vincent, & Raichle, 2007), it is possible to argue that ERPs might reflect aspects of intrinsic spontaneous fluctuations in relevant networks. Especially

since the spontaneous BOLD signals used to identify these fluctuations in brain activity is found to correlate with fluctuations in the spectral power of EEG frequency bands across different associated neuro-anatomical networks in a potential EEG-signature for a default network (Laufs et al., 2003). Additionally, attention networks associated with top-down modulated control of attention has been distinguished on the basis of resting-state correlational patterns (Fox & Raichle, 2007), meaning that attentional networks are identifiable based on dynamic patterns of neural activity. The patterns associated with top-down modulated control of attention is thus distinguishable from other patterns of activity, indicating that the dynamics are not mere random fluctuations in neural activity, but that they indeed might be functionally significant, as well as objectively discernable. One could define such a pattern of neural activity as a kind of neural signature.

Decreased gray matter in regions normally involved in the modulation of pain might be connected to degradation as a consequence of altered default mode networks. In a commentary by Buckner & Vincent (2005) they draw attention to studies showing that the same regions where amyloid plaques and resulting structural atrophy are found in early stages of Alzheimer's disease overlap with regions manifesting default activity. They propose the possibility of this activity augmenting some type of metabolism- or activity-dependent cascade in these areas that eventually results in the development of Alzheimer pathology. The same mechanisms might be underlying the chronicity of the pain and fatigue syndromes, with structural changes and cortical atrophy resulting in altered functional connectivity between networks, which thus "anticipates" and interprets sensory information in maladaptive ways. Evidence of altered anatomical, functional and neurochemical structures and processes in the brain of chronic pain patients further supports the argument for a "rewiring" of intrinsic networks resulting in altered central nervous system processing (Tracey & Bushnell, 2009). It thus seems that the intrinsic dynamics of brain activity might modify our perceptions greatly.

Conclusion

A significant MANOVA means that there are significant differences between these three groups along some dimension with some dependent variable combination, and as the effect size was found to be large these results are interpreted to be genuine. The discriminant analysis elucidated this further. As the P3-component has shown itself to be valuable for assessing cognitive function as an index for information processing, and as such possibly serves as a clinical biomarker for some diseases of the brain; it also serves a useful function of possibly discriminating between subtypes or disorders or between pathophysiological mechanisms (Duncan et al., 2009). Alterations to the component may not be specific for a particular disorder, but its sensitivity to the integrity of the attentional system vouches for its clinical usefulness. The results presented here point towards that the patient populations are to a certain degree attentionally on par with healthy controls in a visual continuous performance test, as has also been pointed out in earlier studies of CFS/ME (Scheffers et al., 1992). However, before the Bonferroni corrections, there were indications of differences between the groups regarding some components. Even if they are not deemed significant in this study, they still warrant a discussion as the discriminant analysis demonstrated that they are relevant to differentiation between populations. That some of the components barely missed becoming significant does not necessarily indicate that there are no differences between the groups. On the contrary, it indicates that there actually might be some differences of interest, but that this specific study was unable to demonstrate such a difference. This might have been because of too few participants, or because the variation between the participants was too large. In a future study with a higher *n* and a more narrow research hypothesis, these results might turn out to be statistically significant after all and contribute to further accumulation of knowledge. The failure to reject the null hypothesis for some of the components does not mean that this is a true reflection of reality. It simply means that this particular study could not conclusively uncover these differences. The means between the groups did indeed differ, and demonstrates as such that there is a difference between the groups, it just wasn't significant in this study. As such, this explorative study acknowledges that it is one stepping-stone in a larger research process. Hopefully these data may highlight areas of interest for further studies with different samples.

As Aaron & Buchwald (2001) note, the high degree of comorbidity and wide spectrum of unexplained conditions makes it more probable that a multifactorial model incorporating the interactions of biology, genetics, environment, cultural and psychosocial factors is necessary for the development of pain and chronic fatigue conditions, instead of single factors. This further confounds the hunt for a single biomarker to differentiate between two overlapping and highly heterogeneous conditions like chronic fatigue and chronic pain, as evidenced in this study where the results point to a differentiation along a dimension of combinations of multiple components. As the discrimination seems to be both between the patient populations and healthy controls, and between pain and CFS/ME and controls, this suggests a certain overlap between chronic fatigue and chronic pain. This overlap is made even more relevant as 25% of the subjects in the pain group were wrongly classified as belonging to the Chronic Fatigue group by the discriminant analysis, and 26.9% of the subjects in the Chronic Fatigue group were wrongly classified as belonging to the Pain group. This overlap might be explained by general sensitization mechanisms of the central nervous system and alterations to the immune system. Even more interesting is that 30.8% of subjects from the Chronic Fatigue group were wrongly classified as belonging to the Control group. However, this could also be due to some of the healthy controls carrying a latent vulnerability (high sensitivity), but without being troubled by this. These results warrants further studies in the direction of central sensitization and common underlying factors for the development and expression of both conditions, as both central sensitization of the CNS and infectious alterations and immune system abnormalities might result in a substantial alteration of default mode networks reflected in the as of yet unspecified pathological underlying concepts found by the discriminant analysis. As the specificity seems to be low when examining these two patient populations, ERPs seems to be only usable as supplementary information to traditional diagnostics when encountering either chronic fatigue or chronic pain patients, at least until more definitive biomarkers – single or in combination – are discovered.

Limitations

As the ERPs are dependent upon the protocol and subsequently the protocol is guiding for what inferences and interpretations are made of the ERP data, it is imperative that the protocol is explained and applied uniformly at every single time of measurement. If not, then one can not be sure of what exactly the ERPs are a reflection of. Also, the use of a protocol warrants a degree of a priori. Protocols are defined by which system(s) and what kind of functional activity one is interested in, consequently outlining what is to be measured and investigated and excluding other systems and activity of lesser interest to the study. The kind of protocol chosen thus not only reflects what is possible to investigate, but also what and in what system(s) one expects to find potential deviances. This could bias the following extrapolation and interpretation of the findings. As the exact instructions given to each of these three groups has not been possible to supervise or obtain after the studies, this marks a possible limitation on the results of this study.

Traditionally, most EEG-studies have used peak latency calculations. As this study had more drawn out components, a more accurate method to measure latency was a relative criterion version of the fractional area technique and earlier results may not be optimal to compare with this study.

One of the greatest limitations for this study is the age-differences between the three groups and the poor matching. Peak latency was used in earlier studies that show reduced amplitudes and prolonged latencies for older subjects. However, the older subjects in some of these studies had increased amplitudes frontally, and reduced amplitudes parietally compared to the younger group, and the latency was prolonged only for the P3a-component (O'Connell et al., 2012). The elderly group in this study had a mean age of 70.6 years (n=14), and the young a mean age of 22 (n=15). The differentiation between P3a and P3b also plays a role as the pictures becomes even more differentiated, but considering that we used another approach for measuring amplitude, and that we did not distinguish between P3a and P3b as we only measured the strongest P3 component, the results should not be chalked up to simple age effects. It has also been shown that the P3Nogo latency is affected by age (prolonged), but not the amplitude of the component (Falkenstein, Hoormann, & Hohnsbein,

2002). Another point is that the mean age of our pain group is considerably younger than the elderly groups in earlier studies, which most often is around and above 60 years of age.

The age-related changes of the P3 component has been thoroughly shown for both visual and auditory stimuli, and the trend shows the aforementioned attenuation and prolongation of the component across the age groups (20-80+), more so for auditory than visual stimuli (Polich, 1997), but there has not been shown that the changes are significant between a group of 20-year olds and 40-50 year olds. A study by Anderer, Semlitsch & Saletu (1996) has shown that the latency reduction is curvilinear with a drastic prolongation in latency after 60 years, and almost four times less per year below the age of 60. In fact, it was only when subjects above the age of 60 years were included in the regression analyses that significant age effects were obtained. Below the age of 60 years, the prolonged P3 latency was not significant between the younger age groups. However, the P3 amplitude did decrease steadily with age. They also confirmed that the P3 amplitude was electrode location dependent across age groups with a greater amplitude decrease parietally. This study underlines the importance of age-matched controls.

The second great limitation of this study is the great number of components we chose to examine. The amount of variables under investigation resulted in such a high Bonferroni-corrected p-value that the different comparisons did not reach statistical significance in a univariate analysis, which prohibited us from running post-hoc analyses on the components that exhibited initial significant levels. This was a risk we were well aware of, and the issue of number of components had been discussed several times before the study. However, considering we wanted to investigate if, and most importantly how, the three groups potentially might differ, we resolved to investigate at such a wide scope because earlier ERP-studies had not included either the P3-Nogo or the cueP3, and the amount of ERP-studies done on CFS/ME was sorely lacking in general. As such, we considered this study a preliminary exploratory study into the matter, and the results here seems to vindicate our design choice and have given clear indications of where future studies could investigate further.

A final methodological issue could have been the heterogeneity of the patient group in general, but in this study the Levene's Test (and Welch's F) showed that the variance within and between groups was within acceptable limits. The MANOVA is supposed to be robust to slight breaches of assumptions, but clinical data are rarely suited for parametric analyses and a different test might have been more apt. However, as there is no non-parametric equivalent test to the MANOVA (Pallant, 2013), we have done all we can to ensure that the data used have fulfilled all the criterions for the use of a MANOVA. Even if the variation was within acceptable limits, the standard deviations were still high, and as such highlights the heterogeneity in clinical samples in general, especially these two patient populations. Also, as Michiels and Cluydts (2001) mention in their review, since the etiology of CFS/ME is unclear and the heterogeneity of affected subjects has to be taken into account, the Bonferroni corrections done in this study are necessary for methodological reasons, but the corrections might be too stringent. As there is still much uncertainty surrounding the profile of both CPS and CFS/ME, there is a very real possibility of committing type II errors, which is why this study reports both statistical significant results, power and trend results, as they may contribute to further understanding of these two syndromes.

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