Effects of Anodal Transcranial Direct Current Stimulation on Experimentally Induced Heat Pain in Healthy Volunteers

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Preface

This thesis was based on a study designed by Per Aslaksen, who also programmed all the equipment used in the study. The author acted as experimenter, together with two other psychology students. This study was the first at our department to employ tDCS. All statistical analyses were done by the author, with the help of Espen Bjørkedal.

Many persons contributed to the completion of this thesis. Most of all, I would like to express my gratitude to my supervisor Espen Bjørkedal, who provided valuable advice and shared his theoretical and statistical knowledge throughout the process. I am also grateful to Per Aslaksen for providing training in the laboratory and for patiently answering all my questions about study design. I want to thank Magne Arve Flaten, who introduced me to the research field on pain and placebo and inspired me to write my thesis on this topic. I would also like to acknowledge Tove Irene Dahl for her commitment to improving the quality of the Master Programme, and for practical advice. Thanks to my fellow master students for interesting discussions and inspiration. Finally, I am grateful to my family and friends, who have provided their kind support throughout this process. Special thanks to Burbuqe Latifi and Kristian Berg for their unconditional support and reassurance, and for proofreading this thesis.

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Sammendrag

Transkraniell stimulering med likestrøm (tDCS) er en ikke-invasiv nevromodulerende teknikk som kan dempe smerte. Den har mildere bivirkninger enn farmakologiske behandlinger og har blitt påvist å dempe kronisk smerte. I denne studien undersøkte vi 1) effekter av anodal tDCS på smerteintensitet og smerteterskel, 2) placebokomponenten i den smertedempende effekten av tDCS og 3) hvorvidt stress og negativ affekt modererer den smertedempende effekten av tDCS. Sekstifire deltakere (32 kvinner) mottok tre blokker av varmestimuli, 43° C, 45° C og 47° C i hver blokk. Behandlingsgruppen mottok anodal tDCS av 2 mA styrke i 7 minutter, placebogruppen mottok placebostimulering i 30 sekunder og naturlig historie-gruppen mottok kun smertestimuli. Deltakerne rangerte smerteintensitet med CoVAS. Terskelen ble målt før den første og etter den siste blokken. Subjektiv stress ble målt ved hjelp av to SACL spørsmål og negativ affekt ble målt ved hjelp av spørreskjemaene FPQ, PANAS og BFI. Sammenlignet med naturlig historie reduserte tDCS smerte med 28%, kun for 47° C stimuli. Sammenlignet med placebostimulering, reduserte tDCS smerte med 11%, men denne reduksjonen var bare marginalt signifikant. Det var ingen placeborespons og ingen effekt av tDCS på smerteterskel. Frykt for medisinsk smerte predikerte smertereduksjon etter tDCS, større frykt for medisinsk smerte var assosiert med større smertereduksjon. Våre funn bekrefter og utvider tidligere funn fra eksperimentelle og kliniske studier.

Nøkkelord: transkraniell stimulering med likestrøm, anodal, kontaktvarme, smertefrykt, smerteterskel, placebo analgesi, smerte

Abstract

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that can reduce pain. Its side effects are milder than those of pharmacological treatments, and its analgesic effect on chronic pain has been demonstrated. In this study we investigated 1) the effects of anodal tDCS on pain intensity and threshold, 2) the placebo component of tDCS analgesic effect, and 3) whether stress and negative affect moderate the analgesic effect of tDCS. Sixty-four participants (32 females) received three blocks of heat stimuli, 43° C, 45° C, and 47° C in each block. The treatment group received anodal tDCS of 2 mA intensity for 7 minutes, the placebo group received sham stimulation for 30 seconds, and the natural history group received painful stimuli only. Participants rated pain intensity with CoVAS. Threshold was measured before the first and after the last block. Subjective stress was measured by two SACL items, and negative affect was measured by FPQ, PANAS, and BFI questionnaires. Compared to no treatment, tDCS reduced pain by 28%, for 47° C stimuli only. Compared to sham stimulation, tDCS reduced pain by 11%, but this reduction was only marginally significant. There was no placebo response, and no effect of tDCS on pain threshold. Fear of medical pain predicted pain reduction by tDCS, higher fear of medical pain was associated with larger pain reduction. Our findings confirm and extend those of earlier experimental and clinical studies.

Keywords: transcranial direct current stimulation, anodal, contact heat, fear of pain, pain threshold, placebo analgesia, pain

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Despite the advances in understanding of the physiological and psychological mechanisms of pain, chronic pain continues to be a significant problem for millions of people worldwide. European estimates of chronic pain prevalence in the adult population range from 18% (Bekkering et al., 2011) to 50 % (Elliott, Smith, Penny, Smith, & Chambers, 1999). In addition to individual suffering, chronic pain poses high financial costs for society. In 2004 Norway spent 41.4 billion kroner (NOK) (approximately 5 billion Euros) on disability pensions, the largest proportion of which (33%) was received by patients with disorders of the musculoskeletal system, such as arthritis and back disorders (NAV, 2005). In their survey of chronic pain in Europe, Breivik, Collett, Ventafridda, Cohen, & Gallacher (2006) found that 30% of the Norwegian respondents suffered from chronic pain. The most commonly reported cause of pain was arthritis (34% of chronic pain sufferers) and the most common locations were the back (42%) and joints (40%). The researchers also found that 19% of chronic pain sufferers had lost their jobs because of their pain, 47% were currently unemployed or retired, and those who were employed, reported to have lost on average 10.8 work days during the last 6 months.

In addition to its impact on general health, chronic pain is associated with low quality of life and depression. For example, in a Danish study Becker et al. (1997) found that health-related quality of life was lower in patients with chronic pain than in the general population, and was among the lowest for any medical condition. Patients with low back pain and multiple pain locations have the lowest quality of life (Lamé, Peters, Vlaeyen, Kleef, & Patijn, 2005). Although several studies have suggested a causal relationship between chronic pain and depression whereby depression is the consequence of a chronic pain condition (Brown, 1990; Fishbain, Cutler, Rosomoff, & Rosomoff, 1997), alternative explanations for the association between pain and depression are possible. Depression might increase the perceived severity of pain, or depression and pain might arise simultaneously due to a common biological mechanism. Regardless of the direction of the relationship, there is evidence that prevalence of depression is higher among chronic pain sufferers than in the general population (Fishbain et al., 1997). Thus, chronic pain poses a complex problem for the sufferer and society with serious physiological, psychological, social, and financial consequences.

What is pain?

A commonly accepted definition of pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

(Merskey & Bogduk, 1994). Like all sensations, pain is subjective, which means that the same noxious stimulus is not necessarily perceived as being of the same intensity by different individuals. Therefore, scientific and clinical investigations of pain must rely to some degree on subjective reports by participants and patients. Although pain is always unpleasant, like all sensations it has a survival value. The purpose of painful sensation is to warn the organism of tissue damage and to cause withdrawal from the noxious stimulus so that further injury may be avoided. Withdrawal is further ensured by the negative emotional valence accompanying pain sensation.

Although the above definition of pain seems relatively straightforward, there is nothing straightforward about clinical pain conditions. In a normally functioning organism, noxious stimulation followed by tissue damage will produce a painful sensation that corresponds to the extent of damage, and that subsides when the damaged tissue has healed. In contrast, this link between stimulus intensity, the extent of damage, and pain intensity is often lacking in patients with clinical pain conditions. Chronic pain is defined as pain without apparent biological value that has persisted beyond normal tissue healing time (Merskey & Bogduk, 1994). Although healing time varies between 3 and 6 months for different disorders (Apkarian, Baliki, & Geha, 2009), the common feature of chronic pain conditions is that pain does not subside when the tissue has healed. In chronic pain disorders such as irritable bowel syndrome and fibromyalgia, there is often no initial tissue damage at all (Tracey & Bushnell, 2009).

Chronic neuropathic pain is caused by lesions to peripheral nerves, following which the painful location is no longer properly innervated by afferent axons. Such damage should result in a complete loss of sensation from the affected body part, including pain, but paradoxically, it is often followed by chronic pain (Devor, 2006). A special case of neuropathic pain is phantom limb pain. Between 60% and 80% of amputees experience painful sensations referred to the missing limb, and about 10% of those develop chronic phantom pain (Nikolajsen & Jensen, 2006).

Chronic pain is often accompanied by heightened sensitivity to both painful and non-painful stimuli. In hyperalgesia, painful thermal or mechanical stimuli are experienced as more painful by patients compared to healthy persons; in allodynia, a normally non-painful stimulus, such as light touch to the skin, produces pain (Merskey & Bogduk, 1994). Hyperalgesia is an adaptive response that usually follows tissue damage and contributes to healing by limiting movements of the damaged body part. However, in chronic pain it outlasts tissue damage and is thus no longer adaptive. Based on these factors, we can distinguish between nociceptive pain, which arises from damage to non-neural tissue (Merskey & Bogduk, 1994) in an otherwise

normally functioning organism, and chronic pain, which, whether neuropathic or not, is characterized by heightened sensitivity and lack of correspondence between the extent of tissue damage and the intensity of experienced pain. The above definition of pain applies better to nociceptive than to chronic pain.

Neurobiological mechanisms of nociceptive pain

The sensation of pain, or nociception, is initiated by activation of nociceptors, free nerve endings in the skin, muscle tissue, and visceral organs. Nociceptors transduce noxious stimuli into nerve signals. Cell bodies of nociceptors are located in dorsal root ganglia, from which they send one axon to the periphery and the other to the dorsal horn of the spinal cord. Nociceptors are categorized into Aδ and C fibers according to the properties of their axons. Aδ fibers are myelinated, fast-conducting (5-30 m/s) axons that are sensitive to intense mechanical and thermal stimulation. C fibers are unmyelinated, conduct at low velocities (0.5-2 m/s), and respond to noxious thermal, mechanical, and chemical stimuli. Consequently, Aδ fibers carry the sensation of fast, sharp pain, while C fibers are responsible for the delayed, aching pain sensation (Purves et al., 2008). Nociceptors transmit signals by release of neurotransmitters and neuropeptides such as glutamate, substance P, and calcitonin gene-related peptide (CGRP). Nociceptors synapse with second-order neurons mainly in laminae I, II, and V of the dorsal horn. Second-order neurons cross the midline and form the ascending spinothalamic tract, which transmits nociceptive signals to the thalamus. Third-order neurons send projections from the thalamus to several subcortical and cortical areas. Third-order neurons form distinct parallel pathways, which are assumed to mediate the sensory and emotional components of pain. The sensory component, i.e., the intensity and location of painful sensation, is assumed to be mediated by projections from the ventral posterior lateral (VPL) nucleus of the thalamus to the primary (S1) and secondary (S2) somatosensory cortices. The emotional component of pain, i.e., its unpleasantness, is assumed to be transmitted by the pathway that projects from the midline thalamic nuclei to anterior cingulate cortex (ACC) and the insula. Additionally, some fibers from the spinothalamic tract project to brainstem structures such as reticular formation, superior colliculus and periaqueductal gray (PAG), and others project to limbic structures such as hypothalamus and amygdala (Purves et al., 2008). Although the subdivision into sensory and emotional components seems to be widely accepted, there is little support for such distinction, apart from the existence of anatomically disctinct pathways (Apkarian, Hashmi, & Baliki, 2011). Indeed, given the high extent of integration in cortical processing, it is unclear whether we can subdivide pain processing into sensory and emotional, and what significance such a division would have, given that pain is always associated with unpleasantness.

Upon reaching the brain, nociceptive signals are processed by several cortical and subcortical structures. Using neuroimaging techniques, researchers have identified several brain areas involved in pain, a network that has been termed the pain matrix. Brain areas that show activation in response to pain include ACC, insula, S1, S2, thalamus, cerebellum, premotor cortex, inferior parietal cortex, and the basal ganglia (Casey, 1999; Davis, Kwan, Crawley, & Mikulis, 1998; Kong et al., 2010). Although there is evidence that all these regions are involved in pain processing, recent studies have shown that the pain matrix is not pain-specific (Mouraux, Diukova, Lee, Wise, & Ianetti, 2011; Mouraux & Ianetti, 2009). For example, Mouraux et al. (2011) found a large amount of overlap in brain activity elicited by noxious heat, non-noxious touch, auditory, and visual stimuli. Responses in the thalamus, S2, insula, and ACC were very similar for all four modalities, and the responses to noxious heat and non-noxious touch were identical. The authors noted that even though fMRI images appeared identical, noxious and non-noxious stimuli could have been processed by different subpopulations of neurons, which would not be detected by fMRI, because of its spatial resolution being in the order of several millimeters (Mouraux et al., 2011). To resolve this issue, imaging methods with better spatial resolution should be employed, but nonetheless the findings of the above studies suggest that no brain areas should be considered pain-specific. Instead, the pain matrix should perhaps be characterized as a system involved in detection of salient stimuli signaling significant events for the organism, of which pain is just one example (Legrain, Ianetti, Plaghki, & Mouraux, 2011). Further evidence of the non-specific nature of the pain matrix comes from the finding that different clinical pain conditions have unique underlying brain activation patterns, and that patterns of activation during spontaneous pain (i.e., in the absence of noxious stimulation) are different from those evoked by noxious stimuli (Apkarian et al., 2011).

Cortical areas involved in pain processing send descending projections to several brainstem areas and ultimately to the dorsal horn of the spinal cord. These descending pathways exert modulatory effects on afferent pain transmission, either inhibiting or facilitating it. The PAG of the midbrain has a key role in descending inhibition of nociception. Electrical stimulation of the PAG inhibits pain transmission in the dorsal horn and produces analgesia (first demonstrated by Reynolds, 1969). PAG mediates its inhibitory effects through reciprocal connections with locus ceruleus (LC) and rostral ventromedial medulla (RVM), which includes the serotonergic raphe nuclei (Ossipov, 2009). LC sends descending fibers to the dorsal horn, where the release of noradrenaline inhibits the activity of nociceptive neurons. This effect can be offset by administration of noradrenergic antagonists to the spinal cord, and lesions of the

LC have been shown to result in enhanced sensitivity of dorsal horn neurons to nociceptive stimuli (Ossipov, 2009).

Like LC, RVM sends projections to the dorsal horn. This structure contains two types of cells, termed on-cells and off-cells, activation of which exerts opposite effects on pain transmission. On-cells fire in response to noxious stimuli, increase the activity of dorsal horn nociceptive neurons, and are involved in hyperalgesia and allodynia. Off-cells undergo a pause in firing in response to noxious stimulation, and are involved in inhibition of spinal nociceptive transmission (Bardin, 2011). The role of off-cells in pain inhibition is illustrated by the finding that injections of opioids into the RVM result in increased off-cell activity and suppressed on-cell activity, which corresponds to analgesia and can be offset by opioid antagonists (Ossipov, 2009).

The brainstem areas involved in descending pain modulation have high densities of opioid receptors (Purves et al., 2008), which bind both synthetic opioids such as morphine, and endogenous opioids, i.e., opiate-like substances produced by the organism. Endogenous opioids are subdivided into enkephalins, endorphins, and dynorphins. Binding of either synthetic or endogenous opioids by opioid receptors in pain-processing areas produces analgesia. An example of endogenous opioid-mediated inhibition of pain transmission can be seen in neural circuits of the dorsal horn. Here, interneurons containing enkephalin synapse both on nociceptors and on second-order neurons that nociceptors are connected to. Enkephalin release from the interneuron onto the nociceptor inhibits the release of glutamate from the nociceptor and therefore blocks afferent nociceptive signals (Purves et al., 2008).

Neurobiological mechanisms of chronic pain

While the mechanisms of nociception and descending inhibition of pain have been known for several decades, studies of chronic pain have only recently begun to shed light on its complex mechanisms. Chronic pain often persists even when there are no histological abnormalities in the painful tissue. How does the central nervous system maintain a constant painful sensation when there is no noxious stimulation?

There is growing evidence that the central nervous system undergoes considerable reorganization in chronic pain. First, several studies have provided evidence of morphological changes in multiple brain regions. Using voxel-based morphometry, Apkarian et al. (2004) compared gray matter density in chronic back pain patients who have had pain for more than one year with that of age- and gender-matched healthy control subjects. Patients had 11% less neocortical gray matter volume, with 1.3 cm^3 lost for each year of chronic pain. The greatest reduction in gray matter density was observed in the dorsolateral prefrontal cortex (DLPFC),

and the thalamus. DLPFC is important in inhibition of perceived pain (Lorenz, Minoshima, & Casey, 2003), so atrophy in this structure might explain the constant pain experience in patients. Thalamus shows reduced activity in chronic pain (Garcia-Larrea et al., 2006; Iadarola et al., 1995), and because it is tightly interconnected with most cortical areas, atrophy might explain the abnormal pain sensation in chronic pain. A more recent study by Kuchinad et al. (2007) revealed a much greater gray matter loss in female fibromyalgia patients compared to healthy age-matched females, with 10.5 cm^3 lost for each year of diagnosed fibromyalgia. The regions that showed the greatest loss were cingulate gyrus, the insula, medial frontal cortex and parahippocampal gyrus. Of these areas all are involved in pain processing except the parahippocampal gyrus, which is related to stress (Kuchinad et al., 2007).

Because these studies are correlational, we cannot conclude that chronic pain causes gray matter loss, although it seems likely that atrophy might contribute to the maintenance of symptoms. Both abnormal gray matter loss and chronic pain might be partly determined by genetic factors. Indeed, Apkarian et al. (2009) noted that when differences in gray matter volume between patients and healthy controls were extrapolated to the time prior to the diagnosis, gray matter volume was still smaller in patients. Several studies have shown that chronic pain might have a genetic component. For example, MacGregor, Andrew, Sambrook and Spector (2004) compared monozygotic and dizygotic female twin pairs with or without chronic back pain and found heritabilities between 52% and 68%. Pain intensity and duration correlated with heritability, with the most pervasive and severe pain showing a heritability of 68%. Another group of researchers has identified a gene that might be responsible for individual differences in sensitivity to acute pain and the risk of developing a chronic pain condition (Diatchenko et al., 2005).

There is growing evidence of functional changes and neuroplasticity associated with chronic pain. For example, Stern, Jeanmonod, and Sarnthein (2006) examined activation in pain-processing areas in patients with chronic neuropathic pain and found overactivation in the insula, ACC, prefrontal cortex (PFC), inferior parietal cortex, S1, and S2. This overactivation, as well as pain intensity, was reduced after a therapeutic lesion of the thalamus, so the authors suggested that overactivation in pain-related areas was mediated by abnormal, dysrythmic activity in the thalamus. A more recent study (Gifre et al., 2012) provided further evidence of abnormal activity in pain-related areas. The researchers compared connectivity patterns during rest in patients with fibromyalgia with those of healthy controls and found increased connectivity between ACC, the basal ganglia, sensorymotor cortex, and the insula. This network appeared sensitized even at rest, which is consistent with the persistent nature of pain

in fibromyalgia and with the finding that pain-processing areas are overactive in chronic pain patients. Another important finding in that study was reduced functional connectivity between the thalamus, insula, ACC and PAG. Because the PAG is a key area in pain inhibition, disrupted connectivity here might help explain the persistence of pain in terms of ineffectivity of the descending inhibitory pathways.

Another example of plasticity in chronic pain is reorganization of the cortical representations of the painful body part (Flor, Braun, Elbert, & Birbaumer, 1997; Lloyd, Findlay, Roberts, & Nurmikko, 2008). Flor et al. (1997) found that noxious stimuli applied to the back activated a larger area of S1 in chronic back pain patients compared to healthy controls. The cortical representation of the back had expanded into the neighboring leg and foot areas. Also, activation of this expanded area was stronger in patients than in healthy participants, even when stimuli were below the pain threshold. Expanded cortical representations might reflect the brain's attempts of adaptation to the constant overwhelming input from the painful body part and might also explain why chronic pain often radiates to multiple body parts.

In addition to structural and functional cortical reorganization, descending modulatory pathways have a key role in maintenance of chronic pain states (Porreca, Ossipov, & Gebhart, 2002; Vanegas & Schaible, 2004). An important finding is that maintenance of hyperalgesia and allodynia is dependent on descending facilitation of dorsal horn nociceptive activity, which probably arises from on-cells in the RVM (Vanegas & Schaible, 2004). Neuroplasticity in the RVM following the onset of chronic pain results in a domination of facilitatory activity over inhibitory in the descending modulatory pathways. Facilitation from the RVM triggers an enhanced release of glutamate, substance P and CGRP from nociceptors, resulting in further plastic changes in the RVM, which in turn contributes to stronger descending facilitation, and more nociceptor activity (Ossipov, 2009). Hyperalgesia and allodynia are maintained by this positive feedback loop at the subcortical level.

Important factors in descending facilitation of nociception are increased concentrations of cholecystokinin (CCK) and serotonin, and abnormal interactions between glia and neurons. CCK is a pro-nociceptive peptide that appears to mediate facilitation of nociception (Kovelowski et al., 2000). Following injury, the excessive spinal activity triggers an increase in CCK in RVM cells, and this in turn causes an increase in descending facilitation, which sustains peripheral hyperalgesia and allodynia. Because CCK action is opposite to that of opioids, CCK blocks activation of off-cells in the RVM and thus prevents descending inhibition (Vanegas & Schaible, 2004). Antagonizing CCK receptors offsets hyperalgesia and allodynia

and restores the effectiveness of morphine injected into the PAG (Kovelowski et al., 2000). Also, selective ablation of on-cells in the RVM abolishes behavioral signs of hyperalgesia and allodynia in animal models of neuropathic pain (Ossipov, 2009).

It has been shown that injections of serotonin into the neural tissue of healthy participants produce hyperalgesia, and there is evidence that increase in serotonin concentration helps maintain chronic neuropathic pain (Bardin, 2011). Following nerve injury, serotonin concentration in the damaged nerve increases, which might be responsible for peripheral hyperalgesia. Selective ablation of descending serotonergic pathways that project from the RVM reduces hyperalgesia and allodynia in animal models. Moreover, while in healthy organisms descending serotonergic pathways mainly have inhibitory effects, after nerve injury they show facilitatory effects (Bardin, 2011).

There is also evidence that abnormal glial-neuronal interactions contribute to the transition from acute to chronic pain, as well as to the maintenance of chronic pain states, although studies are currently limited to animal models. For example, Wei, Guo, Zou, Ren, & Dubner (2008) found that nerve injury in rats was followed by a hyperactivation of astrocytes in the RVM, which started three days after injury and peaked by day 14. This hyperactivation was followed by excessive release of cytokines from astrocytes. Cytokines contributed to hyperalgesia and allodynia by facilitation of glutamate release, and enhanced synaptic strength by affecting NMDA receptors (Wei et al., 2008). Glial-neuronal interactions might thus contribute to long-term potentiation, which is the underlying mechanism of neuroplasticity.

Evidence discussed in this section indicates that in order to maintain a chronic pain state, the nervous system undergoes reorganization at all levels: from global morphological and functional changes in the brain to the local increase of chemicals in subcortical and peripheral structures. These exciting findings still remain to be integrated into a comprehensive theory of chronic pain, on which development of effective treatments might be based. Theory development is currently in its initial stage, but it has been proposed that chronic pain could be explained in terms of learning and memory (Apkarian et al., 2009; Apkarian et al., 2011). In order to fully understand the basic mechanisms of chronic pain, more research on its neurobiological mechanisms is needed. For example, given the extensive plasticity of the nervous system in chronic pain states, we should investigate processes at the neuronal level, such as interactions between excitation and inhibition, cell interactions in neuronal networks, and changes in neural signaling following the onset of chronic pain (Zhuo, 2008). Also, longitudinal studies are needed in order to better understand the temporal component of the onset and maintenance of chronic pain states.

Current treatments of chronic pain

The most common treatments for chronic pain are analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and weak opioids. NSAIDs are most commonly used to treat chronic inflammatory pain in conditions such as arthritis, and hyperalgesia. Cox enzymes are substances normally present in almost all tissues, including the central nervous system, and are involved in prostaglandin synthesis. Following tissue damage, Cox enzymes are upregulated in the spinal cord as well as in the damaged tissue, resulting in an increased production of prostaglandins, which act to sensitize nociceptors to noxious stimulation and produce hyperalgesia (McMahon, Bennett, & Bevan, 2006). NSAIDs produce analgesia by inhibiting Cox enzymes. Paracetamol has a similar mechanism of action, but it is a weaker inhibitor of Cox enzymes than are NSAIDs. Opioids induce analgesia by binding to opioid receptors in brainstem areas such as the PAG. Activation of opioid receptors in the PAG blocks nociception through the descending inhibitory pathways. When administered locally, opioids interfere with pain transmission in nociceptors and at the first synapse in the dorsal horn (Hunt & Urch, 2006).

Number needed to treat (NNT) is a common measure of the effectiveness of analgesic interventions (McQuay & Moore, 2006a), which conveys both statistical and clinical significance (Cook & Sackett, 1995). NNT is an estimate of the number of patients that need to be treated for one patient to have at least 50% pain relief that is not due to placebo. Thus, an optimal NNT for a treatment would be 1. Although many analgesics can be effective for some patients some of the time, there is high inter-individual variability in response to treatment and a risk of adverse effects. For example, although the highest doses of NSAIDs have NNTs that approach 1, there is increased risk for gastrointestinal bleeding, renal failure, and congestive heart failure with chronic use (McQuay & Moore, 2006b). For opioids, NNTs range between 2.5 for oxycodone and 16.7 for codeine (Schug & Gandham, 2006), with the highest dosages associated with the lowest NNTs. Common adverse effects of opioids are nausea, constipation, and respiratory depression. With long-term usage and high dosage opioids can cause physiological dependence and psychological addiction, hyperalgesia and allodynia, cognitive impairment, and movement abnormalities (Schug & Gandham, 2006).

While NSAIDs and opioids are the most common treatments for chronic inflammatory pain, they are much less effective for patients with chronic neuropathic pain. For this reason, neuropathic pain is often treated with antidepressants and anticonvulsants. Antidepressants were first used for pain treatment in patients with concomitant affective disorders, but were later shown to have separate analgesic effects (Watson, Chipman, & Monks, 2006). Two types

of antidepressants commonly used in the treatment of neuropathic pain are tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). TCAs enhance actions of norepinephrine and serotonin by inhibiting their reuptake, SSRIs act the same way, but only on serotonin. Generally, TCAs have larger effects on chronic pain than SSRIs (Onghena & van Houdenhove, 1992), but SSRIs have fewer adverse effects (Watson et al., 2006). Anticonvulsants are drugs normally used to treat epileptic seizures, but they also have analgesic effects in patients with neuropathic pain, mainly by inhibiting the excessive neural activity following nerve damage. Some anticonvulsants act by blocking voltage-gated sodium channels in a use-dependent manner, while others are agonists at the inhibitory GABA receptors and antagonists at glutamate receptors (Sang & Hayes, 2006). Antidepressants and anticonvulsants are not primary analgesics, and their effects on chronic pain are often limited. A review of randomized controlled trials conducted between 1982 and 2004 concluded that antidepressants and anticonvulsants were effective for neuropathic pain in 24 of 29 trials (Watson et al., 2006). However, these results must be interpreted with caution, because some of the trials reported weak effects only. Generally, NNTs for antidepressants range between 1.7 and 5.2, and anticonvulsants have NNTs between 2.1 and 3.8 (Watson et al., 2006). Examples of adverse effects of antidepressants include sedation, insomnia, delirium, nausea, sexual dysfunction, and hypertension. Anticonvulsants are associated with adverse effects such as nausea, vomiting, constipation, liver damage, cognitive impairment, sedation, headaches, and allergic reactions. An additional problem is that a relatively large proportion of patients treated with antidepressants and anticonvulsants does not experience sufficient pain relief, i.e., 50% or more reduction in pain intensity. For patients with chronic neuropathic pain, none of the available pharmacological treatments provide moderate or better pain relief in more than 50% - 60% of patients (Backonja & Rowbotham, 2006). Because of the lack of response and the risk of serious adverse effects, pharmacological treatments might therefore not be a desirable option for many patients.

Although chronic pain is most commonly treated with pharmacological agents, other options have been tried. Treatments such as deep brain stimulation and spinal cord implants, even when effective (often they are not, and the patient continues to experience pain after the treatment), might not be desirable because of their invasiveness. Psychological treatments such as cognitive behavioral therapy (CBT) and biofeedback have been shown to reduce pain significantly when compared to no treatment (Morley, Eccleston, & Williams, 1999), but the effectiveness of psychological treatments seems to be dependent on the skills of the therapist

and the patient's cooperation (Fregni & Pascual-Leone, 2007). A substantial proportion of patients does not benefit from CBT (Vlaeyen & Morley, 2005).

In summary, none of the currently available treatments reliably provide sufficient pain relief for patients with chronic pain and there is a need for the development of new, more effective, and less invasive options.

Transcranial direct current stimulation and its effects on pain

Recent research on non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) has shown that they affect a range of motor, somatosensory, visual, affective, and cognitive functions (Been, Ngo, Miller, & Fitzgerald, 2007). rTMS uses rapidly changing short magnetic pulses that pass through the skull and induce action potentials in the underlying cortical neurons. tDCS uses weak constant current that does not induce action potentials, but leads to excitability changes in the underlying neural tissue. Although tDCS and rTMS have similar effects, tDCS is better suited for double-blind designs, it is more portable and cheaper than TMS, it allows for stimulation parameters to be tailored to the individual patient, and it does not produce behavioral effects associated with TMS, such as muscle twitches. (Priori, Hallett, & Rothwell, 2009). Research has documented therapeutic effects of tDCS and rTMS in patients with Parkinson's disease, stroke, epilepsy, and chronic pain (for a review see Fregni & Pascual-Leone, 2007).

When tDCS is used in studies of pain, the most common site of stimulation is the primary motor cortex (M1). Nitsche and Paulus (2001) compared several electrode arrangements and found that placing the active electrode over the M1 and the reference electrode over the contralateral orbita resulted in large excitability changes. Following stimulation, there was a 40% reduction in the motor threshold of the muscle represented by the stimulated portion of the M1. The role of the M1 in pain relief has been repeatedly demonstrated. For example, Lefaucheur, Drouot, Menard-Lefaucheur, Keravel, and Nguyen (2006) hypothesized that chronic neuropathic pain might be associated with reduced intracortical inhibition, i.e., reduced excitability in inhibitory GABAergic circuits. After applying rTMS to the portion of the M1 that represented the patients' painful hand, the researchers observed an increase in intracortical inhibition at that site up to a level comparable with control subjects. This reduction correlated with the concomitant pain relief (Lefaucheur et al., 2006). Using tDCS, Antal, Terney, Kühnl, and Paulus (2010) showed similar effects in patients with both neuropathic and non-neuropathic chronic pain. Further evidence for the involvement of M1 in pain relief was provided by Maarrawi et al. (2007), who observed

increased availability of opioid receptors in ACC and the PAG of chronic pain patients following M1 stimulation by subdurally implanted electrodes. The increase in receptor availability correlated with pain relief. This finding suggests that M1 stimulation might relieve pain by activation of the endogenous opioid system. Although the mechanisms by which stimulation of M1 induces analgesia are not completely clear, it has been suggested that it might lead to activation of descending projections from M1 to the thalamus, which in turn leads to the activation of several structures involved in pain inhibition that receive input from the thalamus. Activation of projections from the lateral thalamus to orbitofrontal cortex and ACC is thought to modulate the emotional component of pain, while activation of the PAG might lead to suppression of afferent nociceptive signals (Garcia-Larrea et al., 1999; Garcia-Larrea & Peyron, 2007).

During tDCS two 5 × 7 cm rubber electrodes are attached to the scalp, one serving as the anode (i.e., positive pole) and the other as the cathode (i.e., negative pole). Weak current (0.5 – 2.0 mA) is passed through the electrodes, flowing from the anode to the cathode. Some of the current is diverted by the skull, but approximately 50% reaches the underlying cortical tissue (Nitsche et al., 2008). tDCS does not evoke action potentials in cortical neurons, but it induces changes in excitability, thus affecting the neuronal threshold for the generation of action potentials. Anodal tDCS enhances excitability by depolarizing neurons, and cathodal tDCS reduces excitability by hyperpolarizing neurons (Lang et al., 2005; Nitsche, Fricke, et al., 2003; Nitsche et al., 2005). The effects of tDCS can be short or long-lasting, depending on the duration of stimulation. For example, Nitsche and Paulus (2000) found that when anodal or cathodal stimulation was applied for 5 minutes, the subsequent excitability changes lasted up to 5 minutes. In another study, 13 minutes of anodal stimulation induced after-effects that lasted 60-90 minutes (Nitsche & Paulus, 2001). For cathodal tDCS, 9 minutes of stimulation induced excitability changes that lasted up to 60 minutes (Nitsche, Nitsche, et al., 2003). Using positron emission tomography (PET), Lang et al. (2005) observed increased activity in several cortical and subcortical areas following 10 minutes of anodal tDCS, and decreased activity following cathodal tDCS of the same duration. These changes remained stable for 50 minutes.

Although the mechanisms of neural modulation by tDCS are not completely clear, it has been shown that short-term excitability changes during stimulation depend on membrane polarization, whereby tDCS affects voltage-gated sodium and calcium channels, while long-term effects are controlled by NMDA receptor activity and can be explained by synaptic plasticity mechanisms such as long-term potentiation and long-term depression (Lang et al., 2005; Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2005). Pharmacological

evidence is consistent with this account. For example, Nitsche, Fricke, et al. (2003) showed that long-lasting after-effects of anodal and cathodal tDCS were eliminated by dextromethorphane, an NMDA receptor antagonist. Consistently, it has been shown that long-term excitability changes following anodal tDCS can be consolidated by d-cycloserine, an NMDA receptor agonist. Nitsche et al. (2004) found that administration of a low dose of d-cycloserine resulted in an excitability enhancement lasting 4 hours, although the expected duration of excitability enhancement was 1 hour. For short-term effects of tDCS pharmacological evidence is less clear. For example, Nitsche, Fricke, et al. (2003) reported that excitability enhancement during anodal tDCS was eliminated by carbamazepine (a sodium channel blocker) and flunarizine (a calcium channel blocker), but excitability reduction during cathodal tDCS was not affected.

tDCS is a non-invasive and safe neuromodulatory technique (Nitsche et al., 2004; Poreisz, Boros, Antal, & Paulus, 2007). Because the weak current does not evoke action potentials in neurons, there is little risk of serious adverse effects such as seizures. Moreover, the adverse effects of tDCS are relatively mild. For example, in their review of 567 tDCS sessions Poreisz et al. (2007) concluded that the most common adverse effects of tDCS were mild tingling sensation (reported by 70.6% of the participants), moderate fatigue (35.3%), and light itching sensation (30.4%). Because of its non-invasiveness and mild adverse effects, tDCS might be a better option than pharmacological treatments, provided that it has a consistent and significant effect on pain.

To date, only a few studies have investigated tDCS effects on chronic pain. In one study (Fregni, Boggio, et al., 2006), patients with chronic pain following spinal cord injury received five 20-minute sessions of 2 mA anodal stimulation applied to M1. This treatment resulted in 58% reduction in pain, as evidenced by the decrease in Visual Analog Scale (VAS) scores from 6.2 at baseline to 2.6 after stimulation. In two studies that investigated the effect of anodal tDCS on pain in fibromyalgia the patients reported 59% (Roizenblatt et al., 2007) and 58% (Fregni, Gimenes, et al., 2006) reduction in pain, respectively. Following 21 days with no stimulation, pain scores increased, but were still lower than in the sham stimulation group. Mori et al. (2010) treated patients with chronic neuropathic pain due to multiple sclerosis with anodal tDCS and found that 60% of the patients showed 50% or more reduction in pain ratings. These studies provide initial evidence for a beneficial effect of tDCS on chronic pain.

Experimental studies of tDCS effects on pain might contribute to a better understanding of how tDCS leads to pain relief and how it might best be applied in clinical settings. Experimental evidence is currently limited and the findings are inconsistent with those of clinical studies. For example, Antal et al. (2008) found that 1mA cathodal tDCS applied to S1

for 15 minutes reduced laser-evoked perceived pain intensity ratings by 13%. The amplitude of laser-evoked N2 component recorded by electroencephalography (EEG) was also diminished. Anodal stimulation of the same intensity and duration had no effect. Csifcsak et al. (2009) applied anodal or cathodal tDCS of 1mA intensity to M1 for 10 minutes and found that cathodal stimulation diminished the amplitude of laser-evoked potentials, while anodal stimulation facilitated warmth perception by decreasing perception threshold. Anodal stimulation did not have any effects on laser-evoked potentials or suprathreshold pain perception. On the other hand, Hansen et al. (2011) found that while 1mA cathodal tDCS applied for 20 minutes decreased the amplitude of pain-related evoked potentials elicited by painful electrical stimulation, anodal tDCS of the same intensity and duration increased the amplitude. Thus, cathodal tDCS appeared to inhibit pain processing and anodal to facilitate it (Hansen et al., 2011). Boggio, Zaghi, Lopes, and Fregni (2008) investigated the effects of tDCS applied to M1 and DLPFC on pain threshold. Anodal stimulation applied for 3 minutes resulted in 8.3% increase in pain threshold when applied to M1.

Given the inconsistencies in the findings regarding tDCS effects on experimentally induced pain, the main purpose of our study was to investigate whether anodal tDCS has an effect on the perceived intensity of experimentally induced acute heat pain and on pain threshold in healthy volunteers.

Contextual and emotional factors influence pain perception and analgesia

Every clinical treatment may be influenced by contextual factors such as presence of a therapist, the patient's awareness that a treatment has been given, and the expectation of a positive outcome of the treatment (Benedetti, 2009). It has been shown that contextual effects can lead to pain reduction independently of the pharmacological treatment, a phenomenon that has been termed placebo analgesia. Some of the strongest evidence for the placebo analgesic response comes from the open-hidden design, which compares the effects of a treatment given by a doctor (i.e., openly) with effects of the same treatment administered by an infusion machine (i.e., hidden), without the patient's knowledge. Hidden treatments eliminate the psychosocial context and, consequently, the placebo response (Benedetti, 2009). The general finding in open-hidden studies is that hidden treatments are less effective than openly administered ones (Amanzio, Pollo, Maggi, & Benedetti, 2001; Benedetti et al., 2003).

It has been shown that placebo analgesia is not caused by response bias, but is accompanied by biological processes such as increased activity of the endogenous opioid system (Amanzio & Benedetti, 1999; Petrovic, Kalso, Petersson, & Ingvar, 2002; Zubieta et al., 2005) and dopamine (Scott et al., 2007). Using fMRI, Wager et al. (2004) showed that

administration of placebo was accompanied by reports of pain relief, which correlated with decreased activity in the thalamus, insula, and ACC. Additionally, increased activity in the DLPFC and the PAG was observed during anticipation of pain and following placebo administration, which is consistent with the evidence that placebo analgesia is mediated by the endogenous opioid system (Wager et al., 2004). Placebo analgesic response might therefore partly explain the effects of analgesic treatments.

Although tDCS is well suited for double-blind designs (Gandiga, Hummel, & Cohen, 2006), no study of tDCS effects on pain has yet investigated to what degree pain relief after tDCS might be due to the beneficial psychosocial context surrounding the treatment. The main focus of clinical studies has been on quantification of the tDCS analgesic effect by comparing pain reduction in the treatment group with pain reduction in the sham stimulation group. While providing evidence for the analgesic effect, such designs are not suited to determine how much of the therapeutic effect is caused by a placebo response or by other factors, such as spontaneous remission. In order to detect a placebo response and to rule out spontaneous remission, a comparison between a placebo group and a natural history group is necessary (Colloca, Benedetti, & Porro, 2008). Therefore, the second purpose of this study was to investigate whether the analgesic effect of tDCS is in part due to a placebo response.

While beneficial contextual factors such as expectation of pain relief can help reduce pain, there is substantial evidence that negative emotions and stress can increase pain and block analgesia (Aslaksen & Flaten, 2008; Lyby, Aslaksen, & Flaten, 2010, 2011; for a review, see Wiech & Tracey, 2009). For example, in a study by Benedetti, Amanzio, Casadio, Oliaro and Maggi (1997) verbal suggestions of hyperalgesia induced CCK-mediated anxiety in postoperative patients, which led to an increase in pain. In a more recent study, Bingel et al. (2011) found that when subjects were given verbal suggestions of hyperalgesia, they showed significantly higher levels of anxiety than did the subjects given suggestions of analgesia. Moreover, the expectation of hyperalgesia abolished the analgesic effect of the opioid remifentanil on heat pain, and this was confirmed by fMRI. Lyby, Aslaksen, and Flaten (2010) found that fear of pain was related to higher perceived pain intensity during subsequent painful stimulation and to higher stress levels both during anticipation and administration of painful stimulation.

Thus, evidence shows that negative emotions and stress can have significant impact on the effectiveness of treatment. The effect of stress on pain relief in tDCS studies is particularly worth investigation because of the possibility that the nature of the treatment might induce stress (i.e., when participants are informed that they will be treated with electricity, they may

become concerned about the safety of the treatment). So far, no study of tDCS effects on pain has investigated the impact of negative emotions and stress on pain relief. Therefore, the third purpose of this study was to explore whether negative emotions and stress moderate the effects of tDCS on perceived pain intensity and pain threshold.

Method

Participants

Eighty healthy volunteers were recruited to participate in this study. In order to recruit participants, written advertisements containing information about the nature and purpose of the study were posted around campus and disseminated via e-mail (see Appendix A for a copy of the information sheet). Interested students contacted one of the experimenters, who provided additional information about the study, including answering questions asked by potential participants. The experimenter also screened interested individuals for eligibility. They were regarded as suitable to participate if they fulfilled the following criteria (assessed by verbal report): 1) no history of serious illness, 2) no current use of prescription medications, with the exception of oral contraceptives, and 3) no injuries, scars, or tattoos on the left forearm. There were three experimenters in this study, all female psychology students. The experimenters received training in the procedure prior to the beginning of the experiment.

Data from 15 participants had to be excluded due to technical inconsistencies. First, because of an error in programming the tDCS apparatus, 13 participants received stronger (2.25 mA) or weaker (1.75 mA) stimulation than the planned intensity of 2.0 mA. Secondly, data from two participants had to be excluded because on these sessions there were two experimenters in the laboratory. One additional participant was excluded because of very high pain intensity reported during the pre-test (90.5 for 43°). Data from 64 participants (32 females) were entered in the statistical analyses. Subjects were between 19 and 50 years of age (mean age = 21, *SD* = 4.9). All participants received a gift card (worth 200 NOK, or about 26 Euros). The study was approved by the Regional Committee for Medical Research Ethics North Norway, project number 2010/2256. Written informed consent was obtained from all participants prior to entering the study (Appendix B). The study was conducted at the Department of Psychology, University of Tromsø, Norway, between March and October 2011.

Study design

This experiment included 3 groups: natural history (n = 18), anodal tDCS (n = 20), and sham tDCS (n = 26). All participants received four blocks of stimuli, thus the design was a 3 Group (anodal, sham, natural history) × 4 Test (familiarization, pre-test, treatment, post-test) repeated measures. The first 20 participants enrolled in the study were assigned to the natural

history group, and the rest were randomized into anodal tDCS or sham tDCS group. We chose this option instead of full randomization partly in order to maximize the amount of training for the experimenters before tDCS was employed. Moreover, because participants in the natural history group did not have any exposure to the tDCS apparatus, they were aware of their being assigned to the control group. The initial block was given in order to familiarize participants with the nature of painful stimulation, as well as with the procedure of pain intensity rating. Data from this block were not included in the statistical analyses. Pain threshold was assessed twice during the session, after the familiarization block and after the post-test. In addition to the familiarization block, all participants received three blocks of painful stimuli, termed pre-test, treatment, and post-test. See Figure 1 for a summary of study design and procedure.

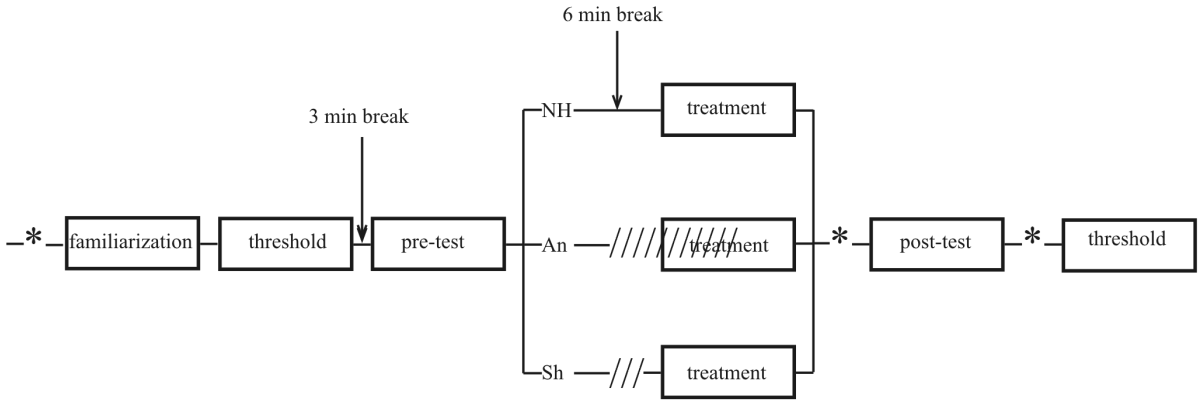

Fig. 1. Summary of design and procedure. * – blood pressure, heart rate, and subjective stress measurement. NH – natural history group; An – anodal tDCS group; Sh – sham tDCS group. /// – tDCS.

Pain stimulation

Painful stimuli were delivered by a pain and sensory evaluation system, Pathway (Medoc, Israel) to the left volar forearm by a 30 × 30 mm aluminum contact thermode. To prevent habituation and sensitization of the skin, the thermode was moved to a different, non-overlapping site (three sites in all) on the forearm after each stimulus block, including threshold measurements.

For the purposes of this study, stimulus intensity of 47° was defined as moderate pain, 45° as weak pain, and 43° as warmth. All blocks consisted of three stimuli, each stimulus lasted 20 seconds. During the familiarization block the first stimulus was 42° C, the second 45° C, and the third 47° C. Inter-stimulus intervals during familiarization were 60 seconds after the first stimulus (42° C) and 120 seconds after the second stimulus (45° C). The pre-test,

treatment, and post-test blocks each consisted of three stimuli with temperatures 43°, 45°, and 47° C, delivered in that order. Inter-stimulus intervals during pre-test and treatment were 240 seconds after the first stimulus (43° C) and 300 seconds after the second stimulus (45° C). Inter-stimulus intervals during post-test were 60 seconds after the first stimulus (43° C) and 120 seconds after the second stimulus (45° C). During inter-stimulus intervals the temperature of the thermode returned to baseline (32° C). Participants rated pain intensity using a computerized visual analog scale (CoVAS). The intensity of each stimulus was rated continuously as the stimulus was being delivered.

Transcranial direct current stimulation

Transcranial direct current stimulation was delivered by a battery-driven, constant current stimulator (NeuroConn, Germany) with a maximum output of 5 mA. Current was transferred from the stimulator to the skull by a pair of 5 × 7 cm surface sponge electrodes, held in place by rubber bands, and soaked in sterile water. Although most tDCS studies use saline-soaked sponges, we opted for sterile water in order to minimize the uncomfortable itching sensation at the stimulation site. Water does not conduct electricity as well as saline, thus for current to pass through the skull, we applied small amounts of conductive paste (Ten20 Conductive EEG Paste, USA) to the sponges and the electrode sites on the scalp. Participants received either anodal or sham stimulation of M1. For both groups, the anode electrode was placed over C3 according to EEG 10-20 system, and the cathode electrode over the contralateral supraorbital area. For both the anodal and the sham groups, stimulation began 3 minutes before the first stimulus in the treatment block was delivered. For anodal stimulation, a constant current of 2 mA intensity was applied for 7 minutes. At the beginning and end of stimulation, current was ramped up and down, respectively, for 20 seconds, in order to minimize discomfort. In the sham group stimulation was of the same intensity as in the anodal group, but stopped automatically after 30 seconds. Stimulation duration of 30 seconds was not considered sufficient for excitability changes to occur. The stimulator was started in the same manner for the anodal and sham groups (i.e., the experimenter entered a 4-digit code and stimulation began immediately afterwards). Because the stimulator was placed out of participants' sight and because the experimenter left the cubicle immediately after the onset of stimulation, neither participants nor experimenters were aware of whether sham or anodal stimulation was being applied, thus a double-blind procedure was ensured.

Measurements

Pain intensity was measured by a computerized visual analog scale (CoVAS). This hand-held device has a slider, which can be moved horizontally across the 100 mm range between the anchors "no pain" and "most intense pain imaginable." Recorded pain intensity range is between 0 (no pain) and 100 (most intense pain imaginable). Participants were instructed to move the slider to a point that corresponded to the intensity of their pain sensation during the delivery of each stimulus and were able to adjust their report if perceived pain intensity changed. The position of the slider was continuously recorded by a computer. Pain intensity was measured in the same manner for all stimuli, across all blocks of stimuli.

During pain threshold measurement the thermode heated from baseline of 32° C at the rate of 1° per second and until the participant reported painful sensation by clicking on a computer mouse. After this the temperature returned to baseline at the rate of 20° C per second. Each threshold measurement consisted of six trials. There were no inter-stimulus intervals between the trials. In order to avoid burns to the skin, the temperature of the thermode was programmed to automatically return to baseline whenever it exceeded 51° C for more than 1 second, even if participants did not report the stimulus as painful.

Subjective stress was measured by two adjective pairs from the Stress/Arousal Adjective Check List (SACL) (Mackay, Cox, Burrows, & Lazzerini, 1978). The adjective pairs were "relaxed – tense" and "calm – nervous," translated to Norwegian. Scores were obtained on two 11-point numerical rating scales (NRSs), with the adjectives "relaxed" and "calm" representing the lower anchor (i.e., 0) and the adjectives "tense" and "nervous" representing the higher anchor (i.e., 10). Participants were asked to rate their current state for each adjective pair, and the responses were recorded by the experimenter. Participants were not informed that this was a measure of stress. Blood pressure and heart rate measurements provided complementary physiological data on stress levels. Blood pressure and heart rate were measured by an automatic blood pressure monitor (BP A100 Plus, Microlife, Switzerland), which was attached to the participants' left forearm immediately before, and taken off immediately after each measurement.

Pain-related emotions were assessed by the Fear of Pain questionnaire (FPQ), which consists of three subscales that measure fear of minor pain, medical pain, and severe pain, each subscale includes 10 items (McNeil & Rainwater, 1998). Mood was assessed by the Positive and Negative Affect Schedule (PANAS), which consists of two subscales, positive affect and negative affect, with 10 items per subscale (Watson, Clark, & Tellegen, 1988). Personality

traits were assessed by the short version of the Big Five Inventory (BFI-10), which consists of two items per personality dimension (Rammstedt & John, 2007). All questionnaires were administered in pen-and-paper form, in Norwegian translations (see Appendices C – E for a copy of each questionnaire).

Procedure

Participants were tested individually, between 8 a.m. and 5 p.m. on weekdays. Upon arrival at the laboratory they were informed about the purpose and nature of the study and given the opportunity to ask questions. In short, participants were told that the purpose of the study was to investigate whether tDCS can reduce heat pain, that the method employed is safe, and that possible side effects are slight itching of the skin at the stimulation sites and redness of the skin on the forearm due to the applied heat. Before the beginning of the study the experimenter informed the participants that all their data would be treated anonymously. Participants were also told that they could withdraw from the study at any point, in which case no explanation for the reason of withdrawal would be required and all their data would be deleted. Written consent was obtained and the questionnaires were filled out. Additionally, personal data such as birthdate, email address, and educational background were requested. Participants were also asked to report on their caffeine and nicotine intake before the study by writing down answers to the questions "how long has it been since your last intake of caffeine?" and the equivalent question for nicotine.

During the experiment participants were seated in a comfortable reclining chair inside a steel cubicle (2.8 × 2.8 m) shielded for electromagnetic disturbances and placed inside a larger room. The apparatus for control of pain stimulation and response recording was placed outside the steel cubicle. To avoid electromagnetic disturbances during tDCS, participants were asked to remove large metal objects. The total duration of the session was about 60 minutes.

Each participant interacted with one experimenter only during the session. The participant was alone in the cubicle except when the experimenter entered before the beginning of the session, as well as between the blocks. The amount of conversation with the participant was held to a minimum.

The study started with the experimenter providing short instructions about pain ratings (i.e., participants were told what the lower and higher anchors of the CoVAS represented, asked to rate pain intensity continuously and to adjust the report if necessary). After this, measurements of blood pressure, heart rate and subjective stress were obtained and the thermode was attached to the participant's forearm. Each blood pressure, heart rate and subjective stress measurement lasted approximately two minutes. The experimenter told the

participant that the first block was about to begin, placed the CoVAS on the participant's lap and left the steel cubicle.

After all stimuli in the familiarization block were delivered, the experimenter moved the thermode to a different site and removed the CoVAS. The participant received a computer mouse, together with the instruction that stimuli gradually increasing in temperature were about to be delivered, and that at the point when the stimulus felt painful, the participant should click the button. The experimenter then left the cubicle and pain threshold was measured. After this, there was a 3-minute break. During the break the participant remained seated and was alone in the cubicle.

After the break the experimenter moved the thermode to a different site, placed the CoVAS on the participant's lap, and informed that the next stimulation was about to begin. Then the pre-test began and after all stimuli were delivered, there was a 6-minute break for the natural history group. For the anodal and sham groups, the electrodes were attached to the participant's scalp during the first 3 minutes of this time. Stimulation began immediately afterwards, thus the set up of the tDCS apparatus and the first 3 minutes of stimulation corresponded to the 6-minute break in the natural history group. The participant was again asked to rate pain continuously, the thermode was moved, and the treatment block began. Thus, during the first 4 minutes of the treatment block, participants in the anodal group received tDCS, while participants in the natural history group received painful stimulation only, and for the sham group tDCS ended 30 seconds after onset and 2.5 minutes before the first stimulus in the treatment block was given. Blood pressure, heart rate and subjective stress were measured again following the treatment block. After all measurements ended, the experimenter removed the tDCS apparatus. The thermode was moved and the last block of stimuli, the post-test, was given.

After the post-test, the final blood pressure, heart rate, and subjective stress measurements were obtained, the thermode was moved, and pain threshold was measured again. In the end of the session the experimenter asked whether the participant had any side effects during the session, and if the answer was affirmative, the participant was asked to rate the severity of side effects on a numerical rating scale ranging between 0 (no side effects) and 10 (very severe side effects). The experimenter recorded the response. Finally, the participant received the gift card and the session ended.

Statistical analyses

Data were analyzed with IBM SPSS Statistics Version 19 package (SPSS Inc., IBM Corporation). Pain intensity scores for each stimulus were obtained by recording the highest

rating for that stimulus that was consistent over a period of at least 3 seconds. Pain reduction scores were computed for each temperature by subtracting the CoVAS scores on the post-test from those on the pre-test. Scores from each threshold measurement were averaged across the six trials, thus one score was obtained for each threshold test. A mean stress score on each measurement was obtained by averaging the ratings on the two SACL items. Stress reduction scores were computed by subtracting the mean stress score on the last measurement from that on the first measurement. The questionnaires were scored according to their scoring manuals. For FPQ, a total score was computed, as well as the scores on the severe, minor, and medical pain subscales. For PANAS, total scores for the two subscales positive affect and negative affect were computed. For BFI, one score was computed for each of the five dimensions extraversion, agreeableness, conscientiousness, neuroticism, and openness.

To test the effect of tDCS on pain, CoVAS scores were entered in three separate repeated-measures analyses of variance (ANOVAs), one for each temperature. The three levels of the within group factor were pre-test, treatment, and post-test scores, and the three levels of the between-subject factor were anodal group, natural history group, and sham tDCS group. To test the effect of tDCS on pain threshold, a repeated-measures ANOVA was carried out on mean threshold scores. The scores on the two measurements were the two levels of the within-subject factor and group was the between-subjects factor. To test the between-group differences in pain intensity and pain threshold, planned comparisons were used. Blood pressure and heart rate data were analyzed with repeated-measures ANOVAs, one for systolic, one for diastolic blood pressure, and one for heart rate. When appropriate, post-hoc tests (Tukey HSD) were conducted. To test whether stress and negative affect moderated tDCS effect on pain, hierarchical regression was carried out. The dependent variable was pain reduction by tDCS, i.e., the difference scores on 47° C stimuli in the anodal group (n = 19). The predictors were entered in separate blocks, one in each block, with pre-test stress entered first, followed by fear of medical pain, fear of severe pain, fear of minor pain, negative affect, and neuroticism entered last. The α level for all significance tests was set at .05.

Results

Baseline characteristics

Because participants in the natural history group were not randomly assigned to that group, we tested for systematic differences between this group and the other two groups. There was a significant difference in age between the natural history and the anodal groups, $F(2, 61) = 4.5$, $p = .02$, 95% CI [0.9, 8.2]. On average, participants in the natural history group were 4.5

years younger (mean age = 20.1 years, *SD* = 1.3) than those in the anodal group (mean age = 24.6 years, *SD* = 7.3).

Another significant difference was found in negative affect scores, $F(2, 58) = 5.8$, $p = .005$. Post-hoc tests showed that natural history group scores were higher than those of the anodal group, $M = 15.6$, $SD = 0.55$ and $M = 12.6$, $SD = 0.26$, respectively, $p = .04$, 95% CI [0.17, 5.97]. Negative affect scores in the natural history group were also higher than in the sham group ($M = 11.9$, $SD = 0.24$), $p = .005$, 95% CI [1.0, 6.5]. There was also a main effect of group on mean stress scores at the first measurement, $F(2, 60) = 5.19$, $p = .008$. Post-hoc tests showed that stress scores were higher in the natural history group ($M = 4.1$, $SD = 1.74$) than in the anodal group ($M = 2.4$, $SD = 1.60$), $p = .006$, 95% CI [0.43, 2.95]. There were no significant differences between groups in the pre-test CoVAS scores: for 43°, $F(2, 61) = 0.13$, $p = .89$, for 45°, $F(2, 61) = 0.85$, $p = .43$, for 47°, $F(2, 61) = 0.68$, $p = .51$. No other baseline differences were found between groups.

Descriptive statistics

All participants who entered the study completed the procedure. Although all participants tolerated tDCS well, 25% of the sample ($n = 16$) reported side effects. The severity of reported side effects ranged from 1 ($n = 8$) to 3 ($n = 4$). The most frequently reported side effect was itching of the skin at the electrode sites following the onset of stimulation. 25% ($n = 16$) of the sample reported nicotine intake less than 3 hours prior to the study, and 15.6% ($n = 10$) reported caffeine intake during the same period.

Table 1 summarizes mean pain intensity scores for all groups. Difference scores for 43° ranged between - 46.0 and 59.0 CoVAS points, $M = 5.5$, $SD = 17.1$; for 45° between - 53.0 and 75.0, $M = 6.0$, $SD = 18.6$; for 47° between - 29.0 and 42.0, $M = 0.9$, $SD = 11.8$. Negative difference scores indicate an increase in pain intensity at the post-test compared to the pre-test.

Threshold scores on the first measurement ranged between 34.7° and 48.4°, $M = 44.8°$, $SD = 2.7$, and on the second measurement between 38.3° and 50.2°, $M = 45.9°$, $SD = 2.3$. Threshold difference scores were between - 11.4 and 1.8, $M = - 1.2$, $SD = 2.3$. Negative difference scores indicate an increase in threshold on the second measurement compared to the first measurement.

Table 1

Mean pain intensity scores (standard deviations in parentheses)

	Anodal tDCS (n = 20)	Natural history (n = 18)	Sham tDCS (n = 26)
Pre-test scores			
43°	22.8 (21.33)	25.6 (23.49)	22.7 (16.96)
45°	29.9 (24.12)	37.0 (20.11)	28.8 (19.74)
47°	57.5 (27.99)	66.7 (24.54)	58.5 (27.57)
Treatment scores			
43°	13.7 (13.68)	22.3 (16.23)	14.7 (12.66)
45°	22.0 (18.84)	35.1 (24.29)	30.1 (22.50)
47°	51.0 (28.37)	69.7 (25.60)	56.5 (27.71)
Post-test scores			
43°	17.4 (17.99)	19.2 (15.81)	17.7 (20.22)
45°	17.5 (19.94)	33.1 (27.24)	26.3 (24.42)
47°	50.9 (26.03)	70.7 (27.06)	58.5 (28.68)

Mean stress score on the first measurement was 3.2, SD = 1.7, range 0 – 7.5; after treatment M = 2.0, SD = 1.8, range 0 – 10.0; after the post-test M = 1.7, SD = 1.5, range 0 – 5.5. Mean stress reduction was 1.5, SD = 1.5, range - 1.0 – 5.0. Total FPQ scores ranged between 53.0 and 103.0 (possible range is between 30 and 150), M = 78.0, SD = 11.5. Mean scores for the subscales were 34.0, SD = 5.1 for severe pain, 19.3, SD = 5.3 for minor pain, and 23.4, SD = 6.9 for medical pain. For PANAS, mean positive affect score was 26.1, SD = 6.1, and mean negative affect score 13.2, SD = 3.9. Possible range for both subscales is between 10 and 50. Mean scores on the BFI were 3.7, SD = 0.9 for extraversion, 3.6, SD = 0.8 for agreeableness, 3.2, SD = 0.9 for conscientiousness, 2.6, SD = 0.9 for neuroticism, and 3.6, SD = 0.8 for openness. Possible range for all dimensions is between 2 and 10.

Effects of tDCS on pain intensity and threshold

A repeated-measures ANOVA with CoVAS scores for 43° revealed a main effect of Test, $F(2, 61) = 6.3$, $p = .002$, $\eta_p^2 = .094$, but no main effect of Group, $F(2, 61) = 0.49$, $p = .62$, and no significant interaction, $F(4, 61) = 0.60$, $p = .68$. Within-subjects contrasts further showed that CoVAS scores were significantly lower during the post-test (M = 18.0, SD = 18.1)

as compared to the pre-test (M = 23.6, SD = 20.0), $F(1, 61) = 6.61$, $p = .013$, $\eta_p^2 = .098$, but no significant difference was found between treatment and pre-test scores, $F(1, 61) = 0.33$, $p = .57$. Figure 2 shows mean CoVAS scores for 43° C. Error bars in Figures 2 – 5 represent standard errors of the means.

A repeated-measures ANOVA with scores on 45° C stimuli showed a main effect of Test, $F(2, 61) = 3.95$, $p = .02$, $\eta_p^2 = .061$, but no main effect of Group, $F(2, 61) = 1.68$, $p = .19$, and no significant interaction, $F(4, 61) = 1.22$, $p = .31$. Tests of within-subjects contrasts showed that pain intensity scores were significantly lower during the post-test (M = 25,5, SD = 24.4) than during the pre-test (M = 31.4, SD = 21.2), $F(1, 61) = 7.23$, $p = .009$, $\eta_p^2 = .106$. Figure 3 shows mean CoVAS scores for 45° C stimuli.

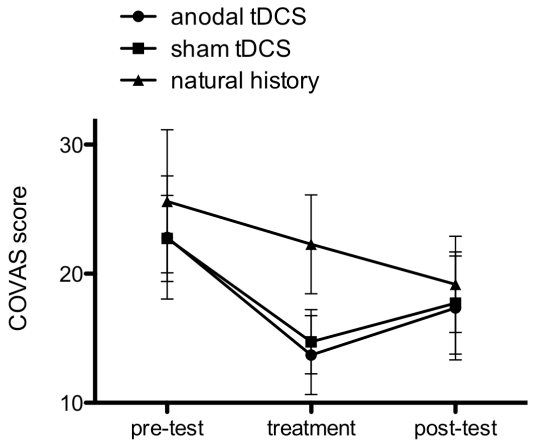

Figure 2. Pain intensity at 43° C.

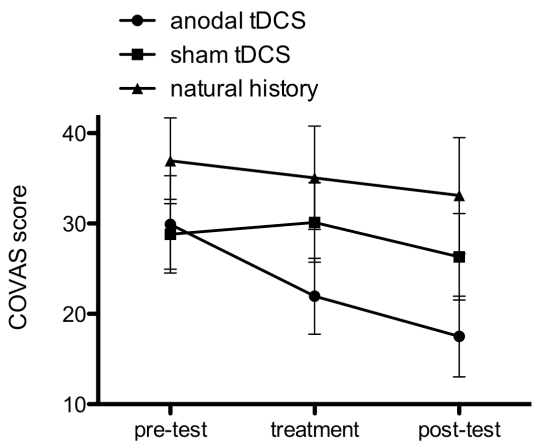

Figure 3. Pain intensity at 45° C.

A repeated-measures ANOVA with 47° scores showed no main effect of Test, $F(2, 61) = 0.89$, $p = .40$, or Group, $F(2, 61) = 1.79$, $p = .18$, but a significant interaction between the two factors, $F(4, 61) = 2.89$, $p = .03$, $\eta_p^2 = .087$. Planned comparisons showed that pain reduction was larger in the anodal group at post-test (a reduction from 57.45, SD = 27.99 at pre-test to 50.85, SD = 26.03 at post-test) than in the natural history group, for which mean pain intensity increased from 66.67, SD = 24.54 at pre-test to 70.67, SD = 27.06 at post-test. This difference was significant, $F(1, 62) = 7.95$, $p = .006$. A significant difference in pain reduction was also found between the anodal group and the natural history group at treatment, $F(1, 62) = 5.51$, $p = .022$. The anodal group reported a reduction in pain intensity from 57.45, SD = 27.99 at pre-test to 51.0, SD = 28.4 at treatment, while for the natural history group pain intensity increased from 66.67, SD = 24.54 at pre-test to 69.67, SD = 25.29 at treatment.

Planned comparisons between the sham group and the other two groups were carried out, using scores on 47° C stimuli. There was no significant difference in pain reduction between the sham group and the natural history group at treatment, $F(1, 62) = 1.76$, $p = .19$, or at post-test, $F(1, 62) = 1.34$, $p = .25$. No significant difference in pain reduction was found between the anodal and sham groups at treatment, $F(1, 62) = 1.40$, $p = .24$, but at post-test the difference was marginally significant, $F(1, 62) = 3.52$, $p = .06$. The anodal group reported a decrease in pain from 57.5, $SD = 27.99$ at pre-test to 50.9, $SD = 26.03$ at post-test, while for the sham group pain intensity did not change, $M = 58.5$, $SD = 27.57$ at pre-test, and $M = 58.5$, $SD = 28.68$ at post-test. See Figure 4 for mean CoVAS scores on 47° stimuli.

A repeated-measures ANOVA with threshold data showed a main effect of Test, $F(1, 61) = 16.92$, $p < .001$, $\eta_p^2 = .217$. On average, pain threshold increased from 44.75°, $SD = 2.68$ to 45.94°, $SD = 1.65$. There was no main effect of Group, $F(2, 61) = 0.71$, $p = .50$, and no significant interaction, $F(2,61) = 1.0$, $p = .36$. Mean threshold scores are shown in Figure 5.

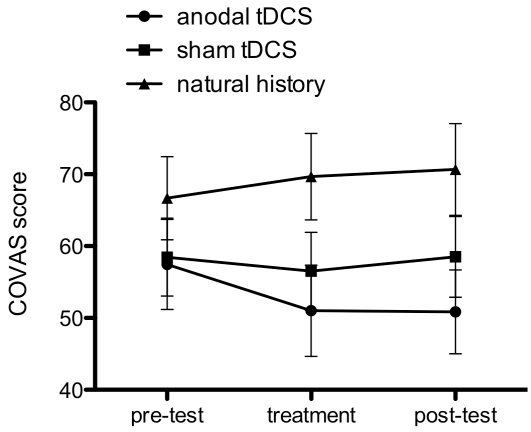

Figure 4. Pain intensity at 47° C.

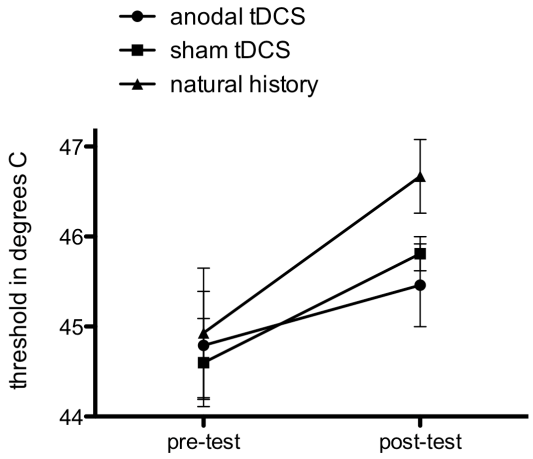

Figure 5. Pain threshold.

Subjective stress, blood pressure and heart rate data

Repeated-measures ANOVA with subjective stress scores showed a main effect of Test, $F(2, 60) = 28.3$, $p < .001$, $\eta_p^2 = .321$ and a main effect of Group, $F(2,60) = 3.40$, $p = .04$, $\eta^2 = .102$, but no significant interaction, $F(4, 60) = 0.91$, $p = .45$. Stress decreased significantly at treatment compared to the pre-test, $F(1, 60) = 23.0$, $p < .001$, from 3.2, $SD = 1.70$ to 2.0, $SD = 1.80$, 95% CI [0.57, 1.77], and further decreased to 1.7, $SD = 1.46$ at post-test, but the difference between treatment and post-test scores was not significant, $p = .21$. Post-hoc tests showed that on average stress was 1.1 points lower in the anodal group than in the natural history group, $p = .04$, 95% CI [0.06, 2.16]. See Table 2 for mean stress scores.

Table 2

Mean stress scores (standard deviations in parentheses)

	Anodal tDCS (n = 19)	Natural history (n = 18)	Sham tDCS (n = 26)
Before pre-test	2.4 (1.60)	4.9 (1.74)	3.2 (1.48)
After treatment	1.7 (1.75)	2.4 (1.15)	2.0 (2.17)
After post-test	1.3 (1.44)	2.2 (1.15)	1.6 (1.60)

For systolic blood pressure there was a main effect of Test, $F(2, 58) = 47.06$, $p < .001$, $\eta_p^2 = .45$, but no main effect of Group, $F(2, 58) = 0.70$, $p = .50$, and no significant interaction, $F(4, 58) = 0.16$, $p = .955$. Systolic blood pressure was significantly lower at treatment as compared to the pre-test, a reduction from 132.36, $SD = 13.85$ to 121.21, $SD = 10.47$, $p < .001$. At post-test, mean systolic blood pressure increased to 122.32, $SD = 10.72$, but the reduction remained significant, $p < .001$.

There was a reduction in diastolic blood pressure as well, $F(2, 58) = 26.46$, $p < .001$, $\eta_p^2 = .31$, but it was not significantly different between groups, $F(2, 58) = 1.16$, $p = .32$. Overall reduction at treatment compared to the pre-test was from 80.71, $SD = 8.68$ to 77.07, $SD = 7.92$, $p < .001$, and further reduction at post-test to 75.78, $SD = 7.73$, $p < .001$.

Heart rate decreased significantly across tests, $F(2, 49) = 20.3$, $p < .001$, $\eta_p^2 = .113$. A reduction from 69.8, $SD = 13.77$ at pre-test to 65.1, $SD = 11.08$ at treatment was significant, $p < .001$, and there was further reduction to 64.9, $SD = 10.50$, $p < .001$ at post-test. There was also a significant interaction between the two factors, $F(4, 49) = 3.12$, $p < .03$, $\eta_p^2 = .113$. None of the post-hoc tests reached significance. Decreases in blood pressure and heart rate were not related to stress reduction, Pearson $r = .18$, $p = .17$ for systolic blood pressure, $r = .13$, $p = .32$ for diastolic blood pressure, and $r = .22$, $p = .11$ for heart rate. The decrease in blood pressure across tests was not related to pain reduction, $r = .06$, $p = .66$ for systolic blood pressure, and $r = .00$, $p = .99$ for diastolic blood pressure. Heart rate reduction was not related to pain reduction, $r = -.21$, $p = .13$.

Effects of stress on pain reduction by tDCS

Hierarchical regression showed that only fear of medical pain significantly predicted pain reduction by tDCS, $b^* = .62$, $b = 1.0$, $SE = 0.33$, $p = .007$, 95% CI [0.32, 1.72]. Thus, for each one-point increase in fear of medical pain, there was a one-point increase in pain

reduction. R^2 change was .37, thus fear of medical pain explained 37% of the variance in the effect of tDCS on pain.

Discussion

In this study we investigated the effects of tDCS on perceived pain intensity and pain threshold in healthy volunteers. Compared to sham stimulation, tDCS did not reduce pain at treatment, but at post-test the anodal group reported 11% less pain for 47° C stimuli, while for the sham group pain intensity did not change. Compared to no treatment, tDCS reduced pain by 28%, although this effect was observed for moderate pain only. Thus, our main hypothesis about the effect of tDCS on pain was partially supported. No difference in pain scores was found between the sham and the natural history groups, thus the hypothesis that sham tDCS would induce placebo analgesia was not supported. No effect of tDCS on pain threshold was found. Fear of medical pain predicted pain reduction by tDCS.

Effects of tDCS on pain intensity

We found no difference in pain intensity between the anodal and the sham groups at treatment, i.e., 340 seconds after the end of tDCS. Thus, anodal tDCS did not reduce pain more than sham stimulation did. This finding is consistent with those of Antal et al. (2008) and Csicsak et al. (2009), who found no difference in pain intensity following anodal tDCS, as compared to sham stimulation. However, this finding is inconsistent with the results of Hansen et al. (2011), who reported that, compared to sham stimulation, anodal tDCS facilitated pain processing, as evidenced by the increased amplitude of pain-related evoked potentials. On the other hand, anodal tDCS did not modulate pain intensity ratings in that study, so it is difficult to interpret the findings of Hansen et al. (2011) in terms of tDCS effects on pain. Pain is a subjective experience and thus pain reduction should be reflected in subjective ratings.

On the other hand, we found that at post-test (i. e., 12 minutes after the end of stimulation) there was a marginally significant difference in pain reduction between the anodal and the sham groups. The anodal group reported 11% less pain at post-test, compared to the pre-test, while for the sham group there was no change in pain intensity. The fact that this difference almost reached the required significance level suggests that it could be interpreted as an effect of anodal tDCS on pain intensity. If interpreted this way, our finding is inconsistent with the results of Antal et al. (2008) and Csicsak et al. (2009), who found no effect of tDCS compared to sham stimulation. This is also inconsistent with our result at treatment, where no effect of tDCS was observed. However, this finding is consistent with those of earlier studies of chronic pain, in which tDCS reduced pain as compared to sham stimulation, although the size of the reduction observed in our study was smaller. For example, after applying anodal tDCS,

Roizenblatt et al. (2007) and Fregni, Gimenes et al. (2006) reported 59% and 58% reduction in the VAS scores of their patients, respectively, while pain reduction in our study was 11%.

Our finding that tDCS reduced pain at post-test, but not at treatment, might indicate that the effect of tDCS increases as more time passes after the end of stimulation. However, there is currently no evidence to support this. A likely interpretation is that tDCS was effective as compared to sham stimulation, but the duration of stimulation in our study was not sufficient to provide consistent results. This interpretation is supported by the difference in findings between experimental and clinical studies. All the aforementioned experimental studies investigated the effects of a single tDCS session. In contrast, in studies of tDCS effects on chronic pain, the duration of stimulation is typically longer than in experimental studies, and repeated tDCS sessions are used. For example, in the studies by Fregni, Gimenes et al. (2006), and Roizenblatt et al. (2007), five anodal tDCS sessions were given on separate days, and each session lasted 20 minutes. In our study participants received a single session of tDCS that lasted 7 minutes, and this might explain the finding that pain reduction by tDCS was only marginally significant. This is in agreement with the finding that repeated tDCS sessions are necessary to reduce pain. In their study of chronic pain, Fregni et al. (2006) first observed significant pain reduction after the second tDCS session. These researchers also noted that the effect of repeated tDCS sessions was cumulative, such that the largest pain reduction was observed after five sessions. This supports the interpretation that tDCS had an effect on pain in our study, but the duration of stimulation was not sufficient to provide consistent results. The effects of repeated tDCS sessions on pain intensity should be investigated with healthy volunteers in order to test the validity of this interpretation.

The inconsistency between our findings and those of earlier experimental studies might in part be due to methodological differences in pain stimulation. In all experimental studies of tDCS to date, researchers have used either laser stimulation or electric stimulation to induce pain. Laser and electric stimuli are very brief, i.e., several milliseconds, affect a skin area of a few millimeters, and are felt as a painful pinprick. In contrast, a contact heat thermode, such as that used in our study, delivers heat of constant intensity to a larger skin area. Moreover, the duration of stimuli in our study was longer (20 seconds) than the typical duration of laser or electric stimuli (several milliseconds). Constant heat applied over a relatively large skin area might result in a sensation that resembles endogenous pain better than that induced by laser or electrical stimulation. Thus, noxious stimulation such as that used in our study might have better ecological validity compared with both laser and electric stimulation, which might

explain why we observed an effect of tDCS on pain, while Antal et al. (2008) and Csicsak et al. (2009) did not.

In randomized clinical trials designed to test the effectiveness of analgesic treatments, the treatment must reduce pain by 50% or more in order to be considered effective. Moreover, pain reduction must be due to the analgesic treatment, and not, for example, to placebo response or spontaneous remission. Thus, pain reduction observed in our study clearly does not fulfill the criteria for clinical effect. Whereas several studies of chronic pain showed more than 50% reduction following anodal tDCS (Fregni, Gimenes et al., 2006, Fregni et al., 2006, Roizenblatt et al., 2007), pain reduction observed in our study was only 11%. On the one hand, this difference in effect might be due to the difference in stimulation duration in our study and the aforementioned clinical studies. On the other hand, the mechanisms of chronic endogenous pain and pain reduction are likely to be different from those in experimentally induced acute pain, and these differences might explain the difference in pain reduction by tDCS between clinical and experimental studies.

Our study was not aimed at investigating the mechanisms by which tDCS leads to pain reduction. Neuroimaging studies should be conducted to compare cortical pain processing before and after tDCS, and to investigate whether the mechanisms of pain reduction by tDCS are different in chronic pain patients and in healthy volunteers. As shown by our results, after-effects of 7 minutes of tDCS can persist for at least 12 minutes, but earlier evidence suggests that after a 13-minute stimulation session, excitability changes may last for over an hour (Nitsche & Paulus, 2001). Thus, it would be possible to conduct an fMRI scan to investigate the mechanisms of tDCS effects on pain processing. Participants could first be scanned as they receive and rate noxious stimuli, then given tDCS, and immediately afterwards a second scan could be conducted, during which noxious stimuli are again delivered and their intensity rated. Effects of repeated tDCS sessions might be examined by performing a scan immediately after each session.

Following tDCS, participants in the anodal group reported 28% less pain as compared to the natural history group, for which there was an increase in pain. Thus, tDCS significantly reduced pain as compared to no treatment, and this reduction was evident both at treatment and at post-test. Participants in the anodal group received tDCS as well as the verbal suggestion that tDCS can reduce pain, while participants in the natural history group received painful stimulation and no verbal suggestions of pain relief. Thus, the difference in pain intensity between the anodal and the natural history groups might best be explained by an additive effect

of tDCS and verbal suggestions of pain relief, as well as any positive expectations of pain relief induced by the fact that a treatment was given.

Placebo response with tDCS

None of the earlier experimental or clinical studies included a natural history group, thus our study was the first to investigate the placebo response with tDCS. In clinical tests of analgesic treatments placebo response is considered irrelevant and the effectiveness of a treatment is defined by comparing it to placebo. However, the placebo component could be exploited in clinical treatments, because by maximizing the placebo response the total effect of an analgesic treatment can be increased. In our study there was no difference in pain intensity between the natural history group and the sham stimulation group, thus no placebo effect was found. Although the participants received a verbal suggestion of pain relief by tDCS, it was given when they arrived at the laboratory and was relatively vague, i.e., "you will receive tDCS, and the purpose of our study is to investigate whether it can relieve pain." In contrast, verbal suggestions in placebo studies are typically more specific, i.e., "you will now receive a potent painkiller" and are given immediately before or together with the treatment. This difference might explain why participants in our study did not show placebo analgesia following tDCS.

It is worth noting that placebo response with tDCS is likely to be smaller than with typical painkillers in the form of capsules or injections, simply because the tDCS apparatus looks nothing like these typical painkillers. Prior experience of pain reduction by a painkiller is a learning process that results in the expectation of pain relief when that painkiller is administered on a later occasion. Therefore, positive prior experience is necessary for the placebo response to be elicited (Benedetti, 2009; Colloca & Benedetti, 2006). Because participants who are treated with tDCS are unlikely to have any prior experience with it, placebo effect in tDCS studies might be small. Also, participants might be anxious because they are being treated with electricity, and, as shown by several researchers, fear and anxiety might offset placebo analgesia (e.g., Bingel et al., 2011, Lyby, Aslaksen, & Flaten, 2011). In order to provide participants with positive prior experience, the classical conditioning paradigm might be employed (Colloca & Benedetti, 2006). Within this paradigm, participants initially receive an intense noxious stimulus, the intensity of which is reduced on the next trial without the participant's knowledge, and at the same time this less intense stimulus is paired with the treatment, e.g., tDCS of short duration. On the next trial, stimulus intensity is increased to the original level, but this time, if the treatment is given, participants are likely to rate the stimulus as less intense than on the first trial. If a conditioning paradigm is employed in tDCS studies,

the possibility that the placebo response might be offset by stress or anxiety could probably be reduced because of repeated exposure.

Pain threshold

No effect of tDCS on pain threshold was found in our study. Instead, pain threshold increased by 2% in all groups. Thus, our results are inconsistent with those of Boggio et al. (2008), who reported a 13% increase in pain threshold following anodal tDCS. This inconsistency might be explained by the difference in time intervals between the end of stimulation and the subsequent threshold measurement. Because excitability changes following tDCS are transient, in our study they may have returned to baseline by the time of the second threshold measurement (i.e., 15 minutes after the end of stimulation). In contrast, Boggio et al. (2008) measured pain threshold 3 minutes after the end of stimulation. This illustrates the importance of keeping in mind the transient nature of tDCS after-effects when designing experiments. Researchers should estimate the expected duration of after-effects so that all necessary measurements can be taken before the excitability changes return to baseline.

The overall threshold increase found in our study might be explained in terms of adaptation level theory (Helson, 1964). This theory states that psychophysical ratings of stimuli are not only based on the stimulus currently being rated, but on other temporally adjacent stimuli as well. Thus, if of two equally intense stimuli one is preceded by a more intense stimulus and the other by a less intense stimulus, the former would be rated as less intense than the latter. In our study, the first threshold measurement was immediately preceded by a 46° C stimulus, and the second by a 47° C stimulus, thus at the second measurement threshold increase could have been due to the more intense stimulus delivered immediately before. Also, by the second measurement, participants had more time to adapt and had received more preceding stimuli, which they could have used for comparison.

Alternatively, threshold increase might be explained in terms of habituation at the neural level, whereby nociceptive signaling became less intense and the amount of neurotransmitter released decreased as more noxious stimuli were delivered.

Fear of medical pain as moderator of tDCS effect on pain

We found that fear of medical pain predicted pain reduction by tDCS. Specifically, higher fear of pain was related to larger pain reduction. Because of the small sample size (n = 19) in our study, this result should be validated with larger samples. The finding that fear of medical pain predicted pain reduction, but not fear of severe pain or fear of moderate pain might be explained by the differences in the nature of these constructs. Whereas fear of medical pain is associated with medical context (i.e., fear of injections), fear of moderate and severe

pain is associated with injuries and accidents (i.e., fear of biting one's tongue while eating), thus fear of medical pain might be more relevant in the laboratory settings than fear of severe and moderate pain. The finding that higher fear of medical pain was related to larger pain reduction is inconsistent with the results of Lyby et al. (2010), who reported that higher fear of medical pain was associated with increased pain. One explanation for this inconsistency is the complexity of the relationships between pain and affective states. Whereas the general finding of earlier studies is that negative emotions and stress increase pain, it has also been shown that experimentally induced fear can reduce VAS ratings of fixed duration thermal stimuli (Rhudy & Meagher, 2003). These researchers proposed that when amygdala is activated by fear, it exerts influence on descending pain modulatory pathways, which inhibit afferent nociception. Arguably, participants who reported high fear of medical pain in our study, feared the upcoming noxious stimuli, and this fear might have inhibited pain. Fear-induced pain inhibition might have added to the effect of tDCS, thus producing larger pain reduction. Alternatively, participants who reported higher fear of medical pain might have used coping strategies such as diverting their attention away from the painful stimuli in order to minimize the anticipated discomfort. The inconsistencies of our results with those of Lyby et al. (2010), as well as inconsistencies in the results of earlier studies, indicate that the relationships between affective states and pain are complex and are likely to vary across situations and individuals. In order to understand these relationships studies should be conducted that are specifically aimed at the relationship between negative emotions and pain relief. Additionally, if affective states were induced experimentally, this would probably result in better-controlled experiments and results would be affected to a lesser degree by individual differences.

Limitations of the study

The main limitation of our study was lack of randomization in the natural history group, thus pain reduction could be attributed to baseline differences among groups. Pre-test stress levels were higher in the natural history group than in the anodal group, and this might explain the difference in reported pain intensity between these groups. However, it seems unlikely that the difference in stress alone could account for the observed pain reduction. First, there were no differences among groups in the pre-test pain ratings; secondly, pre-test stress only explained 5% of the variance in pain reduction when regressed against it; and, finally, regression analysis showed that pre-test stress did not significantly predict pain reduction.

Conclusions

In summary, our results confirm and extend those of earlier experimental and clinical studies of tDCS effects on pain, and show that, as compared to sham stimulation, tDCS results

in pain reduction in healthy volunteers. Future studies should investigate the mechanisms by which tDCS produces pain relief and whether these mechanisms differ in chronic pain patients and healthy participants.

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Appendix A

Forespørsel om deltakelse i forskningsprosjekt

Transcranial Direct Current Stimulation

(tDCS) som behandlingsmetode for smerte

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å utforske mekanismene for hvordan hjernen bearbeider smerte. Denne forespørselen om deltakelse er knyttet til et prosjekt som omfatter smertebehandling i fibromyalgi, og vi ønsker å forespørre deg om deltakelse for å inngå i en kontrollgruppe i denne studien. Vi ønsker å teste hvorvidt såkalt transkraniell direkte stimulering (tDCS) kan dempe varmesmerte.

Vi ønsker å forespørre friske personer i alderen 18 til 60 år om å delta. Denne studien er et samarbeid mellom Institutt for Psykologi, UIT, Smerteavdelingen UNN, og Radiologisk Avdeling UNN.

Hva innebærer studien?
Gjennomføringen av eksperimentet skjer ved Institutt for Psykologi, UiT. Eksperimentet gjennomføres ved at deltakerne gjennomfører smertetester samtidig som fysiologiske og subjektive reaksjoner måles. Smertetestene foretas i form av varme på en liten flate av huden på armene. Smertebehandlingen vil foregå ved at du får svært svak strøm (2 milliampere) til motorisk hjernebark i ca 7 minutter via elektroder som festes til hodebunnen. Til sammenlikning gir en lyspære på 60 watt ca 350 milliampere strøm. Dette er en ufarlig og velprøvd vitenskapelig metode som ikke gir noen bivirkninger utover at enkelte kan merke svak kløe under elektrodene mens stimuleringen pågår. Strømstyrken som benyttes i denne studien er for svak til å gi noen form for komplikasjoner, men sterk nok til å dempe smerteprosesser i hjernen. Ikke alle deltakerne får aktiv behandling, noen deltakere vil få montert tDCS elektroder uten at det gis strøm. Eksperimentatorene som gjennomfører eksperimentet vil ikke vite om du faktisk får aktiv behandling eller placebobehandling og de fleste vil heller ikke kunne merke dette fordi strømstyrken er for svak til å gi noen opplevelse av stimuleringen. En tredje gruppe vil ikke få montert elektrodene, og vil bare få smertestimulering uten behandling. Denne gruppen vil være en kontrollgruppe.

Hele eksperimentet vil ta ca. 45-55 minutter, dette inkluderer instruksjoner og oppsett av utstyr.

Mulige fordeler og ulemper
På grunn av at vi påfører varme på huden kan huden bli rød i opptil to dager etter eksperimentet. Dette er ufarlig og medfører ingen kjente bivirkninger. Dersom du er i gruppen som får tDCS behandling kan du oppleve kløe under stimuleringen, og du vil måtte vaske håret etter at eksperimentet er fullført fordi elektrodene er smurt med strømledende gel. Det er ingen kjente bivirkninger ved tDCS behandling utover svak kløe, men i svært sjeldne tilfeller kan man oppleve svak hodepine i noen timer etter behandlingen.
Denne studien gir ikke noen personlige fordeler for deg, utover at du vil få innsikt i hvordan eksperimentell forskning utføres.

Hva skjer med informasjonen om deg?
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og resultater gjennom en navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Navnelisten som brukes i dette eksperimentet vil bli slettet så snart studien er fullført for alle deltakerne.

Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få noen konsekvenser for deg. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det får noen konsekvenser for deg.

Kapittel A – utdypende forklaring av hva studien innebærer

Kriterier for deltakelse: Vi søker etter forsøkspersoner av begge kjønn mellom 18 og 40 år. De som deltar må ha god helse, ikke være gravid, ikke ha eller ha hatt alvorlige sykdommer av noen art eller bruke reseptbelagte legemiddel, med unntak av p-piller. Du kan ikke ha kjente allergier overfor legemidler. Man kan heller ikke ha skader i huden på armene, eller ha en kronisk smertelidelse. Det er også viktig å merke seg at denne studien ikke er en medisinsk undersøkelse og at eksperimentet er ikke egnet for å avdekke noen form for sykdom.

Pasientens/studiedeltakerens ansvar: Som deltaker i denne studien er det ditt ansvar å lese informasjonen vedrørende deltakelse.

Eventuell kompensasjon til og dekning av utgifter for deltakere: Etter gjennomført eksperiment vil du få et Sentrumsgavekort pålydende kr 200,- for kompensasjon for tidsbruk. Dette kan brukes i de fleste butikker i Tromsø sentrum.

Kapittel B – personvern, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er navn, alder, fødselsdato og kjønn. Navn vil bli lagret separat fra resultatene som framkommer i eksperimentet og vil bare bli brukt for å sende deg rapport på funnene for hele studien etter at studien er fullført for alle deltakerne. Navnelister vil bli slettet så snart studien er fullført for alle deltakerne. Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og

fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og resultater gjennom en navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Navnelisten som brukes i dette eksperimentet vil bli slettet så snart studien er fullført for alle deltakerne.

Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Universitetet i Tromsø ved administrerende direktør er databehandlingsansvarlig.

Rett til innsyn og sletting av opplysninger om deg
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi og Universitetet i Tromsøs rolle

Studien er finansiert utelukkende gjennom forskningsmidler fra Universitetet i Tromsø. Det er ingen økonomiske interessekonflikter som kan påvirke gjennomføringen av studien, eller publiseringen av resultatene.

Forsikring

Alle deltakere i denne studien er dekket av Produktansvarsloven.

Informasjon om utfallet av studien
Dersom du ønsker det, vil du få tilsendt en skriftlig rapport om resultatene fra denne studien så snart alle deltakerne har gjennomført. Dersom du ønsker dette, ber vi deg om å føre opp kontaktadresse på samtykkeerklæringen som vi beholder.

Appendix B

Samtykke til deltakelse i studien

Jeg er villig til å delta i kontrollgruppen for studien tDCS og behandling av smerte.

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien.

(Signert, rolle i studien, dato)

Appendix C

Fear of pain questionnaire – III

Instruksjon: Setningene under beskriver smertefulle opplevelser. Les hvert spørsmål og tenk på hvor redd du er for å oppleve SMERTEN som er forbundet med hver opplevelse. Hvis du aldri har opplevd smerte knyttet til en av situasjonene, svar slik du forventer at FRYKTEN ville vært dersom du hadde en slik opplevelse. Sett en sirkel rundt tallverdien for å rangere din FRYKT FOR SMERTE i forhold til hver opplevelse.

GRAD AV FRYKT

Ikke i det hele tatt	Litt	En god del	Veldig mye	Ekstrem	
1	**2**	**3**	**4**	**5**	1. Være med i en bilulykke.
1	**2**	**3**	**4**	**5**	2. Bite deg i tungen mens du spiser.
1	**2**	**3**	**4**	**5**	3. Brekke armen.
1	**2**	**3**	**4**	**5**	4. Skjære deg i tungen på en konvolutt.
1	**2**	**3**	**4**	**5**	5. Noe tungt treffer deg i hodet.
1	**2**	**3**	**4**	**5**	6. Brekke en fot.
1	**2**	**3**	**4**	**5**	7. Slå deg på et følsomt sted på albuen.
1	**2**	**3**	**4**	**5**	8. Ta en blodprøve med en sprøyte.
1	**2**	**3**	**4**	**5**	9. Noen slenger en tung bildør over hånden din.
1	**2**	**3**	**4**	**5**	10. Ramle ned en betongtrapp.
1	**2**	**3**	**4**	**5**	11. Få en injeksjon med en sprøyte i armen.
1	**2**	**3**	**4**	**5**	12. Brenne fingrene på en fyrstikk.
1	**2**	**3**	**4**	**5**	13. Brekke nakken.
1	**2**	**3**	**4**	**5**	14. Få en injeksjon med en sprøyte i hoften.
1	**2**	**3**	**4**	**5**	15. Få en flis i fotsålen og deretter få den fjernet med pinsett.

Fortsetter på neste side.

GRAD AV FRYKT

Ikke i det hele tatt	Litt	En god del	Veldig mye	Ekstrem	
1	**2**	**3**	**4**	**5**	16. Få et objekt som sitter fast i øyet ditt fjernet av en lege.
1	**2**	**3**	**4**	**5**	17. Få en injeksjon med en sprøyte i munnen.
1	**2**	**3**	**4**	**5**	18. Bli brent i ansiktet av en sigarettglo.
1	**2**	**3**	**4**	**5**	19. Kutte en finger på papir.
1	**2**	**3**	**4**	**5**	20. Måtte sy sting i leppa.
1	**2**	**3**	**4**	**5**	21. Få en vorte på foten fjernet av en lege med et skarpt instrument.
1	**2**	**3**	**4**	**5**	22. Kutte deg med en skarp barberhøvel når du barberer deg.
1	**2**	**3**	**4**	**5**	23. Svelge en varm drikk før den er avkjølt.
1	**2**	**3**	**4**	**5**	24. Få sterk såpe i øynene mens du dusjer eller bader.
1	**2**	**3**	**4**	**5**	25. Få en dødelig sykdom som gir deg daglig smerte.
1	**2**	**3**	**4**	**5**	26. Få trekt en tann.
1	**2**	**3**	**4**	**5**	27. Kaste opp flere ganger på grunn av matforgiftning.
1	**2**	**3**	**4**	**5**	28. Få sand eller støv blåst inn i øynene.
1	**2**	**3**	**4**	**5**	29. Bli boret i en tann.
1	**2**	**3**	**4**	**5**	30. Få muskelkrampe.

Appendix D

PANAS (oversatt av Peter Lyby)

De følgende ordene beskriver ulike følelser og emosjoner.

Vær vennlig å angi hvordan du føler deg akkurat nå ved å tegne en sirkel rundt det svaralternativet som passer best for hver følelse.

1 = Svært lite eller ikke i det hele tatt
2 = Litt
3 = Moderat
4 = En god del
5 = Ekstremt (svært mye)

(1) = Svært lite eller ikke i det hele tatt **(2) = Litt** **(3) = Moderat** **(4) = En god del** **(5) = Ekstremt (svært mye)**

	Svært lite/ikke i det hele tatt	Litt	Moderat	En god del	Ekstremt (svært mye)
1. Interessert	1	2	3	4	5
2. Bekymret	1	2	3	4	5
3. Oppstemt	1	2	3	4	5
4. Oppskaket	1	2	3	4	5
5. Sterk	1	2	3	4	5
6. Skyldig	1	2	3	4	5
7. Redd	1	2	3	4	5
8. Fiendtlig	1	2	3	4	5
9. Entusiastisk	1	2	3	4	5
10. Stolt	1	2	3	4	5
11. Irritabel	1	2	3	4	5
12. Årvåken	1	2	3	4	5
13. Skamfull	1	2	3	4	5
14. Inspirert	1	2	3	4	5
15. Nervøs	1	2	3	4	5
16. Bestemt	1	2	3	4	5
17. Oppmerksom	1	2	3	4	5
18. Urolig	1	2	3	4	5
19. Aktiv	1	2	3	4	5
20. Engstelig	1	2	3	4	5

Appendix E

Big Five Inventory – 10

Hvor godt mener du at de følgende utsagnene beskriver din personlighet?

Jeg er en person som…

	Helt uenig	Litt uenig	Verken enig eller uenig	Litt enig	Helt enig
Er reservert	(1)	(2)	(3)	(4)	(5)
Stoler på andre	(1)	(2)	(3)	(4)	(5)
Tenderer til å være lat	(1)	(2)	(3)	(4)	(5)
Er avslappet, håndterer stress bra	(1)	(2)	(3)	(4)	(5)
Har få kunstneriske interesser	(1)	(2)	(3)	(4)	(5)
Er utadvendt og sosial	(1)	(2)	(3)	(4)	(5)
Bruker å påpeke feil hos andre	(1)	(2)	(3)	(4)	(5)
Fullfører det jeg har begynt på	(1)	(2)	(3)	(4)	(5)
Blir lett nervøs	(1)	(2)	(3)	(4)	(5)
Har en livlig fantasi	(1)	(2)	(3)	(4)	(5)