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Autonomic activation and muscle activity in relation to musculoskeletal pain

Thesis for the degree philosophiae doctor

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Norwegian University of Science and Technology

Faculty of Medicine

Department of Neuroscience



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Preface and acknowledgement

The present work was conducted at the Norwegian University of Science and Technology, Faculty of Medicine, Department of Neurosciences. The data collection was done from January 2000 to August 2003. Analyses of the data was performed from July 2003 until March 2007. The work was funded by grants from the Norwegian Research Council and the Department of Neurosciences. I worked full time with the thesis in two periods, August 1999 - August 2000, and July 2003 – January 2004. In other periods the work with the thesis has been besides my medical studies (cand. med 2003), besides clinical work, or besides my work as lecturer in neurology (bedside teaching).

I am very thankful to a number of people. I am sincerely grateful to my supervisor Trond Sand for his outstanding supervision throughout my PhD. He has introduced me to the field of pain and neurophysiology by carefully guiding me through complex mechanisms, at all times with constructive and encouraging comments. I am also very thankful to my co-supervisor Rolf Westgaard who included me in his research group at the Department of Industrial Economics and Technology Management and provided constructive criticism to me in the early and irresolute part of the writing process. I thank the neurology group at the Department of Neuroscience, especially the co-authors Lars Jacob Stovner, Linda White and Rune Bang Leistad. In particular, I want to thank Grethe Helde for her invaluable assistance at the laboratory and her meticulous and outstanding work in contact with the subjects included in the studies. I also thank the co-authors Magne Rø and Petter Borchgrevink for their contributions to this thesis, and Mari Gårseth and Marit Stjern for their assistance in the laboratory.

I am truly indebted to my wife for supporting me both when I decided to start this work, thereby accepting to stay in Trondheim and reject the job offers she had in Oslo, and later for the encouragement to finalize this work.

Summary in English

Background and objectives:

Musculoskeletal pain is frequent and the most common cause of sick leave in Norway. Although chronic musculoskeletal pain is conceived to be related to social or mental stress, the mechanism for such a relation is not known. The overall objective of the present thesis was to elucidate whether stress-associated musculoskeletal pain and stress-induced muscle activity may be related to activation of the autonomic nervous system.

Methods:

The present work is carried out in the laboratory where subjects performed a complex two-choice reaction time test designed to mimic mental load in a work place, resembling stressful and repetitive office work. Subjects were investigated while performing this stressful task for one hour, as well as during a baseline period immediately before and during a recovery period. We measured muscle activity and different parameters indicative of activity in the autonomic nervous system, as well as subjective variables as pain, tension and fatigue. We included patients with generalised (fibromyalgia) and patients with regionalised (shoulder/neck) musculoskeletal pain, as well as healthy controls. A group of patients with musculoskeletal pain were also subject to a block of peripheral sympathetic nerves with a unilaterally anaesthetic block of the lower cervical sympathetic ganglion before the stressful task.

Results:

We found the vascular response to the stressful task to be more protracted than other bodily responses (paper I). We found the muscular responses to the stressful task to be an unlikely explanation for the simultaneously developing pain response for all subjects, irrespective of diagnostic group (paper II). We found delayed pain recovery in both patients groups, but not in the healthy controls (paper II). We found an attenuated cardiovascular response to the stressful task in the fibromyalgia group compared to the healthy controls, with the shoulder/neck pain patients in an intermediate position (paper III). We also found an inverse relation between the heart rate response and the pain

response for the fibromyalgia group (paper III). Lastly, we found that a block of peripheral sympathetic fibres did not affect neither pain nor muscle responses to the stressful task for patients with musculoskeletal pain.

Conclusions:

From the studies presented in the present thesis one may conclude that stress-associated musculoskeletal pain is probably not directly related to muscle activity or autonomic activation at a peripheral level. We found indications of central sensitisation of pain in both patient groups. In patients with generalised musculoskeletal pain (fibromyalgia), the pain may be related to a reduced physiological ability to respond adequately to stress.

Summary in Norwegian:

Bakgrunn:

Muskel/skjelett smerter er svært hyppig og er den vanligste årsaken til sykefravær i Norge. Til tross for en svært vanlig oppfatning av at kroniske muskel/skjelett smerter er relatert til sosialt eller psykisk stress er eventuelle mekanismer for en slik sammenheng ukjent. Hovedmålet for denne doktorgraden var å finne ut om stressindusert muskel/skjelett smerte og stressindusert muskelaktivitet er relatert til aktivisering av det autonome nervesystemet.

Metoder:

Forsøkspersoner ble undersøkt i et laboratorium mens de utførte en sammensatt tovalgstest under tidspress som var utviklet for å etterligne den psykiske belastning en finner på en arbeidsplass med mye stress og rutinepreget arbeid. Forsøkspersonene ble undersøkt mens de utførte denne stressende arbeidsoppgaven i en time, samt i en periode før og en periode etter arbeidet. Vi målte muskelaktivitet og ulike markører for aktivitet i det autonome nervesystemet i tillegg til de subjektive variablene smerte, anspenthet og tretthet. Vi undersøkte pasienter med generalisert (fibromyalgi) og regionalisert (skulder/nakke) muskel/skjelett smerte i tillegg til friske kontroller. En gruppe pasienter med muskel/skjelett smerter ble også undersøkt etter en blokade av perifere sympatiske nerver med en bedøvende blokade av det nedre sympatiske gangliet på den ene siden av halsen.

Resultater:

Vi fant ut at den vaskulære reaksjonen på arbeidsoppgaven var mer langvarig enn de andre kroppslige reaksjonene (artikkel I). Den muskulære reaksjonen på den stressende arbeidsoppgaven er neppe forklaringen på den samtidige smertereaksjonen, verken for pasienter eller kontroller (artikkel II). Vi fant forsinket restitusjon av smertereaksjonen i begge pasientgruppene, men ikke hos de friske kontrollene (artikkel II).

Fibromyalgipasientene hadde mindre puls og blodtrykksendring enn de friske kontrollpersonene som reaksjon på den stressende arbeidsoppgaven, med skulder/nakke pasientene i en mellomstilling (artikkel III). Vi fant også en omvendt sammenheng mellom pulsendingen og smertereaksjonen for fibromyalgigruppen (artikkel III). Til slutt viste vi at en blokade av perifere sympatiske fibre ikke affiserer verken smerten

eller muskelaktiviteten som utvikles under en stressende arbeidsoppgave for en gruppe av pasienter med muskel/skjelett smerter.

Konklusjon:

Ut fra arbeidet som er gjort i denne doktorgradsavhandlingen kan en konkludere med at stressindusert muskel/skjelett smerter trolig ikke er direkte relatert til muskelaktivitet eller aktivering av det autonome nervesystemet på et perifert nivå. Vi fant tegn til sentral sensitivisering av smerte i begge pasientgruppene. Generalisert muskel/skjelett smerte kan være relatert til en manglende evne til å reagere kroppslig på stress.

List of papers

Paper I :

Nilsen KB, Sand T, Stovner LJ, Leistad RB, Westgaard RH. Autonomic and muscular responses and recovery to one-hour laboratory mental stress in healthy subjects. *BMC Musculoskelet Disord* 2007; 8(1): 81.

Paper II:

Nilsen KB, Westgaard RH, Stovner LJ, Helde G, Rø M, Sand T. Pain induced by low-grade stress in patients with fibromyalgia and chronic shoulder/neck pain, relation to surface electromyography. *European Journal of Pain* 2006; 10(7): 615-27.

Paper III:

Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White L, Leistad RB, Helde G, Rø M. Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. *Eur J Pain* 2007; 11(7): 743-55.

Paper IV:

Nilsen KB, Sand T, Borchgrevink P, Leistad RB, Rø M, Westgaard RH. A unilateral sympathetic blockade does not affect stress-related pain and muscle activity in patients with chronic musculoskeletal pain. (submitted)

General introduction

Musculoskeletal pain is a frequent complaint in the general population [1-3] and the most common cause of sick leave in Norway [4]. The aetiology is most often not obvious and these patients represent a huge challenge for the clinician.

Both epidemiological and laboratory studies, as well as studies with a qualitative design has related chronic musculoskeletal pain to mental stress, and especially to stressful work situations [5-11]. There is a large literature on both stress and musculoskeletal pain, but relatively little solid evidence exist on the mechanisms linking the two phenomena.

Stress, autonomic activation and autonomic-somatomotor interactions

The word stress may have different meanings depending on the context. When referring to stress at work one usually put weight on the cognitive or mental aspects of the word. A dictionary may define stress as: “one of bodily or mental tension resulting from factors that tend to alter an existent equilibrium” [12], and a textbook of physiology may define stress as: “a state of threatened homeostasis” [13]. The bodily reactions to stress are mediated by the central autonomic network which coordinates the physiological and behavioural response to a stressful stimulus (Figure 1). Depending on the emotional significance of the stressful stimulus the central autonomic network will respond through endocrine, autonomic or somatomotor outputs. The central integrator for the central autonomic network is the paraventricular nucleus of the hypothalamus which controls the balance between the autonomic nervous system and the neuroendocrine system [14]. The cardiovascular response to stress is an example of an effect through the autonomic nervous system, and the secretion of cortisol in the adrenal cortex in response to ACTH secreted from the pituitary gland (the hypothalamo-pituitary-adrenocortical (HPA) axis) is an example of a response in the neuroendocrine system [15-18]. The autonomic response to stress is multifaceted. The concept of the stress response as generalised withdrawal of parasympathetic activity and increased sympathetic activity which is found in most textbooks [19] as originally introduced by

Hans Selye [20], has been questioned [21]. Several reports during the last decade indicate that the stress response is probably much more organ-specific and differential than suggested by Selye [22-24]. For example, orthostathic stress have opposite circulatory effects in skin and muscle [25].

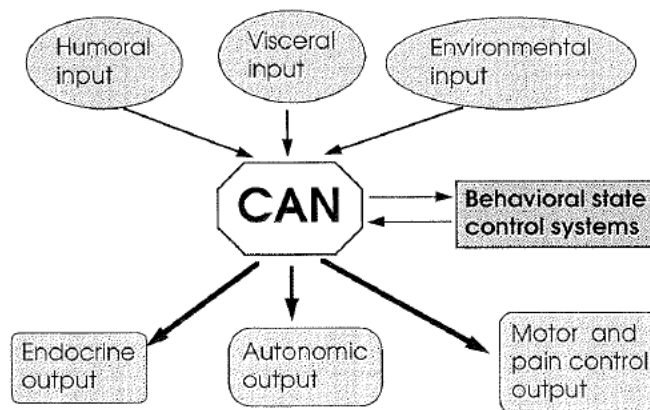


Figure 1. The central autonomic network (CAN) receives and integrates humoral, viscerosensory and environmental inputs to generate specific endocrine, autonomic and somatomotor outputs. The central autonomic network has reciprocal connections with the brain stem and basal forebrain involved in behavioural state control. (From Eduardo E. Benarroch: Central autonomic network, Futura Publishing company, New York, 1997)

While the endocrine and autonomic responses to stress are well described, less is known about the somatomotor responses to stress. Respiratory and sacral motoneurons are known to be controlled by the autonomic nervous system. Respiration is regulated by the parabrachial nucleus, and the urethral sphincter is regulated from an area in the rostral dorsolateral pons. The central autonomic network will also affect the somatomotor system expressed as emotionally motivated motor behaviour [13]. However, there exists some evidence that the central autonomic network may affect motoneurons directly and not only indirectly by changing motor behaviour. The concept of a descending “emotional motor system” was introduced by Holstege [26, 27], and the existence of dual-function neurons with projections to both somatomotor and sympathetic targets has been found in the brainstem of rats [28]. Others have shown that transmission of signals from the upper to the lower motor neuron is not always in a 1:1 ratio, but is modulated by brainstem monoaminergic inputs [29-31].

Another question is whether there exist any peripheral autonomic-somatomotor interactions. There exist a large number of publications on the potential sympathetic modulation of muscle spindles [32-38]. However, the vast amount of these studies is animal studies, and the conclusions cannot with certainty be applied to humans. One human study report sympathetic modulation of muscle spindles [39]. However, while the animal studies describe a depression of the stretch reflex during sympathetic activation, this human study reports the opposite; a facilitation of the stretch reflex during sympathetic activation. At least two studies are published with negative results regarding the possible sympathetic modulation of muscle spindles in humans [40, 41].

Furthermore, although the force of a motor unit is normally considered to be a result solely of the discharge rate of the accompanying motor neuron, there are some reports describing a modulation of muscle force mediated through beta-adrenergic receptors on skeletal muscles [42-46].

Autonomic activation and pain

It is known that acute stress with autonomic activation has an antinociceptive effect referred to as stress-induced analgesia (SIA)[47, 48]. The central autonomic network is important for this effect, and the midbrain periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) is essential for stress-induced antinociception and other homeostatic autonomic effects [49]. The analgesia provided by the PAG-RVM-dorsal horn circuit during acute stress is considered to be opioid-dependent and closely related to placebo analgesia [47, 50].

Some animal studies indicate that chronic stress may have the opposite effect on nociception, in other words a nociceptive effect [51-56]. However, less is known about the potential mechanisms of this phenomenon although peripheral effects of circulating adrenaline may be relevant [57].

Diffuse pain in one part of the body may also inhibit acute pain in another part of the body. This mechanism is known as “diffuse noxious inhibitory control” (DNIC). However, this mechanism is not necessarily a result of the sympathetic activation which pain causes, as this mechanism is independent of PAG and RVM [58, 59].

From a biochemical point of view, several of the neurotransmitters associated with the autonomic nervous system are important for central pain regulation at both the brainstem and the spinal level. Central modulation of pain involves both facilitating and inhibiting mechanisms, and neurotransmitters such as noradrenaline, dopamine, serotonin, acetylcholine and nitric oxide are important for these mechanisms [60-63].

The peripheral sympathetic nervous system is not directly involved in pain transmission in healthy tissues [64-67]. However, in some pathophysiological conditions the peripheral sympathetic nervous system may interact directly with afferent neurons [64, 68-76], but also have an antinociceptive effect through interaction with peripheral immune cells [77].

Theoretical models for the potential deleterious effects of stress on health

How organic disease may be related to a psychobiological process as stress has been discussed for a long time [20, 78]. Various theoretical models have been developed in order to describe how stress may lead to disease and subjective complaints, and these models have been tested experimentally to a varying degree. It must be noted that not all of these models are easily amenable to experimentally testing.

Karasek and Theorell formulated a model which describes how psychological demands and decision latitude at work predict health [79]. Melin and Lundberg formulated another model which incorporated the off-work situation, and hypothesized that certain work conditions cause slow physiological “unwinding” (recovery) with sustained endocrine and muscular responses after work causing musculoskeletal pain for the exposed individual [80].

A few years before Melin and Lundberg presented their model another and more general model of the stress – disease relationship was presented by McEwen and Stellar. They introduced the concept “allostatic load”, i.e. the strain on the body produced by elevated and repeated stress responses, ultimately leading to disease [81]. This model was later refined with more emphasis on how lack of adaptation and prolonged responses lead to disease [82]. McEwen’s model is less focused on the work situation

and muscle activity with a more general physiological approach than Melin and Lundberg's model.

Another model presented by Eriksen and Ursin also focus on prolonged stress responses. The model is named "The cognitive activation theory of stress" (CATS). With elements both from cognitive psychology and neurophysiology they describe how stress and sustained arousal may lead to subjective health complaints [83, 84]. In the CATS model lack of coping is a prerequisite for the deleterious effect of stress on health, and thus incorporates elements from the model of Karasek and Theorell.

Neuronal plasticity and pain

Neural transmission is not only a function of the stimuli applied. Neurons may change their properties over time and are highly modifiable. This is relevant for both primary and dorsal horn pain associated neurons, and such neuronal plasticity is involved in the development of pain hypersensitivity. Some forms of this plasticity are brief with transient changes in ion channel properties, others relatively long-lasting involving changes in protein phosphorylation and altered gene expression, and some are even irreversible with loss of neurons and formation of new synapses [85]. Most knowledge about neural plasticity in pain is from animal studies of activity-dependent neural plasticity, i.e. how activity in pain pathways induce increased pain sensitivity. Little is known about how other stimuli may modulate the transmission of pain. However, there is an increasing awareness that modulation of pain transmission may be a result of physiological processes not directly related to the neural process in question. This includes microglial activation in the central nervous system [86] and peripheral effects of long-term stress [57].

Classic central sensitization of pain refers to the increased synaptic efficacy established in somatosensory neurons in the dorsal horn of the spinal cord following intense peripheral noxious stimuli, tissue injury or nerve damage. This heightened synaptic transmission leads to a reduction in pain threshold, an amplification of pain responses and a spread of increased pain sensitivity to non-injured areas [87]. Normally innocuous stimuli via low-threshold afferents become painful (allodynia), and noxious input results in augmented pain responses (hyperalgesia). However, the term central

sensitisation is often used beyond its classical definition in several kinds of pain hypersensitivity resulting from plasticity in the central nervous system [88].

Amplification of pain responses in second order neurons can be elegantly shown in animal experiments. For example, a progressive increase in action potential output from dorsal horn neurons after repeated peripheral stimulation of nociceptors [89] is a form of activity-dependent neural plasticity and denominated “wind-up”. This may be considered to result from integration of afferent activity to repeated stimuli. A correlate to wind-up can be produced in humans and is then referred to as temporal summation of pain [90-92]. It is more pronounced for the C-fibre mediated second pain than for the A δ -fibre mediated first pain. Temporal summation of pain is also frequency-dependent: stimulation at frequencies lower than 0.3 Hz (3 second intervals) does not normally induce temporal summation [93].

Pain sensations outlasting the stimulus period (painful aftersensations) has been suggested as an additional parameter indicative of sensitised second or higher order neurons [94]. Animal studies has also shown that the pain hypersensitivity induced by repetitive high frequency stimulation (wind-up) can be maintained by subsequent stimulation at low frequencies [95].

Muscle activity and pain

Muscle pain is most often diffuse, dull and aching. The pain is mediated through myelinated A δ fibres (group III) or unmyelinated C fibres (group IV) with free nerve endings which most typically is located in the wall of muscle arterioles or in the surrounding connective tissue. They are not normally activated during physiological muscle contractions but may be sensitised by inflammation or ischemia [96].

Muscle pain may be related to high biomechanical load, i.e. force-demanding work with heavy loads [97]. High biomechanical load is clearly a risk factor for developing musculoskeletal pain, but the vast majority of subjects with chronic musculoskeletal pain are not exposed to heavy loads.

Several models of how chronic muscle pain may be related to low-grade muscle activity have been formulated, but none of them have been experimentally verified. Both ischemia and trauma result in the release of kinins and prostaglandins which again result in vasodilatation and an increase in vascular permeability with edema and increased interstitial pressure as a possible end result. Increased interstitial pressure may

compress venous vessels, resulting in venous congestion and ischemia. In this way a vicious circle is formed [98]. Muscle ischemia may also result in failure of the calcium pump and local tonic contraction due to lack of adenosintriphosphate (ATP). The local muscle contraction is not necessarily a part of the vicious circle, but may be a supplementary mechanism. In other words: the initiating event for such a vicious circle may also be increased muscle contraction via descending motor pathways [98].

Another variant of these vicious circle models is that a painful lesion of whatever origin (trauma, ischemia, inflammation etc.) excites nociceptive muscle afferents which activates γ -motoneurons through spinal interneurons. The activated γ -motoneurons result in contraction of intrafusal muscle fibres, activating α -motoneurons via afferent fibres from the muscle spindle primary endings (Ia afferents). Local muscle contractions may again induce pain by compression of blood vessels and ischemia as delineated above, or by metabolic products related to muscle contraction [99].

These models assume that chronic musculoskeletal pain is a result, partly or entirely, of muscle activity. However, based on a review of the literature on muscle function in several musculoskeletal pain disorders Lund et al (1991) concluded that chronic musculoskeletal pain not likely to be a result of muscular hyperactivity. Instead of pain resulting in increased muscular activation as in the “vicious circles” models they conclude that pain most likely will inhibit motor activity in the afflicted muscle. This model is referred to as the pain-adaptation model [100].

There is still considerable doubt about the extent to which muscle activity is a physiological trigger for chronic musculoskeletal pain in subjects without high biomechanical exposure in their work [101-103].

Objectives

The overall objective of the present thesis was to elucidate whether stress-associated musculoskeletal pain and muscle activity may be related to activation of the autonomic nervous system.

Laboratory studies of physiological responses to stress have mostly used models with short-lasting stress. Furthermore, although relevant theoretical models of the interaction between stress and disease/subjective complaints have focused on the recovery period after the stressful episode, studies on stress-related physiology have not paid attention to the recovery period. In the first paper (paper I) we wanted to describe the physiological response and recovery in healthy controls, including autonomic activation, to mental stress of long duration and discuss the findings with reference to relevant theoretical models.

One earlier study of fibromyalgia patients using the same model showed equivocal results regarding muscle activity as a potential causative factor for the pain development during a stressful task [8]. Regional pain syndromes like chronic shoulder/neck pain have often been perceived as a result of muscular hyperactivity or "overuse" [104]. In paper II we therefore included both patients with generalised pain (fibromyalgia) and patients with regional pain (shoulder/neck pain) in addition to healthy controls. The specific question in this paper was whether the muscular responses to a stressful task were different between the groups and whether the muscular responses were related to pain development.

In the third paper we asked whether the autonomic response to a stressful task was different for the investigated groups, and whether the autonomic response was related to the pain development.

Lastly, in order to specifically test whether the peripheral sympathetic nervous system may be directly involved in the stress-related pain we investigated whether a peripheral sympathetic block influenced the pain and muscle response to a stressful task (paper IV).

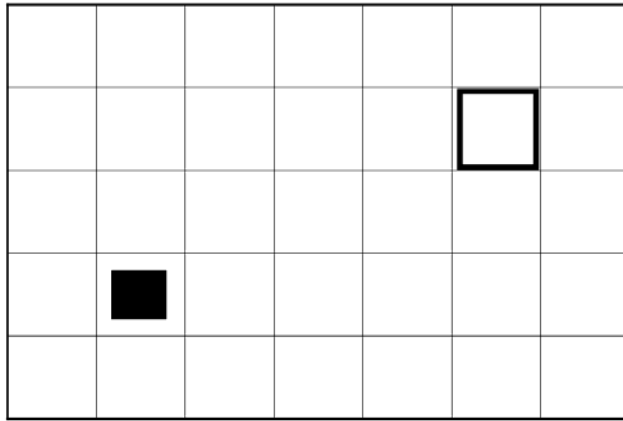
Methods and materials

In the present thesis subjects were investigated in the laboratory while performing a complex two-choice reaction time test designed to mimic mental load in a work place with a high degree of information processing and low general muscle load, i.e. mimicking mentally stressful and repetitive office work [105]. Subjects were investigated while performing this stressful task for one hour, as well as during a baseline period immediately before and during a 30 minute recovery period (10 minute recovery period in study IV). The same model has earlier been used in a series of studies of healthy controls, headache patients and patients with generalised musculoskeletal pain [8, 106-108]. However, while the stressful task induced both pain and muscular activity not related to movements, the former studies did not give any clear conclusions regarding the mechanism of the pain in neither of the patient groups. For the present work the previously used experimental setup was supplemented with measurements of blood pressure, heart rate, respiration frequency and finger skin blood flow as well as biochemical parameters as noradrenaline, adrenaline and cortisol, i.e. different parameters indicative of activity in the autonomic nervous system. In addition to the physiological measurements we obtained the subjects recordings of pain, tension and fatigue every 10th minute during the stressful task and the recovery period.

The experimental procedure

All potential controls and patients first went through a short telephone interview with a research nurse (Grethe Helde). All patients went through a detailed consultation and examination by a specialist in physical medicine and rehabilitation (Magne Rø). Patients and controls not excluded by this initial screening received written information about the general aims of the study, and a questionnaire on background data, within two weeks of the test day. After a short interview on the morning of the test day, venous blood was drawn from the right cubital fossa. Subjects emptied the bladder before starting the test. Brassieres were removed and subjects wore only a light shirt on the upper part of the body. The laboratory temperature was regulated to $24.5 \pm 1^\circ\text{C}$.

The subjects were seated in an office chair with the forearms resting on the table top before, during and after the test. Subjects became acquainted with the work-task by performing a mini-trial with instructions before the test started. The mini-trial was performed before introducing the stress-imposing feedback on reaction time and was used to determine the subjects' habitual, non-stressed reaction time. Short maximal voluntary contractions were performed on each pair of muscles twice (frontalis muscle – raising eyebrows, temporalis – clenching teeth, neck – pushing head back against resistance, trapezius – pushing extended arms upwards against resistance at 45° angle out from the body). The maximal contractions were carried out in order to normalize the muscle activity during test to a percent of maximal force. However, the variability between the two maximal muscle contractions in the frontalis muscle was too large to make a reliable estimate of the maximal muscle force and thus none of the muscle activity measurements were normalized. In order to measure the habitual level of physiological activation the laboratory experiment started with a five minute period which served as a basis for the evaluation of physiological responses during the test and the subsequent rest period. The subjects were alone in the room and were not given any instructions other than to find a comfortable position with their arms resting on the table in front of them (uninstructed rest). A five minute feedback period with muscular activity visualised on a screen followed. The subject experienced how it was possible to influence the level of muscle activity by adopting different postures and thereafter concentrated on minimising any muscle activity. The stressful task was then presented: a two-choice reaction-time test on a monitor, lasting one hour. An open ("frame") and a solid ("brick") quadrangle were placed in a square pattern, and a written suggestion on how to move the brick to superimpose on the frame was given (Figure 2). The subject responded by pressing one of two keys ("correct" or "wrong"), with the right middle or index finger. The test was to be carried out as quickly and correctly as possible. The PC program provided feedback on whether an answer was correct or wrong, and on the response time (very slow, slow, normal, fast, very fast), related to the subject's performance in the mini-trial carried out before the experiment started. Together with the feedback a new task was presented. After the end of the stressful task, all measurements continued for thirty minutes. The subject was instructed to sit still and relax during the recovery period.



2 up 4 right

Figure 2. The stressful task involved a grid (7 columns, 5 rows) in which an open (frame) and a solid quadrangle were placed. A suggestion on how to move the solid quadrangle into the frame was given and the subject answered “correct” or “wrong” by pressing one of two keys.

Pain, perceived tension and fatigue were reported every ten minutes before, during, and after the test by scoring on a 100 mm visual analogue scale (VAS) with the endpoints marked “no pain/tension/fatigue” and “worst imaginable pain/tension/fatigue”.

Perceived tension was considered to reflect subjective stress during and after the test. The subjects were asked to assess pain in locations corresponding to the SEMG electrode positions in the shoulders, neck, temples and forehead on both sides. The subjects were not allowed to see previous records when scoring.

Immediately after the stressful task, before the 30 minute rest period, a second blood sample was drawn. Subjects reported pain, tension and fatigue both before (60 min) and after the venipuncture (65 min). An overview of the experimental procedure is shown in Figure 3.

The laboratory personnel were blinded as to the diagnosis (healthy control, fibromyalgia or shoulder/neck pain) of the subjects, and the subjects were instructed not to disclose their diagnostic status. Furthermore, the laboratory personnel monitored the experiment visually from another room, only communicating with the subjects briefly every 10th minute with a strictly established monologue when subjective ratings were collected, in order to maintain blinding. All data processing before the statistical analysis was made without knowledge of diagnostic status of the subjects.

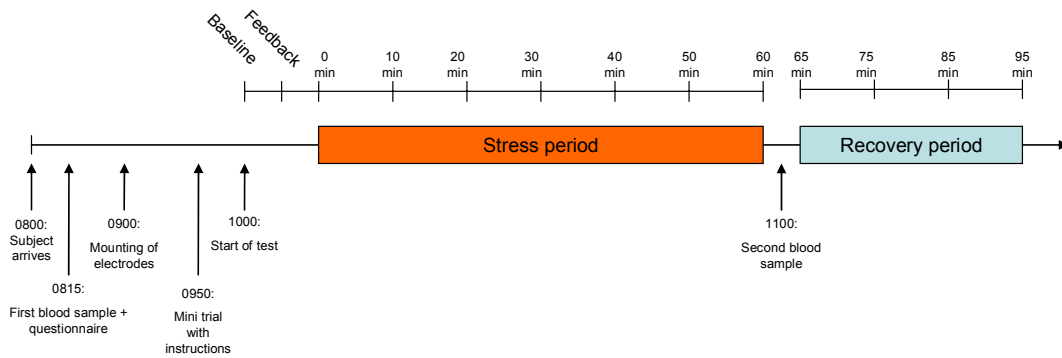


Figure 3. Overview of the experimental procedure

Physiological recordings

Muscle activity was quantified by bipolar recording of surface electromyography with custom made electrode assemblies with built in amplifiers to reduce the degradation of the signals by electrical interference (Ag-AgCl circular electrodes, electrode diameter 6 mm, inter-electrode distance 20 mm). The skin surface at the electrode site was cleaned with custom made pumice stone paste to reduce the electrode-skin impedance. The signals were bandpass-filtered (10-1250 Hz) and stored on a digitizing recorder (Earth Data 128). Data were subsequently reconverted to analogue signals and fed into an A/D converter (Powerlab 16S; ADInstruments Pty Ltd, Sydney, Australia; sampling rate 2kHz, 16 bits), for rectification and calculation of the RMS values (100 ms running time window). Sharp transients and electrical activity from the heart in the SEMG signals were removed with a medianfilter (Matlab ver 6, The MathWorks inc.). The system noise level was less than 1.5 μ V RMS (unpublished results). The recording depth of comparable surface electromyography electrodes is considered to be less than 20 mm [109].

Continuous non-invasive finger blood pressure were measured with Portapres equipment (Portapres, TNO Biomedical Instrumentation, Amsterdam, The Netherlands). This method is based on the Finapres technology which is a fast pneumatic servo system which transmit arterial blood pressure to cuff air pressure. A pressure waveform is created with a sampling rate of 100 Hz. The Finapres technology is a reliable alternative for invasive measurements of continuous blood pressure responses [110-113]

Finger skin blood flow were measured with the laser Doppler technique using surface electrodes with fibre separation 0.5 mm (Moorlab, 4 channels, time constant 0.02s, low-pass filter 22 kHz; Moor Instruments Ltd, Devon, England). The technique uses the Doppler shift of the reflected laser light to estimate the blood volume in the underlying tissue. The probes used in the present thesis gives information about blood flow in the underlying capillaries, arterioles and venules in the tissue down to 1mm from the surface [114-117].

Heart rate was calculated from the blood pressure recordings and respiration frequency were calculated based on recordings from a thermistor (Embla S-AF-010, Flaga, Reykjavik, Iceland) which were placed below the nose with active elements in each nostril and in front of the mouth.

Subjects

Two different patient groups were investigated. Patients included had chronic pain with at least one episode of pain lasting more than 3 months the last year. The pain should be either generalised to the whole body (fibromyalgia) or localised to the shoulder/neck region with local tenderness (chronic shoulder/neck pain).

Patients with generalised pain were diagnosed according to the 1990 ACR criteria [118]. The ACR criteria for classification of fibromyalgia were originally developed as a minimal standard for entry of subjects into research studies, but have later been used also as diagnostic criteria for clinicians. The combination of a typical history of chronic (> 3 months) widespread pain and tenderness to palpation at 18 anatomically defined points exhibited has been shown to differentiate fibromyalgia patients from patients with other pain conditions like rheumatoid arthritis and lupus erythematosus with moderately high sensitivity (88.4 %) and specificity (81.1 %). Widespread pain means bilateral pain from both above and below the waist.

Patients with chronic shoulder/neck pain were included if they had local tenderness. We did not search specifically for “trigger points” [119, 120] because the reproducibility of these have been questioned [121, 122]. Patients with chronic localised pain are labelled with different diagnostic entities highly dependent on the tradition of the particular investigating speciality, often assuming a particular mechanism for the pain. A few examples are: trapezius myalgia, myofascial pain syndrome, repetitive

strain injury, and temporomandibular joint pain. Our chronic shoulder/neck pain patients were included also if they reported pain from other body regions, however, pain in the shoulder and neck region had to be their main problem. No shoulder/neck pain patients fulfilled the ACR fibromyalgia criteria.

Subjects were excluded if they had: (1) neoplastic disease, (2) high blood pressure or were taking anti-hypertensive medication, (3) infectious disease, including those who had caught a cold with fever, cough or muscle pain, (4) metabolic, endocrine or neuromuscular disease, (5) connective tissue disorder, (6) tendinitis or capsular affection of the shoulder joint, (7) recent accident or injury affecting function, (8) symptomatic heart disease or were taking medication for any vascular disease, (9) lung disease affecting function or were taking medication for such, (10) cerebrovascular disease, (11) chronic neurological disease, (12) or if headaches were a major part of the pain syndrome, (13) or were taking any medication with a possible interaction on neural, vascular or muscular function (e.g. antiepileptics, β -blockers, antidepressants).

Statistics

In the first published paper (paper II) we used primarily non-parametric statistics (Kruskal-Wallis test, Mann-Whitney test and Wilcoxon's signed rank test) on summary variables because the subjective response variables pain, tension and fatigue were not normally distributed. Non-parametric statistics were chosen for all variables, also for those variables which were normally distributed. The summary variables were calculated as the mean of the baseline period, the mean of the stressful task period, and the mean of the recovery period for all physiological variables. Summary variables for the subjective variables (pain, tension and fatigue) were calculated as the increase from baseline to the maximal pain during the stressful task. Pain recovery was evaluated by simply counting the number of patients who recovered to baseline during the recovery period. Other methods of assessing the pain recovery were considered [123, 124], but the chosen method were considered to be least biased by either baseline level or the relative response during the stressful task.

After advice from reviewers and our departments' statistician we later used ANOVA models for repeated measurements as the primary statistical model for all variables, including the subjective variables. Thus, by including a value for every 10th minute instead of a single average value for stressful task and a single value for the

recovery period we achieved higher statistical power. While the subjective response summary variables were not Gauss-distributed, the absolute values used in the ANOVA models were all Gauss-distributed, and the assumption of normally distributed data for parametric statistics was thus justified.

Using summary variables instead of more advanced statistical models based on “raw” data results in fewer effects and p-values to consider and the physiological relevance may be easier to interpret [125, 126]. On the other side, repeated measures models may give larger statistical power with less potential for type II errors. Multivariate methods, with or without repeated measures design, is another possible approach for the type of data obtained in the present thesis. Relevant multivariate methods for the present thesis would have been very complex and highly dependent on assumptions on the structure of covariance [127] and were not performed. Furthermore, because of the explorative nature of paper I-III, corrections for multiple comparisons were not performed. Although not correcting for multiple comparisons increase the risk of type I errors [128], several statistical review articles have criticised the use of corrections for multiple comparisons in medical research because the risk of making type II errors markedly increases [129, 130].

Synopsis of results

Paper I : Autonomic and muscular responses and recovery to one-hour laboratory mental stress in healthy subjects.

Kristian B Nilsen, Trond Sand, Lars J Stovner, Rune B Leistad, Rolf H Westgaard

Background:

Stress is a risk factor for musculoskeletal pain. We wanted to use an experimental model to explore stress related physiology in healthy subjects in order to gain insight in mechanisms of pain development which may relate to the pathophysiology of musculoskeletal pain disorders.

Methods:

Continuous blood pressure, heart rate, finger skin blood flow, respiration, surface electromyography together with perception of pain, fatigue and tension were recorded on 35 healthy women and 9 healthy men before, during a 60 minute period with task-related low-grade mental stress, and in the following 30 minute recovery period.

Results:

Subjects responded physiologically to the stressful task with an increase in trapezius and frontalis muscle activity, increased blood pressure, respiration frequency and heart rate together with reduced finger skin blood flow. The blood pressure response and the finger skin blood flow response did not recover to baseline values during the 30-minute rest period, whereas respiration frequency, heart rate, and surface electromyography of the trapezius and frontalis muscles recovered to baseline within 10 minutes after the stressful task. Sixty-eight percent responded subjectively with pain development and 64 % reported at least 30% increase in pain

Conclusion:

The findings suggest that the blood pressure increase and the acral finger skin blood flow reduction to mental stress are more protracted than other physiological stress responses.

Paper II: Pain induced by low-grade stress in patients with fibromyalgia and chronic shoulder/neck pain, relation to surface electromyography

Kristian B Nilsen, Rolf H Westgaard, Lars J Stovner, Grethe Helde, Magne Rø, Trond Sand

Background:

The mechanisms of pain causation in fibromyalgia and chronic shoulder/neck pain are still debated. We wanted to compare muscle activity and pain development during and after low-grade mental stress in fibromyalgia and shoulder/neck pain patients.

Methods:

Twenty-three women with fibromyalgia, 29 women with chronic shoulder/neck pain, and 35 healthy women performed a stressful task lasting 60 minutes followed by a 30 minutes recovery period. We recorded surface electromyography over the trapezius, neck, temporalis and frontalis muscles. Subjects reported their pain at the corresponding locations together with the development of fatigue and perceived tension.

Results:

Significant differences between fibromyalgia and shoulder/neck pain groups were not observed for either muscular or subjective responses. Shoulder/neck pain patients and controls responded with more pain in the trapezius and neck regions than in the forehead, in contrast to fibromyalgia patients who had a more generalized pain response. Development of pain, tension and fatigue was not related to muscle activity for any group.

Conclusion:

The findings suggest that fibromyalgia and shoulder/neck pain patients have similar pain and electromyographic responses to a stressful mentally demanding task. Muscular activity did not explain the pain which developed during the stressful task for either group. Pain lasted longer during recovery in both fibromyalgia and shoulder/neck pain patients compared to healthy controls, possibly a result of disease-related sensitisation in pain pathways.

Paper III: Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients.

Kristian B Nilsen, Trond Sand, Rolf H Westgaard, Lars J Stovner, Linda White, Rune B Leistad, Grethe Helde, Magne Rø

Background:

Psychosocial stress is a risk factor for musculoskeletal pain, but how stress affects musculoskeletal pain is poorly understood. We wanted to examine the relationship between low-grade autonomic activation and stress-related pain in patients with fibromyalgia and localised chronic shoulder/neck pain.

Methods:

Twenty-three female patients with fibromyalgia, 29 female patients with chronic shoulder-neck pain, and 35 healthy women performed a stressful task lasting 60 minutes. With a blinded study design, we recorded continuous blood pressure, heart rate, finger skin blood flow and respiration frequency before (10 minutes), during (60 minutes) and after (30 minutes) the stressful task. The physiological responses were compared with subjective reports of pain.

Results:

The increase in diastolic blood pressure and heart rate in response to the stressful task were smaller in fibromyalgia patients compared with the healthy controls. Furthermore, fibromyalgia patients had reduced finger skin blood flow at the end of the stressful task compared to healthy controls. We also found an inverse relation between the heart rate response and development and recovery of the stress-related pain in fibromyalgia patients.

Conclusion:

We found abnormal cardiovascular responses to a 60 minute long stressful task in fibromyalgia patients. Furthermore, we found a negative association between the heart rate response and the pain which developed during the stressful task in the fibromyalgia group, possibly a result of reduced stress-induced analgesia for fibromyalgia patients.

Paper IV: A unilateral sympathetic blockade does not affect stress-related pain and muscle activity in patients with chronic musculoskeletal pain.

Kristian B Nilsen, Trond Sand, Petter Borchgrevink, Rune B Leistad, Magne Rø, Rolf H Westgaard

Background:

Chronic musculoskeletal pain is often exacerbated by mental and social stress. The association between stress and musculoskeletal pain is potentially mediated by peripheral sympathetic nerves, either directly or indirectly through muscle activity. In the present study we wanted to determine if sympathetic blockade could affect either the pain or the muscular activity seen during mental stress in patients with chronic musculoskeletal pain.

Methods:

We performed a unilateral anesthetic blockade of the lower cervical sympathetic ganglion (ganglion stellatum) in 18 patients with chronic musculoskeletal pain (10 with fibromyalgia and 8 with chronic shoulder/neck pain). After the blockade the patients performed a 60-minute stressful task with low-grade mental stress which has induced pain and muscle activity in earlier experiments. Surface electromyography of the head, neck and shoulders, heart rate and blood pressure were recorded together with ratings of pain.

Results:

Neither pain nor muscle responses were affected by the sympathetic blockade. Other explanatory models must be implemented and tested experimentally in order to further investigate the clinical impression that mental stress exacerbates pain in patients with chronic musculoskeletal pain.

Conclusion:

Peripheral sympathetic activity is probably not directly involved in modulation of pain and muscle responses to a stressful task in patients with musculoskeletal pain.

General discussion

The interpretation and validity of the different results of the study have been discussed in detail in the four papers. Here, some of the results will be discussed in a broader context. A complete overview of all relevant literature is however very difficult to achieve considering the vast amount of published papers on this subject. A search on PubMed in April 2007 revealed 2480 papers with the word fibromyalgia in the title. The default PubMed search including fibromyalgia in all fields revealed 4285 different papers.

Different approaches to the subject with chronic musculoskeletal pain

Research on musculoskeletal pain may be approached very differently depending on the vocational training of the researcher. Medical doctors generally focus on subjects who have attended a physician with musculoskeletal pain and their research subjects are divided into healthy subjects and patients. There is also a large amount of research on this topic performed by researchers with a main focus on occupational safety and health. Supposedly motivated by the high incidence of sick leave related to musculoskeletal pain in different occupations they approach the same subjects but not necessarily with the same division of the subjects into either healthy subjects or patients. The present thesis is an interdisciplinary approach to this group of subjects. The laboratory model is developed by a research group which has had their main focus on occupational health, and the investigated group of subjects was included as either patients or healthy controls. Patients were either diagnosed with chronic generalised pain (fibromyalgia) or with chronic regional pain localised to the shoulder/neck region. It was considered reasonable to compare these two groups partly because they present with different symptom distributions and partly because there has been a “common understanding” that the aetiologies are different. Pain syndromes with a regional distribution have been regarded as more likely to be a result of “overuse” whereas fibromyalgia with its generalised distribution has been considered to be a result of generalised neurosensory dysfunction [104]. An additional reason for including two

different clinical entities is the need to compare a finding in one diagnostic entity with another to see if the finding is specific to one diagnostic entity or if the findings may be a common phenomenon for pain afflicted subjects independent of diagnostic entity.

When comparing two groups with musculoskeletal pain of unknown origin one must bear in mind that there is usually an overlap in the definition of different unexplained clinical conditions [131, 132]. The patients investigated in the present thesis were classified on the basis of the dominating presentation of their pain. Although a generalised pain distribution with mechanical allodynia in all extremities is the defining feature for fibromyalgia patients, they still may have their most intense pain in a localised region. The pain in fibromyalgia patients is reported to be most prevalent in the shoulders, chest and lower back [133]. In the present thesis we found the shoulder and neck region to be the dominating pain region also for the fibromyalgia patients (paper II).

The model

The experimental setup is designed to mimic stressful and repetitive computer work, minimizing the physical activity [105]. The induced muscle activity has been most evident in the trapezius and frontalis muscles and has been labelled “attention-related” or psychogenic [134, 135]. However, while the stressful task induced both pain and muscular activity not related to movements, no consistent relation between the induced pain and the observed muscle activity has been observed [103] except for a weak correlation in the trapezius in a study of fibromyalgia patients [8]. Moreover, subjectively perceived general tension was found to be a powerful risk factor for musculoskeletal pain in field studies [10, 136]. Perceived tension may represent the perception of physiological activation, but not necessarily involving muscle fibre activation, an annotation which was later confirmed by qualitative studies of service workers [137]. On this background the experimental setup was supplemented with measurements of activity in the autonomic nervous system and utilized in the present thesis.

The model is a laboratory approach to the everyday situation of many office workers, and it’s resemblance to real life enhances its external validity. However, one must admit, even after the present and other studies with the same model, that we lack a clear understanding of the pain initiating process. As reported in paper II muscle activity

does not seem to be a cause for the pain development during the stressful task. The results of paper IV implicate that the peripheral part of the sympathetic nervous system is probably not implicated in the pain initiating process, at least not directly.

Importantly, the pain initiating process is not specific to any of the investigated diagnostic entities as 68 % of the healthy controls reported increased pain during the stressful task (paper I). In this context one must mark that the present model is a model of an occupation situation of stressful work with low physical activity and not a reductionistic neurophysiological pain model, i.e. pain is not a stimulus but one of the dependent variables in the model.

The model is complex and not perfect, but nevertheless attractive because of similarity to real life. More experiments must be undertaken in order to increase the understanding of the mechanism for the pain initiated by the stressful task.

Manipulations with the amount of stress has already partially been done [134], but may be extended with more sophisticated experimental design. Extending the experimental model with pharmacological manipulations with different physiological systems may also give valuable information. This may for example be performed with naloxone infusions interfering with the PAG-RVM antinociceptive system in the brainstem [48, 50, 138, 139] or with manipulations with the peripheral autonomic (i.e. beta blockers) or neuromuscular receptors (i.e. botulinum toxin). Microneurographic recordings of sensory nerves during the stressful task are an intriguing but expensive and time-consuming approach.

Musculoskeletal pain as a result of overexertion of muscle fibres

Repeated activation of muscle fibres leading to hypoxia and pain has been suggested as an important mechanism for musculoskeletal pain, i.e. occupational muscle pain [140]. Considering the observation that there is a relatively fixed order of recruitment of motor units at increasing levels of muscle force, often referred to as the Henneman principle [141], this is an attractive hypothesis. Furthermore, prolonged activation of low-threshold motor units as a possible causal factor for development of work-related muscle pain was supported by the finding that type I muscle fibres (slow-oxidative fibres) were selectively injured in a sample of female workers with trapezius myalgia [142]. These two observations is the basis for the so-called Cinderella

hypothesis[143], which has been a popular model for understanding occupational muscle pain, named after the girl who was forced to work continuously in the well known fairy tale. However, injured muscle fibres with damaged mitochondria resulting in the appearance of “ragged-red fibres” have also been found in workers without muscle pain [144] and is thus not consistently linked to the development of occupational trapezius myalgia. Although not related to spontaneous pain, “ragged-red fibres” may be related to the findings of tender points in the trapezius muscle [145].

Higher muscle activity as measured by surface electrodes has been reported for workers with shoulder/neck pain during manual work or work with high work load, but the association between shoulder/neck pain and muscle activity is not consistent for office workers or workers with low work load [11, 146-152]. The lack of correlation between muscle activity and pain development during a stressful task, also for the shoulder/neck pain patients, as reported in the present thesis (paper II), further add to the available evidence that sustained low-level motor activity is not essential for development of shoulder/neck pain in stressful work situations with a low physical workload.

Nevertheless, because measuring every single motor unit in a muscle is not possible with current available methodology it is difficult to completely reject the Cinderella hypothesis. Static muscle contractions in a small subset of muscle fibres, i.e. a focal dystonia in a small part of a muscle, leading to ischemic pain forms the theoretical framework behind the diagnostic term “myofascial pain syndrome” [119, 120, 153] which is a regionalised pain disorder with characteristics not very different from occupational muscle pain [140] but with terminology from another profession. The focal contractions are the presumed cause of tender areas or trigger points in muscles [154, 155], and have been suggested to result either from an endplate dysfunction [156-158] or from sympathetic-motor crosstalk [159-163]. Focal muscle contractions have also been suggested as a mechanism in occupational muscle pain as a result of a vicious feedback loop starting with activation of muscle nociceptors which sensitise muscle spindles through excitation of γ -motoneurons, which secondarily raise the activation level of the α -motoneurons projecting to the primary muscle [99].

The various hypothesis claiming the tender areas in patients with musculoskeletal pain to be a result of excessive muscle activity has been opposed by other studies [164, 165]. Regarding the fibromyalgia syndrome, both increased [166-170], reduced [171-179] and normal muscular activity have been found [165, 180-186]. A few studies have now investigated the muscular response to a stressful task in

fibromyalgia patients, and although one study reported an increased electromyographic activity in the neck muscles (but not other muscles) during a stressful task [8], two studies, including paper II, have reported similar muscular activity during a stressful task for fibromyalgia patients and healthy controls [187 and paper II]

In the studies of the present thesis the tender points of the patients were not investigated in particular, neither in the muscles of the shoulder/neck pain patients, nor in the areas defined by the ACR fibromyalgia criteria [118]. Instead, the thesis focused on the muscle activity as measured by surface electrodes and in particular the muscle activity induced by a stressful task.

Overexertion of muscle fibres is at the time being not the most plausible explanation for musculoskeletal pain in persons with low manual work load. New technology, i.e. functional magnetic resonance imaging, may in the future make it possible to fully test the Cinderella hypothesis which is difficult with the current available methodology. From paper II one may conclude that the pain response to a stressful task is unrelated to muscle activity as measured by surface electrodes. Paper IV also raises objections to the view that muscle hyperactivity is a more likely explanation for regionalised shoulder/neck pain than to generalised musculoskeletal pain. Based on the results from paper II and the conclusions in several review articles, one must consider other physiological mechanisms than muscle activity as more plausible explanations for both fibromyalgia [101] and shoulder/neck pain [188]. This was also investigated further in paper I, III and IV in the present thesis.

Musculoskeletal pain and the autonomic nervous system

The autonomic nervous system has been suspected as a causal or contributing factor to both localised shoulder/neck pain and fibromyalgia. The sympathetic part of the autonomic nervous system regulates the blood flow throughout the body. Reduced muscular blood flow, or an inability to increase the muscular blood flow on demand, has been suggested as a mechanism for chronic pain in the trapezius region [189-196]. Reduced muscular blood flow in response to exercise has also been suggested as contributing factor to fibromyalgia pain [197]. However, in the present thesis intramuscular blood flow was not investigated.

Other aspects of the autonomic nervous system have been investigated thoroughly for fibromyalgia patients, but less for shoulder/neck pain patients. The

possible autonomic dysfunction in fibromyalgia has been reviewed and a possible blunted stress response has been suggested [198, 199]. The particular studies on blunted cardiovascular stress responses relevant for the findings in the present thesis are discussed in paper III. The present thesis supports the conclusions of the abovementioned review articles as we report a blunted cardiovascular response to the stressful task, but also adds important information on the relation to pain development, as we report an inverse relation between the pain and the heart rate response to the stressful task for the fibromyalgia group. A smaller heart rate response to the stressful task was associated with a higher and longer lasting pain response (paper III). This inverse relation has been hypothesised earlier [200-202]. An inverse autonomic-pain relationship has also been reported between baseline pain obtained by the McGill Pain Questionnaire and the blood pressure decrease in response to ingested buspiron (anxiolytika with effects on dopamine and histamine receptors) in fibromyalgia patients. A reduced ability to respond adequately with an autonomic response to stress may explain a general hypersensitivity to painful stimuli through the mechanism known as stress-induced analgesia [47, 48]. If reduced stress-induced analgesia is an important factor for these patients, this would imply a central cause of the reduced stress response, e.g. a reduced central level of corticotrophin-releasing hormone as suggested by Clauw and Chrousus [201], or reduced central levels of dopamine as suggested by Wood et al. [203]. There are several reports indicative of a reduced central autonomic response to various stimuli in fibromyalgia patients supporting this view [200, 204-209].

Principally, an inverse relation between an autonomic response and pain development is however not necessarily a result of a reduced central stress response. Baroreceptor activation (as during an increase of blood pressure) is known to increase pain threshold [210] also due to activation of lower brainstem reflexes involving the nucleus tractus solitarius and the A5 cell group, but without engaging the more rostrally periaqueductal gray and rostral ventromedial medulla associated with stress-induced analgesia [211].

A peripheral interaction between efferent sympathetic and afferent somatosensory fibres, often referred to as sympathetically maintained pain, has been suggested as a mechanism for the pain experienced in the fibromyalgia syndrome [212]. Although the concept of sympathetically maintained pain is controversial [213, 214] a few important studies make it difficult to reject the concept in general [70, 74]. Sympathetic maintained pain is normally included in the concept “neuropathic pain”. Applying the term neuropathic pain on a syndrome like fibromyalgia (without any

anatomically localised pathology) is highly controversial [215-217] The peripheral sympathetic nervous system has also been suggested as a contributing factor for regionalised muscle pain, though mainly indirectly through interactions with muscle spindles [33, 36-38] or “trigger-points” [162]. The fact that sympathetic blockade did not inhibit pain in our paper IV refutes hypothesis claiming that interaction between peripheral sympathetic fibres and somatosensory afferents or somatomotor fibres is important for the pain seen in fibromyalgia and shoulder/neck pain, at least the pain induced by a stressful task.

Further research on the potential contribution of the autonomic nervous system to chronic musculoskeletal pain is necessary. Based on the findings of an inverse relation between the heart rate response and the pain response to the stressful task for the fibromyalgia patients in paper III, further research should in particular investigate whether the antinociceptive effects of the central autonomic network is deranged in patients with chronic musculoskeletal complaints. This may be done by manipulating the central autonomic network with corticotropin-releasing-hormone agonists or antagonists [218, 219] or by manipulating the baroreflex by unloading baroreceptors in the neck by neck suction techniques [220] while testing for changes in pain thresholds and temporal summation. Furthermore, the autonomic nervous system may contribute to musculoskeletal pain more indirectly than tested in paper IV. For example, one must clarify whether the autonomic nervous system is capable of sensitising nociceptive neurons (and not only test the potential direct pain mediating effect of peripheral sympathetic nerves as in paper IV). Repeated daily iontophoresis of noradrenaline did not sensitise heat sensitive nociceptors in healthy subjects in one study [221], while another study found a decrease in heat pain threshold but no changes for mechanical pain threshold after injection of noradrenaline [222]. The pain sensitising effect of peripherally administered noradrenaline and adrenaline should be tested explicitly for patients with musculoskeletal pain, preferable also in muscle tissue. While the concept of activity-dependent neural plasticity of sensory fibres is widely accepted [87], the idea that sensory fibres may be sensitised by “extra-sensory” stimuli (e.g. stress related hormones or interleukins) is far less investigated. Recent publications do however indicate that “extra-sensory” stimuli may be important for sensitisation of pain transmission, for example reports of activation of microglia in the dorsal horn as a mechanism in chronic pain [86] and enhancement of mechanical allodynia mediated by stress-induced circulating adrenaline [57].

Musculoskeletal pain as a result of sustained arousal

The concept of chronic musculoskeletal pain as a result of sustained activation of one or more physiological systems as delineated in the theoretical models of how stress leads to disease or subjective complaints [82, 83] is attractive. Reported “need for recovery after work” has been found to increase the risk for cardiovascular disease in a large epidemiological study with 7944 workers investigated during 32 months [223]. “Need for recovery after work” also increases the risk for future sickness leave among truck drivers [224]. The variable “need for recovery after work” was in these studies calculated as an average score of 11 questions from a larger questionnaire. However, whether slow physiological recovery after psychological stress really predicts somatic disease has hardly been investigated [225]. In the present thesis we investigated the physiological response and recovery to a stressful task in detail. We found that the blood pressure was surprisingly high even after 30 minutes of recovery, but we were not able to test the predictive value of slow physiological recovery on future health. We also found the delayed blood pressure recovery to be related to the fatigue response to the stressful task (paper I).

The physiological basis for the models of how sustained arousal results in disease is largely unexplored. Future studies must first explore the normal physiology during the recovery period and extend the duration of the recovery period substantially. In addition, one should manipulate with both the quality and the length of the stress applied. Subsequently, one must investigate the predictive value of slow physiological recovery on future health. Because emotional factors is so important for the physiological response to stress and also for the cognitive modulation of pain [226], more knowledge on the neurobiological basis for interaction of emotions on pain may be essential in order to understand how sustained arousal may affect chronic musculoskeletal pain.

Musculoskeletal pain and neural plasticity

The fibromyalgia syndrome has usually been understood as a generalised pain hypersensitivity syndrome, including both hyperalgesia, allodynia and increased temporal summation of pain [227-230]. The hypersensitivity may be a result of primary pathology in central pain modulatory systems. The endogenous pain inhibitory

mechanism known as diffuse noxious inhibitory control (DNIC) has been reported to be deficient in fibromyalgia patients [231-234]. However, other reports have partly opposed these results as relevant for fibromyalgia patients in general [235, 236]. The hyperalgesia, allodynia and increased temporal summation of pain observed in fibromyalgia patients may also be a result of central sensitisation after continuous stimulation from peripheral nociceptive processes. The view of fibromyalgia as a result of primarily peripheral pathology and not a result of pathology in central pain modulatory mechanisms has been advocated in several recent review articles and seems to represent a paradigmatic shift on the view of fibromyalgia among some of the leading “authorities” in the field [133, 237-240]. A primary dysfunction of peripheral afferents has also been proposed as a causal factor in fibromyalgia: based on a series of animal experiments which has demonstrated that cutting vagal afferents results in generalised mechanical allodynia [241, 242], it has been suggested that fibromyalgia is caused by decreased vagal afferent activity [243].

Pain hypersensitivity as a result of central sensitisation is probably also found regionally in patients with chronic shoulder/neck pain as it may be found in any chronic pain state, but is far less investigated. However, one study of healthy subjects reported not only lower pain pressure threshold in the trapezius region compared to the anterior tibial region, but also that temporal summation of muscle pain is more pronounced than temporal summation of cutaneous pain for the trapezius region [244]. This relative difference between painful stimulation of muscle and skin was not found in the anterior tibial region, indicating that the lower pain pressure threshold in the trapezius region is mainly a result of increased muscle sensitivity in this region [244]. This finding from the trapezius region accords with those of other studies where nociceptive input from muscles has been reported to sensitise the central nervous system to a higher extent than nociceptive input from cutaneous tissue [245, 246]. Although a regional dysfunction may be the most plausible explanation for a regional pain disorder, increased pressure pain sensitivity has also been found in a pain-free site for patients with chronic trapezius myalgia. However, the endogenous pain inhibitory system reported to be defective in fibromyalgia is reported normal for these patients [247].

More specifically related to the present thesis is the finding of pain sensations outlasting the stimulation period in fibromyalgia patients. The relative increase in pain score after repetitive painful stimulation of skin with heat and cold [138, 248], as well as with deep mechanical stimulation of muscle tissue [249], is higher in fibromyalgia patients compared to healthy controls. This is interpreted as increased temporal

summation of pain in the dorsal horn, supporting the view of fibromyalgia as a generalised pain hypersensitivity syndrome. These studies also showed that the pain sensations lasted longer for fibromyalgia patients. The pain outlasting the stimulation period was called painful after-sensations. Later, the same group reported that after cessation of the repetitive stimulation which first induced temporal summation of pain, the painful after-sensations could be maintained by continuing with low-frequency repetitive stimulation at a frequency which is not capable of inducing temporal summation on its own [250]. The amount of these painful after-sensations was related to the baseline pain reported by the same fibromyalgia patients [251].

In the present thesis both patients groups were found to recover from the pain more slowly than the healthy controls (paper II). Although the experimental model in the present thesis is completely different from the different experimental setup of Staud et. al. our observation of reduced pain recovery in the patient groups may be interpreted as painful after-sensations. The finding may indicate that central sensitisation is a phenomenon found in both patient groups alike. Based on the findings in the present thesis one may draw the conclusion that central sensitisation of pain is probably essential for chronic musculoskeletal pain disorders of unknown aetiology, whether the pain is localised or widespread.

When studying central modulation of pain and neural plasticity in future studies of musculoskeletal pain one must keep in mind that the division between regional and generalised pain syndromes may not reflect fundamental differences in pathogenetic mechanisms. Because of the problems with diagnostic accuracy with these patient groups, combining functional genetic methodology (studying the expression of genes) with laboratory studies of pain physiology may be a more fruitful approach for future studies. In order to understand the pain related mechanism one must not restrict the pain measurements to self reported pain or pain threshold measurements, but include measurements of parameters reflecting descending modulatory mechanisms and pain amplification.

Conclusions

The overall objective of the present thesis was to elucidate whether stress-associated musculoskeletal pain and muscle activity may be related to activation of the autonomic nervous system.

First, we found that the vascular response to a stressful task as measured by blood pressure and finger skin blood flow is more protracted than other physiological responses. This is new knowledge and is of great value when designing new studies to experimentally test the available theoretical hypotheses on how stress relates to musculoskeletal complaints.

Second, we found no differences in the muscular response to a stressful task when comparing patients with generalised musculoskeletal pain (fibromyalgia), patients with regionalised musculoskeletal pain (shoulder/neck pain), and healthy controls. The muscle response was not related to pain development for neither group.

Furthermore, both patient groups had a delayed pain recovery which indicate that sensitisation in pain pathways was not specific for either group.

Third, we found an attenuated cardiovascular response to the stressful task when comparing the fibromyalgia group to healthy controls, with the shoulder/neck pain patients with an intermediate response between healthy controls and fibromyalgia patients.

Furthermore, there was a negative association between the heart rate response and pain development for the fibromyalgia group.

Fourth, we found that a peripheral sympathetic block did not affect neither pain nor muscle responses to a stressful task in patients with musculoskeletal pain.

From the studies presented in the present thesis one may conclude that stress-associated musculoskeletal pain is probably not directly related to muscular activation or to autonomic activation at a peripheral level. In patients with generalised pain as in fibromyalgia, the pain may be related to a reduced physiological ability to respond adequately to stress.

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Contributions (Paper I-III)

Paper I :

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Autonomic and muscular responses and recovery to one-hour laboratory mental stress in healthy subjects

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Abstract

Background:

Stress is a risk factor for musculoskeletal pain. We wanted to explore stress related physiology in healthy subjects in order to gain insight in mechanisms of pain development which may relate to the pathophysiology of musculoskeletal pain disorders.

Methods:

Continuous blood pressure, heart rate, finger skin blood flow, respiration, surface electromyography together with perception of pain, fatigue and tension were recorded on 35 healthy women and 9 healthy men before, during a 60 minute period with task-related low-grade mental stress, and in the following 30 minute rest period.

Results:

Subjects responded physiologically to the stressful task with an increase in trapezius and frontalis muscle activity, increased blood pressure, respiration frequency and heart rate together with reduced finger skin blood flow. The blood pressure response and the finger skin blood flow response did not recover to baseline values during the 30-minute rest period, whereas respiration frequency, heart rate, and surface electromyography of the trapezius and frontalis muscles recovered to baseline within 10 minutes after the stressful task. Sixty-eight percent responded subjectively with pain development and 64 % reported at least 30% increase in pain. Reduced recovery of the blood pressure was weakly correlated to fatigue development during stress, but was not correlated to pain or tension.

Conclusion:

Based on a lack of recovery of the blood pressure and the acral finger skin blood flow response to mental stress we conclude that these responses are more protracted than other physiological stress responses.

Background

A substantial epidemiological literature has shown that mental and social stress is a risk factor for development of musculoskeletal pain, especially for pain in the shoulder and neck [1-4]. Different theoretical models for possible causal links between stress and health complaints have been described. Eriksen and Ursin [5] describe a process of psychological sensitisation and arousal leading to intolerable subjective complaints. McEwen and co-workers [6, 7] describe a similar model with more emphasis on physiological responses, introducing the concept of allostatic load (i.e., the physiological result of chronic exposure to stress). The lack of physiological recovery after stress is considered by both groups a key factor linking stress and disease. Furthermore, laboratory studies indicate that autonomic activation and dysfunction is implicated in chronic pain [8]. In the search for possible biological correlates for the link between stress and disease, earlier laboratory studies have used short lasting stressors with analytical focus on the physiological reactivity (response to the stress), while the important physiological recovery period has received little attention [9]. Little is known about the physiology of the recovery period after stressful and repetitive work-related tasks.

In order to explore further the physiological basis for the link between stress and muscle pain, which again may relate to chronic pain development, we performed this study on healthy subjects performing a long-lasting stressful task (1 hour) with a 30 minute recovery period. We used a stressful task of sufficient duration to mimic real-world (e.g. work-related) stress, adding external validity to the methodology [10]. The stressful task has previously been used to explore the development of subjective complaints and muscular activity to stress in pain-free controls [11] and in patient groups with musculoskeletal pain or headache [12-15]. However, activity in the

autonomic nervous system was not assessed in the previous studies. In the present study we measured muscle activity (surface electromyography) together with blood pressure, heart rate, acral finger skin blood flow and respiration frequency 10 minutes before, during the 60 minute stressful task and 30 minutes after. Development of pain, fatigue and tension was recorded immediately before and every 10 minutes during the stressful task and in the 30 minute rest period.

Firstly, we wanted to describe the autonomic and muscular response and recovery profiles after low-grade mental stress of long duration in healthy subjects. Secondly, we hypothesized that development of subjective complaints during a long lasting low-grade stressful task were related to the physiological response to the task. Lastly, we hypothesized that those variables with the slowest recovery profile would be related to the subjective complaints induced by the stressful task.

Methods

Subjects

Forty-four healthy subjects participated in the study (Table 1). The participants were recruited as controls for a group of pain patients with a female predominance, and therefore comprised thirty-five women and nine men. They were recruited from public institutions and private companies in Trondheim. Subjects were excluded if they fulfilled all of the three following criteria: (1) headache or musculoskeletal pain for more than one day per month, and (2) had visited a physician, and (3) took medication for the complaint (all three conditions to be fulfilled). In addition, subjects considering their headache or pain to be more than “unpleasant” (i.e. a higher degree of pain) were excluded if (1) they experienced the pain more than one day per month, or (2) had visited a physician for the pain, or (3) took medication for the pain (i.e. any

of the three conditions fulfilled). No participants took drugs with a possible interaction with neural, vascular or muscular function (e.g. antiepileptics, β -blockers, and antidepressants)

Procedure

All subjects answered a questionnaire on biographical data (marital status, weight, medication, and stimulants), exercise habits, and the neuroticism index of the Eysenck Personality Questionnaire (EPQ-N)[16]. The questionnaire further included an index of symptoms concerning the autonomic nervous system (“autonomic symptom index”). For this purpose a subset of ten questions were chosen (No. 26-35) from the Composite Autonomic Symptom Profile [17]. The questions assessed different domains of autonomic symptoms (orthostatic, sudomotor, gastrointestinal, visual, vasomotor, reflex syncope). Sub-indexing different autonomic domains was not done due to the limited number of questions. The answers were graded. A serious extent of a symptom was given a higher value than a less serious. E.g. the answer to the questions: "In the last year, to what extent have you been in a cold sweat?", were graded as : "have not had" (value 0), mild (value 1), moderate (value 2), severe (value 3). The highest possible sum score was 30.

All potential participants went through a short telephone interview to exclude those not fulfilling inclusion criteria. Subjects not excluded by the initial screening received the questionnaire by post within two weeks of the test day. On the morning of the test day the subjects first went through a short interview controlling the answers from the questionnaire. Afterwards venous blood was sampled from the right cubital fossa. Subjects were instructed to empty their bladder before starting the test. Brassieres were removed and subjects wore only a light shirt on the upper part of the

body. The laboratory temperature was regulated to 24.5 ± 1.0 °C and was recorded every ten minutes during the experiment.

The subject was seated in an office chair with the lower arms resting on the table top before, during and after the test. Subjects got acquainted to the work-task by performing a mini-trial with instructions before the test started. The mini-trial was performed without introducing stress-imposing feedback on reaction time and was used to determine the subjects' habitual, non-stressed reaction time. Short maximal voluntary contractions were performed on each pair of muscles twice (frontalis muscle – raising eyebrows, temporalis – clenching teeth, neck – pushing head back against resistance, trapezius – pushing extended arms upwards against resistance at 45° angle out from the body). The maximal contractions were carried out in order to normalize the muscle activity during test to a percent of maximal force. However, the variability between the two maximal muscle contractions in the frontalis muscle was too large to make a reliable estimate of the maximal muscle force and thus none of the muscle activity measurements were normalized. In order to measure the subjects habitual level of physiological activation, the laboratory experiment started with a five minute period which served as a baseline period for the physiological variables. The subjects were alone in the room and were not given any instructions other than to find a comfortable position with their arms resting on the table in front of them. To ensure that all subjects had the same low level of muscle activity before the test started a five minute feedback period with muscle activity visualized on a screen followed. The subject experienced how it was possible to influence the level of muscle activity by adopting different postures and thereafter concentrated on minimising any muscle activity. The stressful task [18] was then performed: a two-choice reaction-time test on a monitor, lasting one hour. An open ("frame") and a solid ("brick") quadrangle

were placed in a square pattern, and a written suggestion on how to move the brick to superimpose on the frame was given. The subject responded by pressing one of two keys ("correct" or "wrong") with the right middle or index finger. The task was to be carried out as quickly and correctly as possible. The PC program provided feedback on whether an answer was correct or wrong, and on the response time (very slow, slow, normal, fast, very fast) related to the subjects performance in the mini-trial carried out before the experiment started. Together with the feedback a new task was presented. After the end of the stressful task, all measurements continued for thirty minutes. The test person was instructed to sit still and relax during the rest period. Pain, perceived tension and fatigue was reported immediately before (baseline) and every ten minutes during and after the test by scoring on a 100 mm visual analogue scale (VAS) with the endpoints marked no pain/tension/fatigue and worst imaginable pain/tension/fatigue. The subjects were asked to assess pain in locations corresponding to the electromyography electrode positions; in the shoulders, neck, temples and forehead on both sides. The subjects were not allowed to see previous records when scoring.

A second blood sample was drawn during 5 min immediately after the test, before the 30 minute recovery period. Blood analysis was not a major aim of the study and these results are reported elsewhere (Nilsen et al., submitted).

Physiological recordings

Muscle activity was quantified by bilateral bipolar recording of surface electromyography (SEMG) (electrode diameter 6 mm, inter-electrode distance 20 mm). The system noise level was less than 1.5 μ V root mean square (RMS). The signals were bandpass-filtered (10-1250 Hz) and stored on a digitizing recorder (Earth Data 128). Data were subsequently fed into an A/D converter (Powerlab 16S;

ADInstruments Pty Ltd, Sydney, Australia; sampling rate 2kHz) for calculation of the RMS values (100 ms running time window). Sharp transients and electrical activity from the heart in the SEMG signals were removed with a median filter (Matlab ver 6, The MathWorks inc.).

The following electrode sites were used: (1) Frontalis muscle; both electrodes placed on a vertical line crossing the pupil, 10 mm and 30 mm above the upper border of the eyebrow. (2) Temporal muscle; the lower electrode 10 mm posterior to the lateral canthus of the orbit, and the second electrode 20 mm above. (3) Splenius muscle; upper electrode 35 mm lateral to the spinous process of C2, and the second electrode 20 mm below. (4) Trapezius muscle; medial electrode 10 mm lateral to the midpoint of a line connecting the acromion and the spinous process of C7, and the second electrode 20 mm lateral to the first electrode. The ground electrode was placed on the spinous process of C7.

Activity in the autonomic nervous system was assessed by measurements of continuous non-invasive finger blood pressure (Portapres)[19], measurements of skin blood flow with Laser-Doppler flowmetry (Moorlab, 4 channels, time constant 0.02s, low-pass filter 22 kHz), and measurements of the respiration pattern with a thermistor (Flaga, Embla S-AF-010) below the nose with active elements in each nostril and in front of the mouth. The blood pressure cuffs were mounted on the intermediate phalanx at the left middle and ring fingers. Finger skin blood flow was measured bilaterally with the electrodes (fibre separation 0.5mm) placed on the volar side of the distal phalanx (pulp) of the thumb. Signals were sampled at 200 Hz.

Respiration frequency was calculated by the Chart 4.2 software (ADInstruments Pty Ltd, Sydney, Australia). Heart rate and blood pressure were

calculated with the Beatscope 1.0 software (TNO, Amsterdam, the Netherlands). One blood pressure recording could not be analyzed due to technical difficulties.

Technical difficulties resulted in exclusion of seven subjects from analysis of respiration frequency and exclusion of two subjects from analysis of heart rate and blood pressure responses.

Analysis and statistics

Mean values for each 10-minute period were calculated for all physiological recordings. Muscular activity and finger blood flow values are reported as the average of the left and right side for each region because ANOVA repeated measures analysis (rANOVA) revealed no side differences for the finger skin blood flow and muscle activity except for the frontalis muscle SEMG (left side ($10.9 \mu\text{V}$) > right side ($9.2 \mu\text{V}$); $F(43) = 8.0$, $p = 0.007$). However, performing all subsequent tests separately for right and left frontalis muscles did not give deviant results from those reported. Pain scores are reported from the side with the highest response (there were no side differences in neither pain level (side effect) nor pain development (side x time effect) for any of the four regions (rANOVA, $F_s \leq 3.2$, $p \geq 0.08$).

ANOVA with repeated measurements was used for evaluation of subgroup effects (sex, marital status, employment status, regular exercise, smokers, and alcohol drinking introduced sequentially one at a time as between-subject factors) with ten time intervals. For subgroup analysis of the recovery period we calculated a recovery variable (the difference between the mean of the last 10 minutes of rest (85-95 min) and the baseline period mean), a measure considered to be more meaningful than the absolute level when comparing groups [9]. Feedback data is displayed in figures, but feedback was not included in ANOVAs because we intended to study responses

related to stress in this study. Recovery variables were analysed with one-way ANOVA tests.

For evaluation of the total response to the test we first performed repeated measures ANOVA tests (no between-subjects factors, evaluating the within-subject effect of time) with the same time intervals as in the subgroup analysis. For further post-hoc exploration of the response and recovery time-course we performed a series of paired-sample tests (Student's t-tests for physiological variables (Gauss-distributed) and Wilcoxon signed rank test for subjective variables (not Gauss-distributed)): We first evaluated the early response to the stressful task by comparing the first part (0-10 min) of the stressful task to baseline (immediately before the stressful task for the subjective variables). Secondly, changes during the stressful task (adaptation/summation effects) were investigated by a comparison of the first (0-10 min) and the last (50-60 min) part of the stressful task. Thirdly, we evaluated the recovery by comparing the change from the end of the stressful task (50-60 min) with the first part of the recovery period (65-75 min) and the first (65-75 min) and last (85-95 min) part of the recovery period with baseline.

Physiological responses (the difference between the average of the whole stressful task (0-60 min) and the average of the baseline period) and subjective responses to the stressful task (the difference between the maximal value during the 60 minute stress period and the value reported immediately before starting the test) were calculated as summary-variables for correlation analysis. Subjects with a pain response larger than zero were defined as pain responders. For each subject the location with the highest pain response during the task was identified (i.e. only one location for each subject). The pain response in this location (maximal pain location)

was treated as a separate summary variable in the analysis (and it is the pain scores in this specific location we have displayed graphically).

Possible associations between variables were investigated by correlating the muscular responses (trapezius, splenius, temporalis, frontalis) with the autonomic responses (systolic and diastolic blood pressure, heart rate, respiration frequency and finger skin blood flow), and by correlating physiological responses (as above) with subjective responses (maximal pain, tension and fatigue), and finally by correlating the subjective responses with each other (i.e. maximal pain, tension and fatigue). The correlation coefficients between pain and muscular responses were calculated separately for each localisation (i.e. left temple pain with left temporalis muscle activity). Furthermore, as post-hoc analysis we searched for possible correlations between blood pressure/finger skin blood flow recovery variables and physiological responses, subjective responses and other recovery variables. We used Pearson correlation (r_p) for physiological variables (Gauss-distributed) and Spearman's rank order correlation (r_s) when subjective data were involved (not Gauss-distributed).

Because Mauchly's test of sphericity was significant in all ANOVA repeated measures tests with time as a within-subject effect we used Huynh-Feldt correction of degrees of freedom for these results. Two-tailed p-values less than 0.05 were considered to be significant. Because the hypotheses testing in this study involved several autonomic subsystems with insufficient a priori knowledge on possible relation to pain, we did not correct for multiple comparisons.

Ethics

For transport expenses and the inconvenience (total time expenditure for each participant was 4 hours) participants received NOK 500 (USD 75). The Regional Committee for Medical Ethics approved the protocol, and all participants gave written

informed consent before volunteering. Experiments were performed according to the Helsinki Declaration.

Results

All variables are listed in Table 2 with the results of the paired comparisons summarised in Table 3.

Physiological responses

The development of all physiological variables is illustrated in Figure 1, 2 and 3.

The stressful task induced a clear response evident in all physiological variables (Table 2 and 3; baseline vs. 0-10 min, $p \leq 0.006$) except for the splenius ($p = 0.28$) and temporalis muscle SEMG ($p = 0.96$).

Furthermore, age correlated negatively with the average respiration frequency response ($r_p = -0.44$, $p = 0.006$) and height correlated negatively with the average systolic blood pressure response ($r_p = -0.41$, $p = 0.008$). None of the other physiological responses (Table 2) correlated with age, height or weight.

Comparing the last ten minutes of the stressful task to the first ten minutes of the stressful task (Table 2 and 3) revealed a fall in heart rate with 2.5 beats/min ($p = 0.001$) and a reduced respiration frequency with 0.89 breaths/min ($p = 0.04$), indicating adaptation to the task for these two variables only. However, in the same time interval temporalis muscle activity increased with 0.82 μV ($p = 0.03$) and finger skin blood flow showed a trend towards lower values ($p = 0.09$). The other physiological variables were stable throughout the stressful task ($p \geq 0.33$).

The heart rate response correlated with the trapezius muscle response ($r_p = 0.44$, $p = 0.004$) and the temporalis muscle response (temporalis vs. heart rate, $r_p =$

0.41, $p = 0.008$). The other correlations in the SEMG vs autonomic responses matrix were non-significant ($p > 0.06$).

Physiological recovery

Upon cessation of the stressful task, heart rate ($p < 0.001$), respiration frequency ($p < 0.001$) and muscle activity in the trapezius ($p < 0.003$) and the frontalis ($p < 0.002$) decreased significantly (50-60 min vs. 65-75 min). Trapezius and frontalis SEMG recovered to the baseline level (baseline vs. 65-75 min, $p \geq 0.10$) while heart rate and respiration frequency recovered to a level lower than baseline (baseline vs. 65-75 min, $p \leq 0.03$). However, systolic and diastolic blood pressure, finger skin blood flow and muscle activity in the splenius and temporalis muscles did not change significantly upon cessation of the stressful task (50-60 min vs. 65-75 min and 50-60 min vs. 85-95 min, $p > 0.10$). The systolic and diastolic blood pressure level remained elevated and finger skin blood flow was reduced during the whole recovery period (baseline vs. 85-95 min $p \leq 0.001$).

The finger skin blood flow recovery variable (Table 2) correlated negatively the systolic and diastolic blood pressure recovery variables ($r_p = -0.52$, $p = 0.001$ and $r_p = -0.40$, $p = 0.01$ respectively). This means that a high blood pressure at the end of the recovery period was associated with a small finger skin blood flow at the same time. The finger skin blood flow and blood pressure recovery variables did not correlate with other physiological (HR, muscle, respiration) response or recovery variables ($r \leq 0.25$, $p \geq 0.11$).

Subjective responses and recovery

Development of tension, fatigue and pain scores in the maximal pain location is illustrated in Figure 4. Subjects reported increased tension ($p = 0.02$) and increased pain in the temples ($p = 0.03$) and forehead ($p = 0.01$) already ten minutes into the

stressful task (0 min vs. 10 min), while fatigue ($p = 0.52$) and pain in the shoulder and neck ($p > 0.52$) did not increase during the first ten minutes (Table 2 and 3). All subjective variables increased further during the stressful task (10 min vs. 60 min; $p < 0.008$ except for a trend in temple pain ($p = 0.06$)), and were significantly reduced ten minutes into the recovery period (60 min vs. 75 min, $p < 0.008$). However, fatigue and pain in neck (and maximal pain) did not recover to baseline (0 min vs. 95 min; $p < 0.04$). Pain in the shoulders showed a trend towards non-recovery ten minutes into the recovery period ($p = 0.08$) but recovered to baseline after 30 minutes ($p = 0.20$), while tension and pain in temples and forehead returned to baseline ten minutes into the recovery period ($p > 0.48$).

Thirty subjects (68.2 %) reported an increase in pain in at least one location during the test and twenty-eight subjects (63.6 %) had an increase in pain VAS score of more than 30 mm during the test (Table 4). The pain response was most evident in the neck and/or shoulder (Table 4).

Pain responses did not correlate with tension and fatigue responses ($r_s \leq 0.19$, $p \geq 0.20$), however, fatigue and tension responses were correlated ($r_s = 0.48$, $p = 0.001$).

Pain, tension and fatigue responses did not correlate significantly with physiological responses ($r_s \leq 0.28$, $p \geq 0.071$, correlation coefficients between pain and muscular responses were calculated separately for each localisation). However, the fatigue response correlated with systolic ($r_s = 0.34$, $p = 0.03$, Figure 5) and diastolic blood pressure recovery ($r_s = 0.31$, $p = 0.047$) indicating a larger fatigue response during the stressful task for those subjects who recovered less during the rest period. However, no significant correlations were found between the blood pressure recovery and the pain and tension response variables ($r_s \leq 0.16$, $p \geq 0.31$) and finger

skin blood flow recovery was not correlated to subjective responses ($r_s \leq 0.16$, $p \geq 0.29$).

Except for a correlation between the autonomic symptom index (Table 1) and the blood pressure response (Table 2, $r_s = 0.38$, $p = 0.014$), the physiological responses were not correlated to the Neuroticism index or the “autonomic symptom index”. The Neuroticism index (EPQ-N, Table 1) correlated with pain and fatigue responses ($r_s \geq 0.36$, $p \leq 0.016$).

Subgroup analyses

Subgroup analyses with the dichotomized variables in Table 1 (sex, marital status, employment status, regular exercisers, smokers, and alcohol drinking) revealed that women had lower respiratory frequency (15.2 vs. 17.1 breaths/min, rANOVA; sex effect $F(1,35) = 4.5$, $p = 0.04$) and higher frontalis SEMG (11.1 vs. 6.1 μV , rANOVA; sex effect $F(1,42) = 6.7$, $p = 0.01$). Moreover, smokers had higher blood systolic blood pressure level (130 mmHg vs. 120 mmHg, rANOVA; smoking effect $F(1,36) = 4.7$, $p = 0.04$) and we found a time x marital status interaction for maximal pain (rANOVA; $F(3.0,141.2) = 2.6$, $p = 0.048$) with higher maximal pain response for those living alone compared to cohabitants (17.7 vs 14.5 mm VAS). Subgroup analysis of the recovery variables did however not reveal any differences (One-way ANOVA $F_s \leq 2.9$, $p \geq 0.097$). It must be noted that some subgroups had few cases (Table 1), and were not ideal for subgroup effect analysis.

Discussion

Major findings in the present study on stress responses in healthy subjects can be summarized as: 1) A significant proportion of healthy subjects (64 %) respond with a pain increase of more than 30 mm (VAS 0-100) in at least one of the four muscle groups investigated. 2) Pain develops gradually as a response to a stressful task. 3) The trapezius and frontalis muscles are activated in response to the task with fast recovery after a stressful task. 4) The HR-response habituates gradually during a long-lasting stressful task and recovers fully afterwards. 5) There is a lack of skin blood flow and blood pressure recovery after a stressful task of long duration. 6) Physiological responses (and recovery) are not correlated with pain responses, but 7) lack of blood pressure recovery is correlated to the fatigue response to the preceding stressful task.

The most important finding is that blood pressure and finger skin blood flow did not recover to baseline during the 30-min rest period, contrasting the recovery pattern of the other autonomic and muscular responses. The finger skin blood flow apparently had biphasic response pattern with a fast reduction during the first ten minutes of the stressful task and a further monotonic reduction (trend) during the stressful task, while the blood pressure increased during the first ten minutes of the stressful task and stayed elevated both during and after the stressful task.

Slow recovery of blood pressure following experimental stress has previously been reported by Steptoe and co-workers [20, 21]. They applied the colour-word test and mirror tracing for a total stress period of 10 min, causing a stress response marginally higher than in the present series, judged by the increase in heart rate (Δ heart rate ~7 vs. 5 bpm) and blood pressure (Δ blood pressure ~14 vs. 11 mmHg). In their study blood pressure had partially recovered 20-25 min after the test (female

subjects) while in the present study no recovery was observed after 30 min.

Assuming a similar level of stress in the two series, the slower time course of blood pressure recovery in the present study can be due to the longer duration of the stress period.

The present study of healthy controls shows that slow vascular recovery after mental stress is a normal phenomenon and is not related to simultaneous pain development. The theoretical models linking stress and subjective health complaints emphasize lack of recovery after stress as an important factor for development of subjective complaints [5-7]. According to these models, a person with a reduced ability to recover after stress is more prone to develop subjective complaints. However, as the present study illustrates, when re-examining these theoretical models in the laboratory one may have to register physiological variables over longer recovery periods than we have done in our study to be able to detect possible differences in physiological recovery between patients and healthy controls.

A long-lasting, presumably sympathetically mediated vasoconstriction is evident in the present study. Environmental temperature was monitored throughout the experiment and was stable and not related to skin blood flow (data not shown). The slightly different time course of blood pressure and the finger skin blood flow response indicate differential control of vascular beds. This is interpreted as an example of the specificity of different neuroanatomical circuits within the autonomic nervous system [22] and corresponding differentiation of sympathetic responses with respect to target organ and response localisation within the vascular system [23-25].

Although the reduction of finger skin blood flow was not related to subjective complaints in the present study, it is potentially relevant that some patients with musculoskeletal complaints report a cold feeling in wrist/hand [26, 27]. A recent

study, using infrared thermography to measure dorsal hand skin temperature, showed that post-exercise hyperaemia was blunted in patients with chronic upper extremity pain who reported cold hands induced by keyboard use [28].

A previous study on pain-free subjects using a similar protocol , but without measurements of blood pressure, heart rate and respiration frequency, found a correlation between pain development and muscle activity in the right trapezius muscle ($r = 0.37$, $p < 0.03$) during the stressful task [11]. In the present study we found no correlation between pain response and muscle activity. Because the protocols were so similar and the study group were larger in the present study (44 subjects in the present study, 36 subjects in the previous study), we believe the different finding in the present study indicate that the earlier reported correlation may have been a chance finding. In the previous study increased muscular activity during the stressful task was found for the frontalis muscle and for the trapezius muscles (significant for the frontalis and a trend for the trapezius muscles), whereas no response to the stressful task was found for the splenius and temporalis muscles. The present study confirms the earlier findings of the frontalis and trapezius muscles as more responsive to a stressful task than the splenius and temporalis muscles.

In the present study most cardiovascular vs. EMG correlations were not significant. However, we found correlations between the heart rate response and trapezius and temporalis muscle responses. The correlations were strong ($p < 0.005$), and we cannot exclude that it is relevant. The electrical activity from the heart was filtered out of the electromyographic signals, and a correlation with heart rate was not observed for the splenius muscles, hence it is probably not related to an ECG-artefact. Increased muscular activity in a rather large muscle like trapezius is reasonably

paralleled by increased HR if the increased muscular activity demands a higher cardiac output to satisfy the metabolic needs.

The low-grade stress response in the present experiments is shown by the heart rate only being elevated by 4 beats per minute (bpm) on average, and 5 bpm the first 10 min. Other studies of stress responses have exposed subjects to stress for a shorter period of time and report elevated heart rate responses of 10-20 bpm indicating a higher level of stress [29-31]. The pain reported in the present study is indeed low-level and not directly comparable to laboratory studies of acute pain. The level of tension and fatigue was considerably higher than the pain level in the present study. However, the levels of pain, tension and fatigue obtained in this laboratory study corresponds well with the values obtained from healthy subjects in field studies of workers in stressful work situations with low biomechanical load [32, 33]. Therefore, we believe that the level of subjective complaints reported in this laboratory study is comparable to the subjective complaints healthy subjects experience during stressful and repetitive office work, although laboratory experiments never can substitute real-life experiments. Extending the duration of the stress exposure (as we have done in the present study) has been suggested as one way to increase the external validity of studies on cardiovascular responses to stress [10].

The subject's perception of the stressor was not considered in terms of stress level in the present study, but evaluated using the term "tension". Holte et al. [34] investigated the concept of tension in Norwegian subjects with questionnaires and qualitative interviews and found that subjects described tension in terms of both stress-related autonomic symptoms and musculoskeletal activation (the Norwegian word for tension ("anspenhet") conveys almost the same meaning as the word stress). Furthermore, different perception of the stressor may partly explain the large inter-

subject variation in physiological responses [35, 36]. Moreover, the lack of association between pain and tension responses may indicate that the pain is linked to physiological factors and not to cognitive factors alone.

The feedback period was necessary in order to ensure that all subjects had the same low level of muscle activity before the stressful task. The feedback was given solely on muscular activity. The feedback was introduced after the baseline period in order to get a true baseline period without influence from the feedback procedure. It is possible that the feedback procedure influenced the measured muscle activity during the stressful task by teaching the subjects how to relax their muscles. However, this effect was supposedly similar for all subjects. Furthermore, subjects did not receive any feedback on the measured variables during the stressful task.

In the correlation analysis we have used summary variables in order to minimize the number of calculated correlations. While the subjective variables were steadily increasing through the task, most physiological responses were more stable (although not without exceptions). The physiological variables were measured continuously and we did not want to place emphasis on any (possible random) peak value. Instead, the average value was considered a summary variable reflecting the total physiological “burden” of the stressful task. However, the average pain score will in our opinion not reflect the subjective “burden” of the stressful task. An average pain score would underestimate the pain-inducing effect of the stressful task in case the subject’s pain pathways would have been sensitised in any way, thus potentially neglecting the effect of any temporal summation of pain. We have chosen to use the maximal value during the task as an approximation of this “burden”, and this is in line with others [37-39].

Our subgroup analysis did not reveal any differences between groups regarding the recovery variables, and the present study thus confirms the findings of Steptoe [20] who reported no relationship between prolonged cardiovascular stress responses and sedentary lifestyle. We have not found any other studies related to our findings of lower respiration frequency and higher frontalis muscle activity in women. Considering that smoking is well-known risk factor for cardiovascular disease [40] our finding of increased blood pressure among smokers is not surprising. The higher pain response found for those living alone is very difficult to explain and we are not aware of any other study who has investigated this. However, as already noted, subgroup sizes were partly asymmetric and not optimally sensitive for subgroup factor effect analysis.

We are not aware of other studies investigating the relation between development of fatigue during stress and degree of physiological recovery and thus our finding of a correlation between lack of blood pressure recovery and fatigue development during stress should be further investigated. It must be emphasized that the correlation was weak and may be a chance finding because of the large number of correlations performed. Nevertheless, the correlation may indicate that psychological mechanisms are important when considering the mechanisms for the protracted vascular response. Moreover, the correlation between the blood pressure and finger skin blood flow recovery variables may point to a common mechanism responsible for the lack of recovery in these two variables.

Steptoe (2003) proposed sustained changes in centrally mediated neurogenic vasoconstriction, or disturbance of nitric-oxide-dependent endothelial function, as explanations for lack of recovery of blood pressure after mental stress [21]. However,

theories for mechanisms underlying the lack of blood pressure recovery are speculative at this stage.

Conclusion

In the present study of healthy subjects exposed to mental stress in 60 minutes the blood pressure and acral finger skin blood flow response did not recover to baseline even after 30 minutes rest. This was in clear contrast to other physiological stress response variables (heart rate, respiration frequency and muscle activity) which recovered to baseline values early in the rest period. The protracted blood pressure response was correlated to fatigue development, but not to pain development, possibly implicating psychological mechanisms. However, because of the large number of correlations performed in the present study, one must keep in mind that this correlation may be a chance finding. The results imply that a long recovery period is necessary when the physiological recovery to mental stress is studied. Moreover, a thorough exploration of different aspects of the subjective complaints that develops during and after low-grade stress of long duration is needed. Examplewise, a valid and reliable way to distinguish between mild fatigue and unpleasantness in contrast to pain should be established in later studies of the relation between stress and development of subjective complaints. Furthermore, the duration of stress period may be of importance and should be addressed in future studies of physiological recovery after mental stress. Finally, further studies should in a prospective design investigate whether healthy subjects with a slow vascular recovery after mental stress is at risk for developing chronic stress-related disorders later in life.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KBN participated in study design, in collecting the data, carried out the analysis and drafted the manuscript. TS participated in the design, advised and assisted in the statistical analysis and in the progress and drafting of the manuscript. LJS participated in the study design and in the progress of the manuscript. RBL participated in the statistical analysis and in the progress of the manuscript. RHW participated in the design, and in the progress and drafting of the manuscript. All authors read and approved the final manuscript

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Figure legends:

Figure 1: Surface electromyographic (SEMG) activity before (Baseline, Feedback), during (0-10, 10-20,..., 50-60 min) and after (65-75, 75-85, 85-95 min) the stressful task. Mean RMS values for periods of 10 minutes (Baseline, Feedback: 5 min) are shown.

Figure 2: Mean blood pressure and finger skin blood flow (SBF) before (Baseline, Feedback), during (0-10, 10-20,..., 50-60 min) and after (65-75, 75-85, 85-95 min) the stressful task. Mean values for periods of 10 minutes (Baseline, Feedback: 5min) are shown. Au = arbitrary units.

Figure 3: Respiration frequency and heart rate before (Baseline, Feedback), during (0-10, 10-20,..., 50-60 min) and after (65-75, 75-85, 85-95 min) the stressful task. Mean values for periods of 10 minutes (Baseline, Feedback: 5min) are shown.

Figure 4: Tension, fatigue and pain scores in the maximal pain location before (0 min), during (10, 20, ..., 60 min) and after (75, 85, 95 min) the stressful task.

Figure 5: Blood pressure recovery (value at 95 min – baseline) plotted against the fatigue response with linear regression line shown. The association is significant ($r_s = 0.34$, $p = 0.03$).

Table 1. Subject characteristics for the 44 participants

	Mean (SD)	Range
Age all (n=44, years)	41 (12)	21-61
Age women (n=35, years)	40 (12)	21-61
Age men (n=9, years)	37 (12)	19-56
Weight (kg)	72 (14)	47-103
Height (cm)	168 (8)	145-190
Autonomic symptom index	5 (3)	1-13
EPQ-N	7 (4)	0-15
		No. of subjects (%)
Married / cohabitant (n)		31 (71 %)
Working (≥ 50 %) (n)		38 (86 %)
Regular exercisers (≥ 1 session pr. week) (n)		14 (32 %)
Smokers (n)		12 (27 %)
Drinking alcohol ≥ 2 days pr. week * (n)		9 (20 %)

* One person drinking more than 3 days pr. week

Table 2. Mean values and the average responses for all variables

Variable	Baseline		During the stressful task					Response*
	Mean (SD)	0-10 min Mean (SD)	10-20 min Mean (SD)	20-30 min Mean (SD)	30-40 min Mean (SD)	40-50 min Mean (SD)	50-60 min Mean (SD)	Mean (SD)
Surface electromyography								
Trapezius (μV)	6.2 (6.2)	11.8 (13.7)	12.0 (12.8)	11.6 (13.8)	10.5 (11.3)	11.2 (12.4)	10.7 (11.8)	5.1 (11.4)
Splenius (μV)	5.3 (3.2)	4.7 (2.7)	4.6 (2.3)	4.6 (2.6)	4.5 (3.0)	4.6 (3.5)	4.6 (3.1)	-0.7 (3.1)
Temporalis (μV)	6.5 (3.2)	6.4 (4.7)	7.0 (6.1)	6.6 (5.6)	7.1 (5.2)	7.3 (5.5)	7.2 (5.1)	0.5 (5.4)
Frontalis (μV)	8.0 (5.9)	11.1 (5.8)	11.1 (6.1)	11.0 (6.6)	11.3 (6.4)	11.1 (6.5)	11.4 (6.5)	3.2 (4.8)
Systolic BP (mmHg)	112 (16)	126 (17)	122 (16)	122 (15)	123 (15)	123 (15)	125 (15)	11.4 (7.8)
Diastolic BP (mmHg)	62 (11)	72 (13)	69 (13)	69 (11)	71 (12)	70 (11)	71 (10)	8.6 (5.0)
Heart rate (beats/min)	71 (8)	75 (10)	74 (9)	73 (9)	72 (9)	72 (9)	72 (8)	2.3 (4.3)
Respiration (breaths/min)	15 (3)	17 (3)	17 (3)	16 (3)	16 (3)	16 (3)	16 (3)	1.5 (2.5)
Skin blood flow (au)	279 (112)	248 (122)	251 (130)	246 (127)	249 (126)	237 (127)	229 (120)	-35.3 (56.7)
Pain (VAS 0-100 mm)		10 min	20 min	30 min	40 min	50 min	60 min	
Maximal location (mm)	2.4 (6.1)	3.0 (5.3)	3.6 (5.8)	6.7 (11.1)	9.0 (14.4)	11.9 (15.5)	14.0 (17.1)	15.4 (18.0)
Shoulder (mm)	2.8 (6.3)	2.4 (5.6)	4.5 (7.0)	5.4 (8.8)	6.5 (12.4)	8.7 (13.3)	10.3 (14.4)	12.9 (16.1)
Neck (mm)	2.4 (5.1)	3.1 (5.6)	3.5 (6.4)	5.0 (9.1)	6.4 (8.2)	8.6 (12.2)	9.8 (11.9)	11.5 (13.7)
Temples (mm)	1.0 (2.2)	2.3 (5.2)	1.9 (4.1)	3.7 (8.2)	4.2 (9.1)	5.6 (10.8)	5.5 (11.7)	7.5 (13.7)
Forehead (mm)	1.1 (2.5)	1.6 (3.3)	2.5 (6.0)	3.8 (8.8)	4.2 (9.1)	4.7 (9.5)	5.3 (11.1)	6.3 (12.0)
Fatigue (VAS 0-100 mm)	8.9 (15.3)	7.7 (13.5)	10.8 (14.6)	19.0 (20.5)	22.2 (21.2)	29.8 (22.5)	33.1 (25.4)	27.2 (23.1)
Tension (VAS 0-100 mm)	7.0 (12.4)	11.2 (13.2)	12.9 (14.0)	18.0 (19.1)	19.4 (20.2)	21.7 (20.6)	25.3 (23.1)	21.2 (21.2)
Recovery period								
Variable		65-75 min	75-85 min	85-95 min	Recovery §			
Surface electromyography								
Trapezius (μV)		5.4 (4.7)	5.6 (4.5)	6.2 (6.4)	0.14 (7.7)			
Splenius (μV)		4.7 (2.7)	4.9 (3.0)	4.9 (3.4)	-0.33 (3.6)			
Temporalis (μV)		7.7 (4.9)	7.4 (5.3)	7.1 (4.2)	0.68 (3.8)			
Frontalis (μV)		9.0 (6.9)	8.2 (5.5)	8.3 (5.1)	0.26 (3.9)			
Systolic BP (mmHg)		123 (15)	122 (14)	124 (14)	12.1 (11.7)			
Diastolic BP (mmHg)		71 (10)	69 (9)	71 (10)	9.5 (6.6)			
Heart rate (beats/min)		69 (7)	69 (8)	69 (8)	-1.9 (3.8)			
Respiration (breaths/min)		14 (2)	14 (2)	14 (3)	-0.68 (2.7)			
Skin blood flow (au)		215 (105)	229 (111)	211 (106)	-67.5 (89.1)			
Pain (VAS 0-100 mm)		75 min	85 min	95 min				
Maximal location (mm)		6.9 (15.2)	7.6 (14.9)	5.8 (13.5)	3.3 (11.4)			
Shoulder (mm)		6.2 (15.0)	6.2 (14.9)	5.3 (13.7)	2.5 (11.4)			
Neck (mm)		5.5 (11.0)	6.1 (12.5)	5.5 (11.5)	3.0 (10.1)			
Temples (mm)		1.9 (5.9)	1.7 (4.5)	1.7 (5.2)	0.67 (4.7)			
Forehead (mm)		2.2 (6.1)	1.8 (4.5)	1.8 (5.1)	0.63 (4.6)			
Fatigue (VAS 0-100 mm)		17.2 (20.2)	17.5 (21.8)	15.0 (20.2)	6.7 (19.3)			
Tension (VAS 0-100 mm)		8.2 (16.0)	8.1 (16.5)	4.8 (12.0)	-1.4 (12.0)			

au: arbitrary units. BP: blood pressure

* Response = Average during stressful task (0-60 min) – baseline for the physiological variables, and maximal during stressful task (0-60 min) – baseline for the subjective variables.

§ Recovery = The last ten minutes of the recovery period (85-95 min) – baseline (summary statistics used in correlation analysis).

Table 3. Test statistics for evaluation of the response and recovery to the stressful task

Variable	rANOVA*	Baseline vs. 0-10 min	0-10 vs. 50-60 min	50-60 vs. 65-75 min
Surface electromyography				
Trapezius (μV)	$F(2.5,105.6) = 7.3, p < 0.001$	$t(43) = -2.9, p = 0.006$	$t(43) = 1.0, p = 0.33$	$t(43) = 3.1, p = 0.003$
Splenius (μV)	$F(3.3,144.0) = 0.96, p = 0.42$	$t(43) = 1.1, p = 0.28$	$t(43) = 0.5, p = 0.62$	$t(43) = -0.2, p = 0.80$
Temporalis (μV)	$F(2.7,117.8) = 1.2, p = 0.31$	$t(43) = 0.0, p = 0.96$	$t(43) = -2.3, p = 0.03$	$t(43) = -0.9, p = 0.39$
Frontalis (μV)	$F(3.2,138.2) = 11.3, p < 0.001$	$t(43) = -3.8, p < 0.001$	$t(43) = -0.4, p = 0.69$	$t(43) = 3.3, p = 0.002$
Systolic blood pressure (mmHg)	$F(2.8,14.3) = 11.4, p < 0.001$	$t(40) = -7.0, p < 0.001$	$t(40) = 0.3, p = 0.78$	$t(41) = 1.5, p = 0.15$
Diastolic blood pressure (mmHg)	$F(3.0,118.2) = 17.4, p < 0.001$	$t(40) = -7.6, p < 0.001$	$t(40) = 0.4, p = 0.66$	$t(41) = 0.1, p = 0.96$
Heart rate (beats/min)	$F(2.6,103.2) = 24.1, p < 0.001$	$t(40) = -4.5, p < 0.001$	$t(42) = 3.7, p = 0.001$	$t(42) = 8.1, p < 0.001$
Respiration (breaths/min)	$F(4.3,155.2) = 21.7, p < 0.001$	$t(36) = -4.6, p < 0.001$	$t(36) = 2.1, p = 0.04$	$t(36) = 6.1, p < 0.001$
Finger skin blood flow (au)	$F(2.6,113.2) = 6.2, p < 0.001$	$t(43) = 3.6, p = 0.001$	$t(43) = 1.8, p = 0.09$	$t(43) = 1.6, p = 0.12$
Pain (VAS 0-100 mm)				
Maximal location (mm)	$F(3.2,139.4) = 7.8, p < 0.001$	$Z = -1.4, p = 0.17$	$Z = -4.6, p < 0.001$	$Z = -4.0, p < 0.001$
Shoulder (mm)	$F(2.7,112.5) = 3.8, p = 0.02$	$Z = -0.3, p = 0.75$	$Z = -4.3, p < 0.001$	$Z = -3.5, p < 0.001$
Neck (mm)	$F(2.4,98.9) = 4.5, p = 0.01$	$Z = -0.6, p = 0.52$	$Z = -4.3, p < 0.001$	$Z = -3.2, p = 0.001$
Temples (mm)	$F(2.0,86.5) = 4.1, p = 0.02$	$Z = -2.2, p = 0.03$	$Z = -1.9, p = 0.06$	$Z = -2.7, p = 0.006$
Forehead (mm)	$F(2.1,89.5) = 4.0, p = 0.02$	$Z = -2.5, p = 0.01$	$Z = -2.7, p = 0.008$	$Z = -2.7, p = 0.008$
Fatigue (VAS 0-100 mm)	$F(3.2,129.0) = 17.0, p < 0.001$	$Z = -0.6, p = 0.52$	$Z = -5.2, p < 0.001$	$Z = -4.4, p < 0.001$
Tension (VAS 0-100 mm)	$F(2.6,104.7) = 16.1, p < 0.001$	$Z = -2.4, p = 0.02$	$Z = -4.5, p < 0.001$	$Z = -4.9, p < 0.001$
		50-60 vs. 85-95 min	Baseline vs. 65-75 min	Baseline vs. 85-95 min
Surface electromyography				
Trapezius (μV)		$t(43) = 2.8, p = 0.008$	$t(43) = 0.9, p = 0.40$	$t(43) = -0.12, p = 0.99$
Splenius (μV)		$t(43) = -7.1, p = 0.48$	$t(43) = 1.4, p = 0.16$	$t(43) = 0.65, p = 0.54$
Temporalis (μV)		$t(43) = 0.2, p = 0.83$	$t(43) = -2.0, p = 0.05$	$t(43) = -1.2, p = 0.24$
Frontalis (μV)		$t(43) = 4.5, p < 0.001$	$t(43) = -1.7, p = 0.10$	$t(43) = -0.44, p = 0.67$
Systolic blood pressure (mmHg)		$t(41) = 0.54, p = 0.60$	$t(40) = -7.1, p < 0.001$	$t(40) = -6.5, p < 0.001$
Diastolic blood pressure (mmHg)		$t(41) = -0.4, p = 0.69$	$t(40) = -9.5, p < 0.001$	$t(40) = -9.2, p < 0.001$
Heart rate (beats/min)		$t(42) = 7.0, p < 0.001$	$t(40) = 3.1, p = 0.004$	$t(40) = 3.2, p = 0.003$
Respiration (breaths/min)		$t(36) = 5.6, p < 0.001$	$t(36) = 2.2, p = 0.03$	$t(36) = 1.5, p = 0.14$
Finger skin blood flow (au)		$t(43) = 1.7, p = 0.10$	$t(43) = 5.4, p < 0.001$	$t(43) = 5.0, p < 0.001$
Pain (VAS 0-100 mm)				
Maximal location (mm)		60 vs. 95 min $Z = -4.0, p < 0.001$	0 vs. 75 min $Z = -2.5, p = 0.01$	0 vs. 95 min $Z = -2.4, p = 0.015$
Shoulder (mm)		$Z = -3.5, p < 0.001$	$Z = -1.7, p = 0.08$	$Z = -1.3, p = 0.20$
Neck (mm)		$Z = -2.7, p = 0.007$	$Z = -2.1, p = 0.04$	$Z = -2.2, p = 0.03$
Temples (mm)		$Z = -2.7, p = 0.007$	$Z = -0.4, p = 0.72$	$Z = -0.51, p = 0.61$
Forehead (mm)		$Z = -2.7, p = 0.007$	$Z = -0.7, p = 0.48$	$Z = -0.40, p = 0.69$
Fatigue (VAS 0-100 mm)		$Z = -4.4, p < 0.001$	$Z = -3.2, p = 0.001$	$Z = -2.6, p = 0.009$
Tension (VAS 0-100 mm)		$Z = -4.8, p < 0.001$	$Z = -0.3, p = 0.78$	$Z = -1.5, p = 0.13$

au: arbitrary units. BP: blood pressure

* ANOVA repeated measures (no between-subjects factors, time effect) with ten time intervals (baseline, 0-10, ..., 85-95 min) and Huynh-Feldt corrected degrees of freedom. All other statistics are paired statistics (Student's paired t-tests for physiological variables and Wilcoxon paired statistics for subjective variables used in explorative contrast analysis).

Table 4: Subjective responses categorized in three groups

	VAS = 0	VAS 1-30	VAS > 30
Pain:			
Shoulders (n (%))	17 (38.6%)	3 (6.8%)	24 (54.5%)
Neck (n (%))	19 (43.2%)	1 (2.3%)	24 (54.5%)
Temples (n (%))	27 (61.4%)	5 (11.4%)	12 (27.3%)
Forehead (n (%))	24 (54.5%)	8 (18.2%)	12 (27.3%)
Maximal pain location ^b	14 (31.8%)*	2 (4.5%)	28 (63.6%)
Fatigue (n (%))	5 (11.6%)	1 (2.3%)	37 (86.0%)
Tension (n (%))	4 (9.5%)	3 (7.1%)	35 (83.3%)

^a Pain response = (maximal pain during test – pain before test), ^b Maximal pain response irrespective of location, *= No pain development in any location.

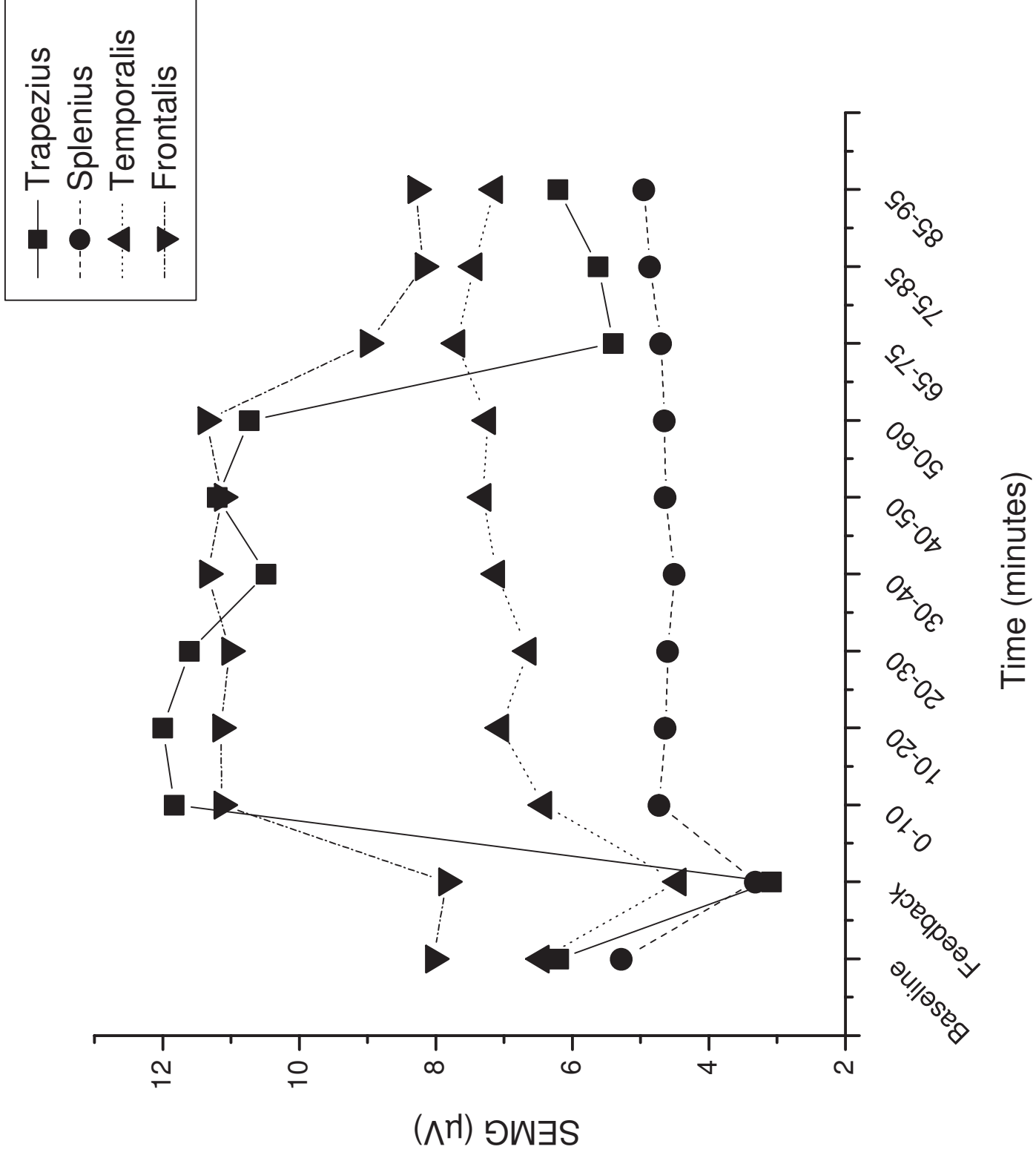


Figure 1

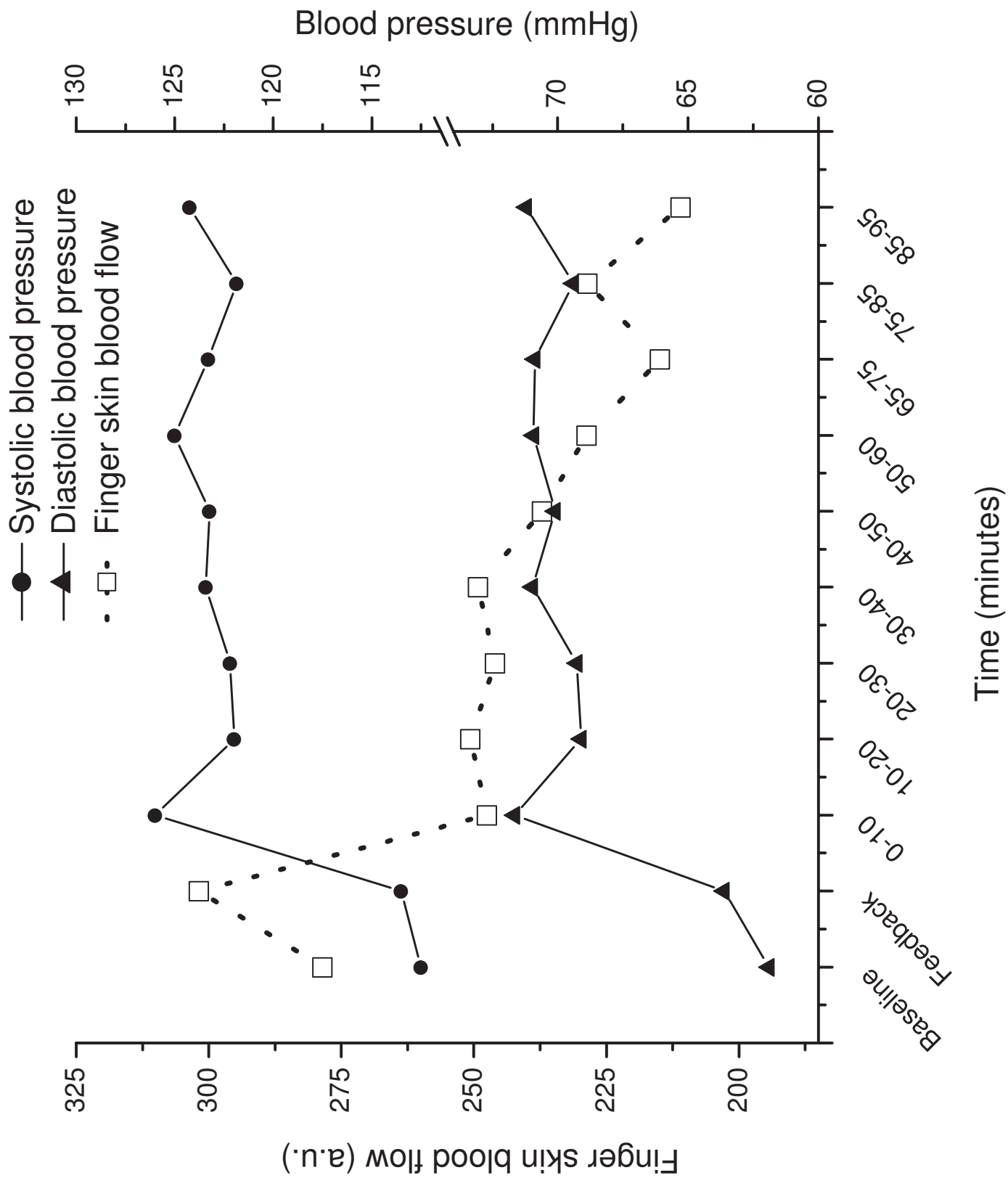


Figure 2

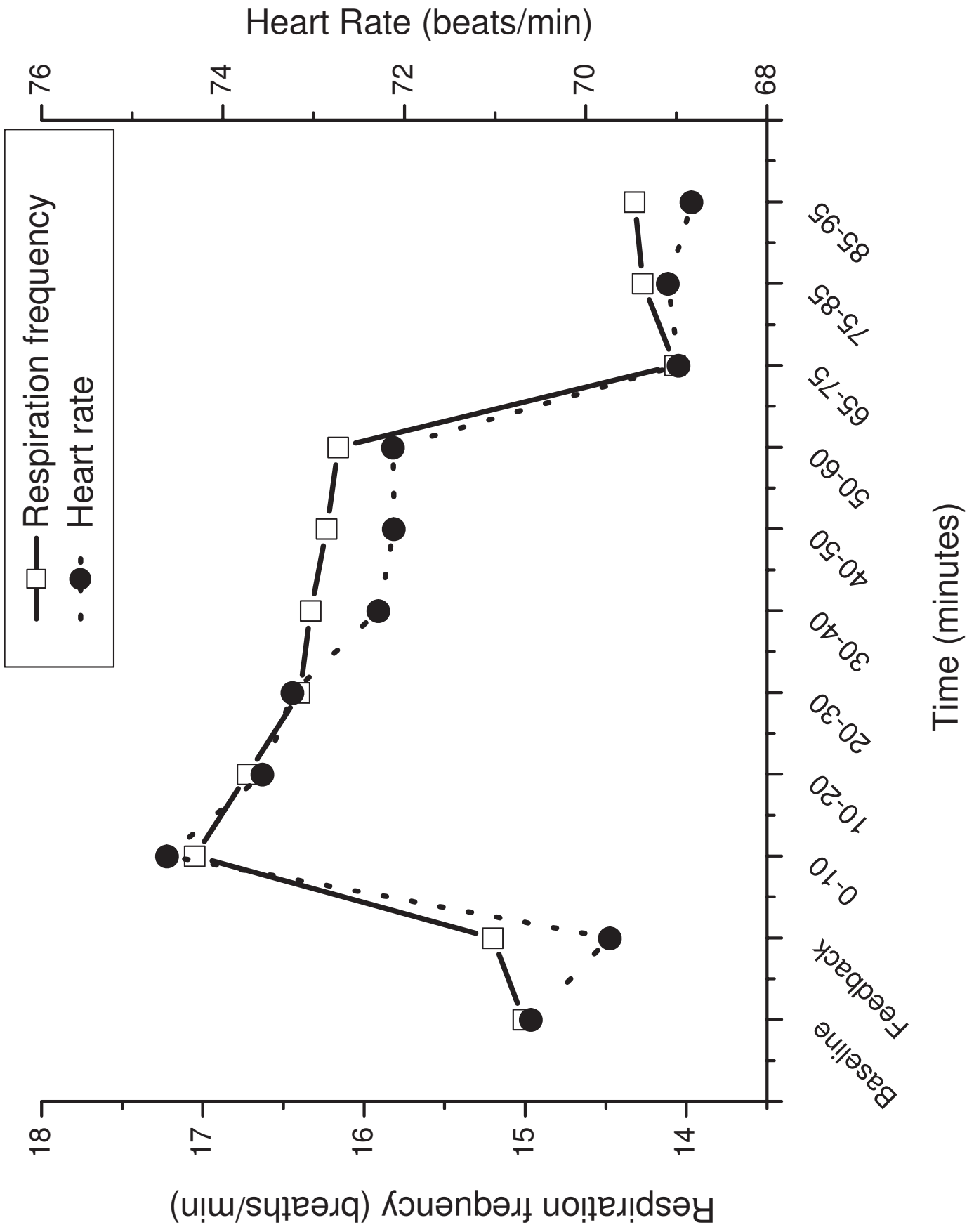


Figure 3

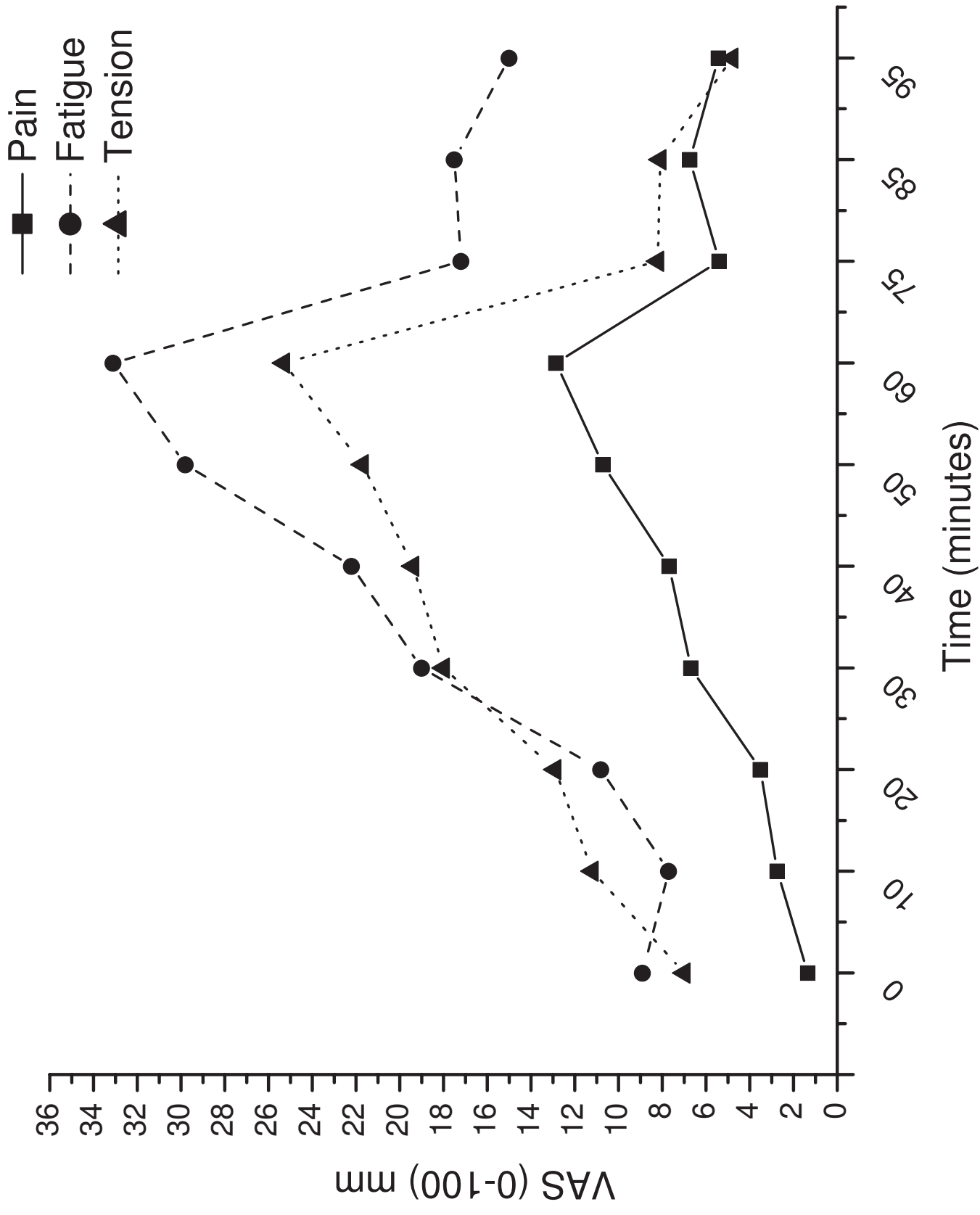


Figure 4

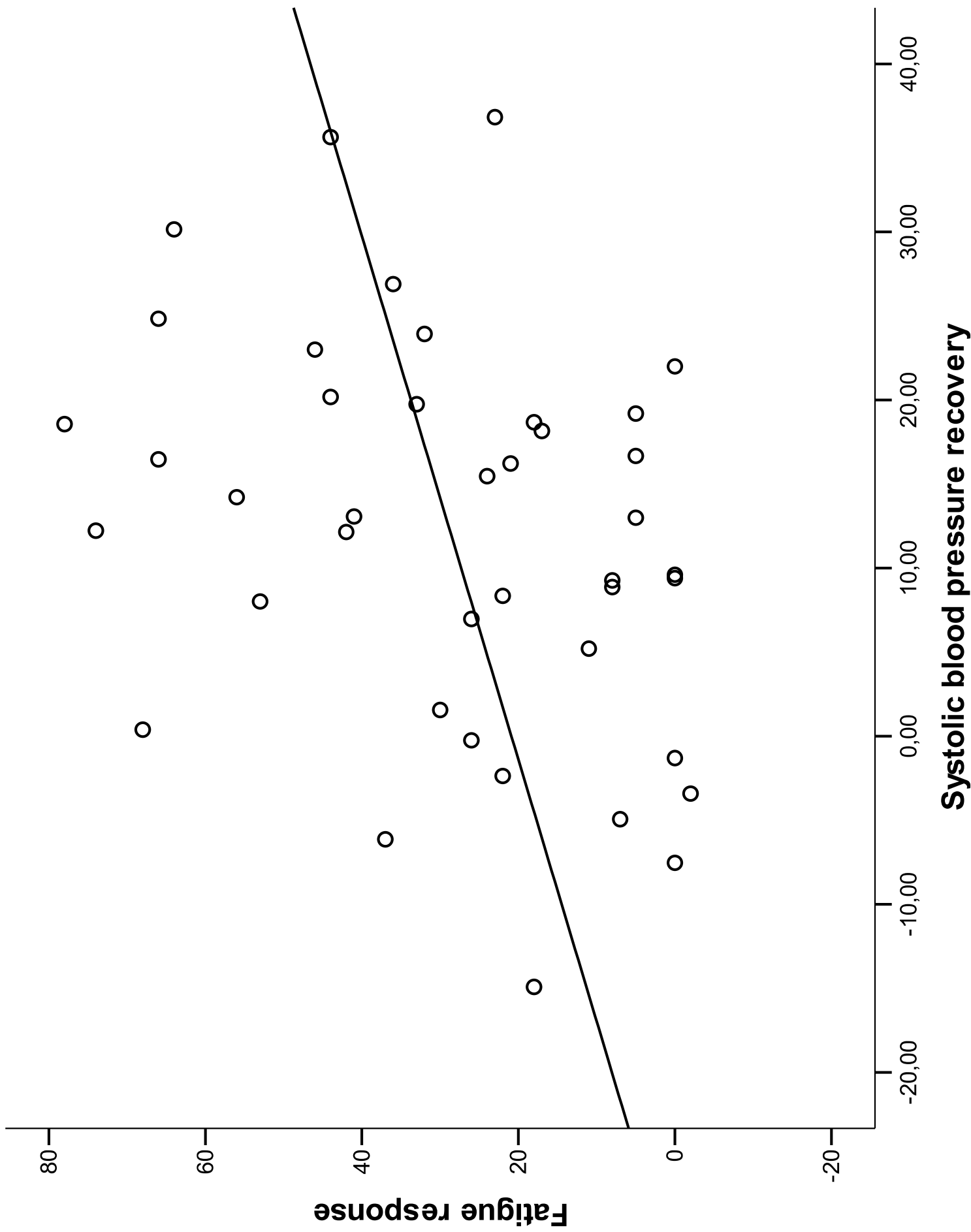


Figure 5

Paper II:

Nilsen KB, Westgaard RH, Stovner LJ, Helde G, Rø M, Sand T. Pain induced by low-grade stress in patients with fibromyalgia and chronic shoulder/neck pain, relation to surface electromyography. *European Journal of Pain* 2006; 10(7): 615-27.



Pain induced by low-grade stress in patients with fibromyalgia and chronic shoulder/neck pain, relation to surface electromyography

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Abstract

The mechanisms of pain causation in fibromyalgia (FMS) and chronic shoulder/neck pain (SNP) are still debated. We wanted to compare muscle activity and pain development during and after low-grade mental stress in FMS and SNP patients. Twenty-three women with FMS, 29 women with chronic SNP and 35 healthy women performed a stressful task lasting 60 min followed by a 30 min recovery period. We recorded surface electromyography over the trapezius, neck, temporalis and frontalis muscles. Subjects reported their pain at the corresponding locations together with the development of fatigue and perceived tension. Significant differences between FMS and SNP groups were not observed either for muscular or subjective responses. SNP patients and controls responded with more pain in the trapezius and neck regions than in the forehead, in contrast to FMS patients who had a more generalized pain response. Development of pain, tension and fatigue was not related to muscle activity for any group. We conclude that FMS and SNP patients have similar pain and electromyographic responses. The results suggest that similar pathophysiological mechanisms are involved although the responses are more generalised in FMS than in SNP patients. Muscular activity did not explain the pain which developed during the stressful task for either group. Pain lasted longer during recovery in both FMS and SNP patients compared to healthy controls, possibly a result of disease-related sensitisation in pain pathways.

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Keywords: Musculoskeletal pain; Myofascial pain; Aftersensation; Psychosocial

1. Introduction

There is a long-standing discussion among clinicians as to whether generalised and localised non-arthritis musculoskeletal pain, as in patients with fibromyalgia (FMS) or shoulder-neck pain (SNP), represent different entities or are on a pain continuum with the same etiological factors (McCain and Scudds, 1988; Wolfe et al., 1992; Goldenberg, 1999; Buskila, 2001). A noted similarity between FMS and SNP patients is pain in

response to sustained psychosocial or mental stress, which is also a risk factor for musculoskeletal pain in a healthy population (Linton, 2000; van der Windt et al., 2000; Ariens et al., 2001; Bongers et al., 2002). Low-grade cognitive stress in a laboratory environment (intended to simulate office work) has been shown to induce both upper-body pain and increased muscle activity in FMS patients (Bansevicius et al., 2001) and in healthy controls (Bansevicius et al., 1997). However, there is still considerable doubt about the extent to which muscle activity is a physiological trigger for musculoskeletal pain (Simms, 1996; Westgaard, 1999; Sjøgaard et al., 2000).

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In the present study, we intended to compare pain and muscle activity during and after cognitive stress in patients with generalised musculoskeletal pain (FMS) and localised chronic shoulder/neck pain (SNP) using a blinded study design. Furthermore, we intended to investigate whether musculoskeletal pain, subjective fatigue and perceived tension correlated with muscular activity during and after stress. One may posit that similar physiological and subjective responses to stress in the two patient groups point to similar physiological mechanisms for pain generation and pain modulation, while response differences may indicate that these mechanisms differ between the syndromes in question.

In this study, we measured muscular activity (with surface electromyography) and pain development in the trapezius, neck, temporal, and frontal regions before and during 60 min of low-grade stress, and in the following 30 min rest period.

2. Subjects and methods

2.1. Subjects

Twenty three female FMS patients, 29 female patients with chronic SNP and 35 healthy women (controls) participated in the study (Table 1). Patients were mainly referred from primary care centres and physiotherapists. Controls were recruited from public institu-

tions and private companies in Trondheim, and they answered specific pain-related questions in a structured interview. Controls were allowed to report sporadic or situation-related minor headache and/or muscle aches because of the universal nature of such symptoms. Controls who described these symptoms as unpleasant but not as bothersome pain were only excluded if two of the following three conditions were fulfilled: (1) symptoms for more than one day per month, (2) had visited a physician for the complaint, and (3) usually took medication for the complaint. Controls who considered their headache or pain to be more than “unpleasant” (i.e. bothersome pain) were excluded if at least one of the three conditions above was fulfilled.

Inclusion criteria for all participants were: (1) adults aged 18–65 years and (2) submitted written informed consent. FMS patients were included if they fulfilled the 1990 American College of Rheumatology Criteria (ACR criteria) for fibromyalgia (Wolfe et al., 1990). SNP patients were included if they reported chronic shoulder/neck pain (more than 3 months during the previous year) with local tenderness or triggerpoints. SNP patients were included although they reported pain also from other body regions, however, pain in the shoulder and neck region had to be their main problem. No SNP patients fulfilled the ACR criteria.

Subjects were excluded if they had: (1) neoplastic disease, (2) high blood pressure or were taking anti-hypertensive medication, (3) infectious disease, including

Table 1
Subject characteristics

	Controls (<i>n</i> = 35)		Fibromyalgia (<i>n</i> = 23)		Shoulder/neck pain (<i>n</i> = 29)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age (years)	39.7 (12.3)	21–61	48.3 (7.2)	32–63	41.1 (11.3)	19–59
Weight (kg)	70.9 (12.7)	47–103	69.4 (12.4)	51–96	70.5 (12.2)	50–95
Height (cm)	167.3 (7.3)	145–179	166.1 (5.6)	157–178	169.0 (6.7)	155–182
Duration of pain (years)			11 (9)	1–40	8 (8)	1–30
EPQ-N score	7.7 (4.3)	0–15	11.8 (4.8)	2–21	10.4 (4.4)	3–18
Autonomic Symptom Index	5.3 (3.0)	1–13	12.5 (4.4)	5–21	8.7 (4.3)	1–16
General tension (last 3 months) (VAS)	28.6 (24.5)	0–84	47.8 (22.9)	0–100	43.4 (23.9)	8–89
<i>Answers to selected questions from questionnaire</i>						
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Married/cohabitant	11	31.4	12	52.2	14	48.3
Working ($\geq 50\%$)	32	91.4	13	56.5	22	75.9
Habitual trainers (≥ 1 session pr. week)	21	60.0	17	73.9	17	58.6
Smokers	24	68.6	15	65.2	19	65.5
Drinking alcohol ≥ 2 days per week	31	88.6	11	47.8	24	82.8
I have problems falling asleep more than once a month	5	14.3	22	95.7	16	55.2
I have problems with day-time sleepiness more than 7 days per month	7	20.0	17	73.9	9	31.0
I have continuous and undisturbed sleep	22	62.9	4	17.4	11	37.9
I have frequent mood changes	13	37.1	13	56.5	15	51.7
I do sometimes feel depressed without reason	18	51.4	16	69.6	19	65.5
Life is often a strain for me	13	37.1	16	69.6	16	55.2
I have forebodings about the future	7	20.0	10	43.5	11	37.9
I am anxious about something or somebody most of the time	3	8.6	6	26.1	5	17.2
My complaints cause reduced activity in my leisure time			23	100.0	14	48.3

those who had caught a cold with fever, cough or muscle pain, (4) metabolic, endocrine or neuromuscular disease, (5) connective tissue disorder, (6) tendinitis or capsular affection of the shoulder joint, (7) recent accident or injury affecting function, (8) symptomatic heart disease or were taking medication for any vascular disease, (9) lung disease affecting function or were taking medication for such, (10) cerebrovascular disease, (11) chronic neurological disease, (12) or if headaches were a major part of the pain syndrome, (13) or were taking any medication with a possible interaction on neural, vascular or muscular function (e.g. antiepileptics, β -blockers, antidepressants).

Fourteen FMS patients used analgesics on a regular basis, three of these used prescription drugs (Tramadol or Paracetamol/Codein combination). Sixteen SNP patients used analgetics, eight of these used prescription drugs (Piroxicam, Meloxicam, Karisoprolol, Celecoxib or Paracetamol/Codein combination). Analgesics were withdrawn 2 days prior to the experiment. None of the healthy controls used analgesics on a regular basis.

2.2. Questionnaire and interview

All subjects answered a questionnaire on biographical data (marital status, weight, medication, and stimulants), exercise habits, and the neuroticism index of the Eysenck Personality Questionnaire (EPQ-N) (Eysenck and Eysenck, 1981). The questionnaire further included an index of symptoms concerning the autonomic nervous system (“autonomic symptom index”). For this purpose a subset of 10 questions were chosen (No. 26–35) from the Composite Autonomic Symptom Profile (Suarez et al., 1999). The questions assessed different domains of autonomic symptoms (orthostatic, sudomotor, gastrointestinal, visual, vasomotor, reflex syncope). Sub-indexing different autonomic domains was not done due to the limited number of questions. The answers were graded. A serious degree of a symptom was given a higher value than a less serious; e.g. the answers to the question: “In the last year, to what extent have you been in a cold sweat?” were graded as: “have not had” (value 0), mild (value 1), moderate (value 2), severe (value 3). The highest possible total score was 30.

A structured interview guide concerning musculoskeletal complaints (distribution, severity, and duration) was formulated. Subjects were asked to grade pain in different body regions on a VAS scale (0–100 mm). They were also asked to grade their level of general tension (last 3 months) on a VAS scale. The comprehension of tension was not specified by the investigators. The Norwegian word for tension (“anspenthet”) conveys almost the same meaning as the word stress. Holte et al. investigated the concept of tension in Norwegian subjects with questionnaires and qualitative interviews and found that subjects described tension in terms of both

stress-related autonomic symptoms and musculoskeletal activation (Holte et al., 2003).

2.3. Procedure

All potential controls and patients first went through a short telephone interview. All patients went through a detailed consultation and examination by a specialist in physical medicine and rehabilitation. Patients and controls not excluded by this initial screening received written information on the study background, and a questionnaire on background data, within two weeks of the test day. After a short interview on the morning of the test day, venous blood was drawn from the right cubital fossa. Subjects emptied the bladder before starting the test. Brassieres were removed and subjects wore only a light shirt on the upper part of the body. The laboratory temperature was regulated to 24.5 ± 1 °C.

The subjects were seated in an office chair with the forearms resting on the table top before, during and after the test. Subjects became acquainted with the work-task by performing a mini-trial with instructions before the test started. The mini-trial was performed before introducing the stress-imposing feedback on reaction time and was used to determine the subjects’ habitual, non-stressed reaction time. Short maximal voluntary contractions were performed on each pair of muscles twice (frontalis muscle-raising eyebrows, temporalis-clenching teeth, neck-pushing head back against resistance, trapezius-pushing extended arms upwards against resistance at 45° angle out from the body). The maximal contractions were carried out in order to normalize the muscle activity during test to a percent of maximal force. However, the variability between the two maximal muscle contractions in the frontalis muscle was too large to make a reliable estimate of the maximal muscle force and thus none of the muscle activity measurements were normalised. In order to measure the habitual level of physiological activation the laboratory experiment started with a 5 min period which served as a basis for the evaluation of physiological responses during the test and the subsequent rest period. The subjects were alone in the room and were not given any instructions other than to find a comfortable position with their arms resting on the table in front of them (uninstructed rest; “UIR”). A 5 min feedback (“FB”) period with muscular activity visualised on a screen followed. The subject experienced how it was possible to influence the level of muscle activity by adopting different postures and thereafter concentrated on minimising any muscle activity. The stressful task (Westgaard and Bjørklund, 1987) was then presented: a two-choice reaction-time test on a monitor, lasting one hour. An open (“frame”) and a solid (“brick”) quadrangle were placed in a square pattern, and a written suggestion on how to move the brick to superimpose on the frame was given (Fig. 1).

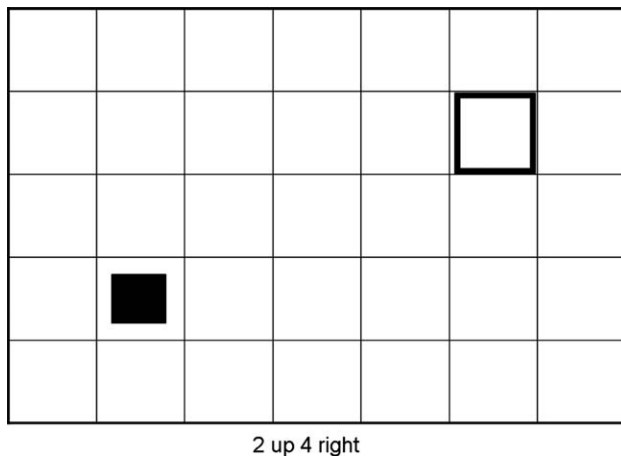


Fig. 1. Example of one possible trial configuration in the stressful task. The alphanumeric text suggests how to move the solid square (brick) to superimpose the open quadrangle (frame). In this case the suggestion is correct.

The subject responded by pressing one of two keys (“correct” or “wrong”), with the right middle or index finger. The test was to be carried out as quickly and correctly as possible. The PC program provided feedback on whether an answer was correct or wrong, and on the response time (very slow, slow, normal, fast, very fast), related to the subject’s performance in the mini-trial carried out before the experiment started (Wærsted et al., 1994). Together with the feedback a new task was presented. After the end of the stressful task, all measurements continued for 30 min. The subject was instructed to sit still and relax during the rest period.

Pain, perceived tension and fatigue were reported every 10 min before, during, and after the test by scoring on a 100 mm visual analogue scale (VAS) with the endpoints marked “no pain/tension/fatigue” and “worst imaginable pain/tension/fatigue”. Perceived tension was considered to reflect subjective stress during and after the test. The subjects were asked to assess pain in locations corresponding to the SEMG electrode positions in the shoulders, neck, temples and forehead on both sides. The subjects were not allowed to see previous records when scoring.

Immediately after the stressful task, before the 30 min rest period, a second blood sample was drawn. Subjects reported the pain, tension and fatigue both before (60 min) and after the venipuncture (65 min). The results of the blood analysis are not reported in this article.

The laboratory personnel were blinded as to the diagnosis (healthy control, FMS or SNP) of the subjects, and the subjects were instructed not to disclose their diagnostic status. Furthermore, the laboratory personnel monitored the experiment visually from another room, only communicating with the subjects briefly every 10th minute with a strictly established monologue when subjective ratings were collected, in order to maintain

blinding. All data processing before the statistical analysis was made without knowledge of diagnostic status of the subjects.

2.4. Physiological recordings

Muscle activity was quantified by bilateral bipolar recording of surface electromyography (SEMG) (electrode diameter 6 mm, inter-electrode distance 20 mm). The system noise level was less than 1.5 μV root mean square (RMS). The signals were bandpass-filtered (10–1250 Hz) and stored on a digitizing recorder (Earth Data 128). Data were subsequently reconverted to analogue signals and fed into an A/D converter (Powerlab 16S; ADInstruments Pty Ltd, Sydney, Australia; sampling rate 2 kHz) for calculation of the RMS values (100 ms running time window). Sharp transients and electrical activity from the heart in the SEMG signals were removed with a medianfilter (Matlab ver 6, The MathWorks inc.).

The following electrode sites were used: (1) Frontalis muscle; both electrodes placed on a vertical line crossing the pupil, 10 and 30 mm above the upper border of the eyebrow. (2) Temporal muscle; the lower electrode 10 mm posterior to the lateral canthus of the orbit, and the second electrode 20 mm above. (3) Splenius; upper electrode 35 mm laterally to the spinous process of C2 and the second electrode 20 mm below. (4) Trapezius; medial electrode 10 mm laterally to the midpoint of a line connecting the acromion and the spinous process of C7, and the second electrode 20 mm laterally to the first electrode. The ground electrode was placed on the spinous process of C7. Signals were stored with a sampling rate of 200 Hz.

2.5. Data analysis

Subjective responses (pain, tension, fatigue) were defined as the difference between the maximal rating of pain, tension and fatigue during the 60 min stress period and the corresponding ratings at baseline immediately before the start of the test. Pain responses were calculated for all locations (shoulders, neck, temples, and forehead on each side). The maximal pain response was defined as the highest pain response irrespective of location. The mean pain responses for each anatomic region (average of right and left side) were also calculated. For evaluation of the pain recovery we counted the number of subjects who did not recover to baseline pain (0 min) after 10 min (early pain recovery) and 30 min (late pain recovery) of rest for each anatomic region and for the maximal pain location.

Mean RMS values in μV for each 10-min period were calculated for the SEMG recordings. Main outcome variables for SEMG recordings were defined as: (1) SEMG before test (UIR period); (2) SEMG test mean

(mean value of the 60 min stress period); (3) SEMG after test (mean value of the 30 min rest period). Correlation analyses between SEMG and pain responses were carried out by using the pain responses corresponding to the SEMG locations (e.g. the pain response in the left temporal region with SEMG in the left temporalis muscle), using the SEMG values from before, during and after test.

2.6. Statistics

Between-group comparisons were made with Mann–Whitney tests comparing the patient groups. Wilcoxon's signed rank test was used for within-subject comparisons of response magnitudes, and for possible side differences. Difference in responder rates was evaluated with χ^2 tests in 3×2 tables and for post-hoc analysis also in 2×2 tables (Yates' correction was applied). Correlations between the different SEMG variables, and between the SEMG variables and the subjective variables were calculated using Spearman's rank order correlation. Subgroup analysis were performed with the Mann–Whitney test (within each diagnostic group). Pain, tension and fatigue scores and responses were not normally distributed and are thus reported as median values in the tables, while means have been reported in the figures.

Repeated measures analysis of variance (rANOVA) with patient group as between-subject factor, time as within subject factor and age as covariate was performed for square-root transformed EMG and pain-response data at each anatomical region, in order to get an overview of the results. Pearson correlations were computed between age and transformed pain/EMG variables.

Two-tailed *p*-values less than 0.05 were considered to be significant.

2.7. Ethics

The Regional Committee for Medical Research Ethics approved the protocol, and all participants gave written informed consent before volunteering. For transport expenses and inconvenience (total time expenditure for each participant was 4 h) participants received NOK 500 (USD 75). Experiments were performed according to the Helsinki Declaration.

3. Results

Background variables are presented in Table 1. The average age was higher for the FMS group than for the SNP group and the controls (Kruskal–Wallis test $p = 0.022$). For this reason we did also compare FMS-group to an age-matched control subgroup ($n = 23$, mean age = 45.8 years, s.d. 8.7 years, range 34–61 years). The EPQ-N score, Autonomic Symptom Index

and level of general tension were all higher for the patient groups compared to healthy controls (Kruskal–Wallis test $p < 0.005$), but FMS and SNP patients differed only in the magnitude of the Autonomic Symptom Index (FMS > SNP, Mann–Whitney test $p = 0.018$). Interestingly, FMS patients reported more habitual exercise than the other groups. FMS patients have particularly high scores on questions about sleep problems and restricted leisure time activity (Table 1). However, neither age, EPQ-N score, Autonomic Symptom Index nor general tension were correlated to the physiological variables. Furthermore, those patients who exercised more than 1 day per week did not respond differently to the stressful task than the patients with less habitual exercise (Mann–Whitney test).

Background body pain for different body regions reported in the structured interview is shown in Table 2. The two patient groups did not differ in reported neck pain but FMS patients reported more pain in the shoulder, lower back, hands and feet than SNP patients (Mann–Whitney test $p < 0.008$). Therefore, we considered responses as previously defined, to be more appropriate than absolute levels of pain, fatigue and tension when comparing the groups.

3.1. Electromyographic recordings

The SEMG results are presented in Fig. 2 and Table 3. The frontalis muscle SEMG during test was higher than before test for both patient groups and the controls (Wilcoxon test $p < 0.008$ for all groups). The trapezius muscle SEMG was higher during test than before test for the controls and the SNP group (Wilcoxon test $p < 0.001$ for both groups), but the difference did not reach significance for the FMS group (Wilcoxon test $p = 0.16$). Frontalis EMG during test was lower in FMS patients than in an age-matched control subgroup (Mann–Whitney test, $p < 0.05$; Fig. 2). We found no side differences in muscle activity, either when comparing the left and right side, or when comparing the side with the highest pain response to the side with less pain response (Wilcoxon test). ANOVA repeated measures analysis with age as a covariate revealed no differences between groups for any region (between subjects $p > 0.15$). Significant correlation between age and EMG was found in the temporal region ($p < 0.0005$), and frontal region ($p = 0.05$).

3.2. Subjective variables

The reported level of pain immediately before test was higher in both shoulders, neck, and temples for FMS compared to the SNP patients (Kruskal–Wallis test $p < 0.019$, Mann–Whitney test $p < 0.025$ for all three regions). The two patient groups also differed in baseline fatigue, but not subjective tension (Table 4).

Table 2

Body pain reported in the structured interview to the question: “Did you have bothersome pain or stiffness in muscles or joints in the specified regions during the last 6 months?” (VAS)

	Median (range)		
	Controls (<i>n</i> = 35)	Fibromyalgia (<i>n</i> = 23)	Shoulder/neck pain (<i>n</i> = 29)
Neck pain	0	59 (0–81)	50 (6–86)
Shoulder pain ^a	0	62 (29–80) ^b	45 (0–86)
Low back pain ^a	0	47 (3–100) ^b	14 (0–100)
Hand pain ^a	0	53 (0–83) ^b	3 (0–100)
Foot pain ^a	0	30 (0–85) ^b	0 (0–76)

^a Groups are different (Kruskal–Wallis test, $p < 0.05$).

^b Different from SNP patients (Mann–Whitney test, $p < 0.05$).

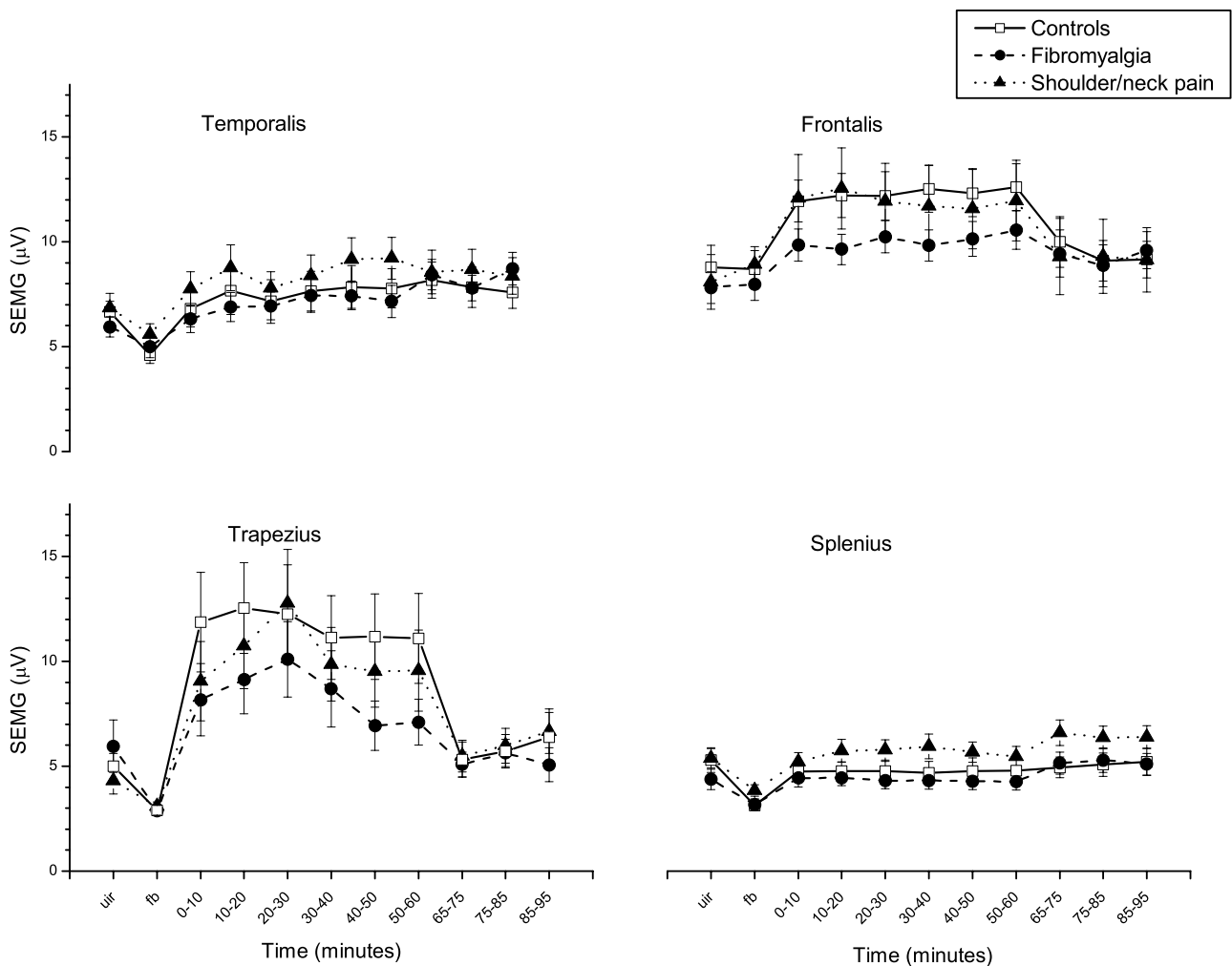


Fig. 2. Mean surface electromyographic (SEMG) amplitudes (root-mean-square values in μV), before test (uninstructed rest period = UIR; 5 min), in the feedback period (fb; 5 min), during test (0–60 min), and during the rest period (75–95 min). Error bars show \pm one standard error of the mean.

Mean pain scores are shown in Fig. 3. Median values for the subjective responses and the number of subjects responding with an increase in pain score during the stress period are presented in Table 5. We found no side differences (Wilcoxon test) and thus only the average of the right and left side is presented in the table. Pain, tension and fatigue increased during the stressful task for

all groups (Table 5). The groups were different regarding the number of subjects who increased their pain in the temples and in the maximal pain location (χ^2 tests in 3×2 tables $p \leq 0.025$), and post hoc 2×2 table analysis revealed that FMS patients responded more often than the controls (Table 5). For the SNP group and the control group, the pain responses in the trapezius and neck

Table 3
Surface electromyographic amplitudes (root-mean-square values in μV) before (uninstructed rest period), during (mean of the 60 min stress period), and after (mean of the 30 min rest period) the test

	Mean (SD)		
	Controls	Fibromyalgia	Shoulder/neck pain
<i>Trapezius</i>			
Before	5.0 (3.6)	6.0 (6.0)	4.3 (3.4)
During	11.7 (12.0) ^a	8.4 (6.8)	10.3 (9.7) ^a
After	5.8 (5.1)	5.3 (2.8)	6.0 (4.4) ^b
<i>Splenius</i>			
Before	5.3 (3.5)	4.4 (2.3)	5.4 (2.4)
During	4.8 (3.0)	4.3 (1.7)	5.6 (2.3)
After	5.1 (3.0)	5.4 (2.7)	6.5 (2.9) ^b
<i>Temporalis</i>			
Before	6.6 (3.1)	5.9 (2.3)	6.9 (3.7)
During	7.5 (5.7)	7.0 (3.2)	8.5 (4.7) ^a
After	7.9 (5.0)	8.2 (3.2) ^b	8.5 (5.1) ^b
<i>Frontalis</i>			
Before	9.4 (7.2)	8.6 (5.0)	8.5 (6.1)
During	13.3 (7.7) ^a	10.8 (4.5) ^a	12.7 (9.1) ^a
After	10.5 (7.2)	10.2 (6.1) ^b	9.7 (7.0)

Values are the average of the right and left sides.

There were no significant differences between the groups (Kruskal–Wallis test).

^a significant difference during test versus before test, $p < 0.05$ (Wilcoxon test).

^b significant difference after test versus before test, $p < 0.05$ (Wilcoxon test).

Table 4
Pain, tension and fatigue immediately before the stressful task (VAS)

	Median (range)		
	Controls ($n = 35$)	Fibromyalgia ($n = 23$)	Shoulder/neck pain ($n = 29$)
Shoulder pain ^a	0.0 (0–10)	18.0 (0–57) ^{b,c}	5.0 (0–43) ^b
Neck pain ^a	0.0 (0–19)	19.0 (0–60) ^{b,c}	6.5 (0–66) ^b
Temples pain ^a	0.0 (0–10)	2.5 (0–100) ^{b,c}	0.0 (0–20)
Forehead pain	0.0 (0–9)	0.0 (0–100)	0.0 (0–26)
Fatigue ^a	0.0 (0–74)	7.0 (0–51) ^{b,c}	0.0 (0–82)
Tension ^a	0.0 (0–43)	9.0 (0–82) ^b	3.5 (0–70)

^a Groups are different (Kruskal–Wallis test, $p < 0.05$).

^b Different from controls (Mann–Whitney test, $p < 0.05$).

^c Different from SNP patients (Mann–Whitney test, $p < 0.05$).

regions were higher than the pain responses in the forehead (Table 5). In contrast, for the FMS patients, the pain responses were not different in the various anatomic regions, indicating a more generalised pain response in this patient group (Table 5).

Both patient groups recovered less (i.e. more slowly) from the induced pain than the healthy controls (Fig. 4). The percentage of subjects without late pain recovery was generally higher for both patient groups compared to controls, indicating less pain recovery in the rest period for patients (Table 6). Although not visible in the figures which present the average pain level

(Fig. 3) and average pain response (Fig. 4) except for FMS group in the neck region, some subjects actually report more pain after 30 min of rest than after 10 min of rest (Table 6). The difference in pain recovery between SNP patients and controls was more evident after 10 min of rest than after 30 min of rest, while the difference in recovery between FMS patients and controls was most evident after 30 min. However, there was no difference in pain recovery between the FMS and SNP patients for any location. Those subjects without pain recovery (either early or late) did not differ from the subjects with pain recovery regarding background variables and muscle activity (Mann–Whitney tests performed separately for each diagnosis group).

The maximal pain response correlated better with both the fatigue response ($r_{\text{SFMS}} = 0.50$, $p = 0.016$; $r_{\text{SNP}} = 0.49$, $p = 0.009$) and the tension response ($r_{\text{SFMS}} = 0.52$, $p = 0.011$; $r_{\text{SNP}} = 0.59$, $p = 0.001$) for the patient groups than for the healthy control group ($r_s = 0.18$, $p = 0.30$ and $r_s = 0.17$, $p = 0.33$, respectively).

ANOVA repeated measures analysis with age as a covariate revealed no differences between groups regarding the development of pain in any region (time \times diagnosis $p > 0.37$). Furthermore, age did not affect pain development ($p > 0.31$). Within group correlation between age and pain variables were not significant in FMS and control subjects. In SNP-patients neck pain response increased with age ($r = 0.38$, $p = 0.04$).

Categorical pain and recovery responses in FMS patients were also compared with responses in the age-matched control subgroup. Results were generally unchanged (Tables 5 and 6).

3.3. Correlation between subjective complaints and electromyography

Associations between SEMG and the subjective variables were explored by comparing SEMG before test, SEMG test mean, and SEMG after test, both with pain responses at the corresponding locations and with the maximal pain response irrespective of location. Muscular activity did not correlate with the subjective variables pain, tension, or fatigue, with the exception of the temporalis muscle SEMG during test for the FMS group which correlated with the tension response ($r_s = 0.65$, $p = 0.0007$).

4. Discussion

The stressful task induced pain and muscular activity in both FMS and SNP patients. FMS patients had a more generalised pain response than SNP patients. More FMS patients responded with pain during test compared to controls, while delayed pain recovery was observed in both FMS and SNP patients. However,

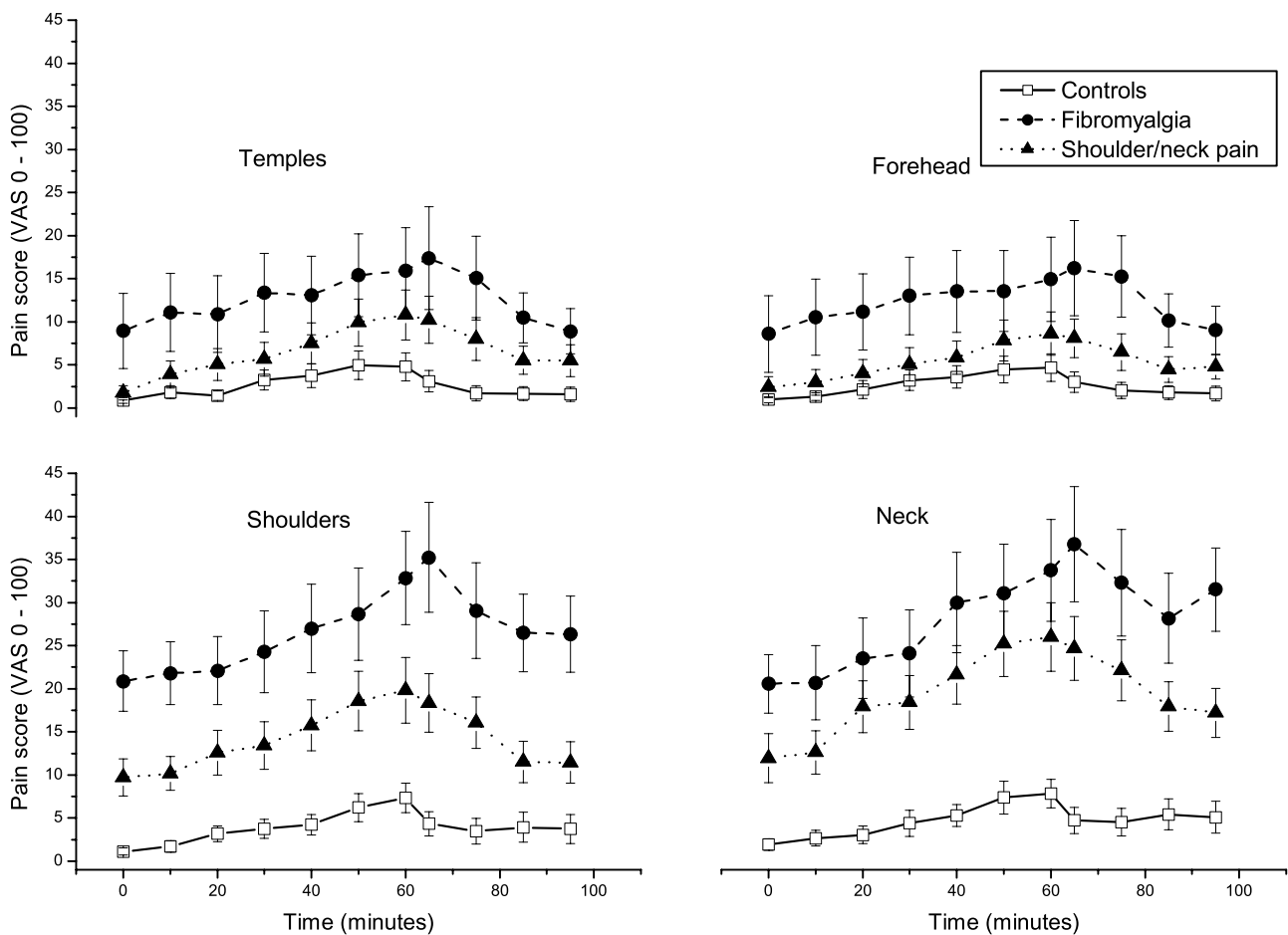


Fig. 3. Mean pain ratings scored on a visual analogue scale (VAS) 0–100 mm, reported every 10th minute immediately before (0 min), during the stress period (10–60 min), after the venipuncture (65 min) and during the rest period (75–95 min). Error bars show \pm one standard error of the mean (SEM).

the magnitude of the muscular response did not differ significantly between groups. Furthermore, the pain, tension and fatigue responses to the stressful task were not related to muscular activity for any group.

The first objective of the present study was to compare muscular and subjective responses to low-grade stress in patients with FMS, patients with SNP and healthy controls. The pain responses were more widespread in the FMS group than in the SNP group and more FMS patients developed pain during the stressful task than controls. However, none of the groups were different regarding the magnitude of the pain responses.

Surface-recorded muscular activity was not enhanced compared to controls in either pain syndrome. This is in accordance with another study on FMS patients investigating the muscular response to a stressful task (Svebak et al., 1993), but contrast the finding of Bansevicius et al. (2001) on FMS patients who found increased EMG activity in the neck muscles compared to healthy controls using a study design similar to the present study. The FMS group did not respond significantly with increased muscle activity in the trapezius muscle to the

stressful task. This contrasts with the study of Bansevicius et al. who found an increase in EMG activity during test relative to pretest only for the trapezius muscle. Inactivation of muscle activity as a response to pain (Lund et al., 1991) is one possible explanation for this finding. Relatively high basal EMG in FMS patients may also explain why the moderate EMG-increase during test did not reach statistical significance. A type II error is another probable explanation.

Various authors have investigated muscular activity in FMS patients with electromyography. Both increased (Elert et al., 1989, 1992, 2001; Donaldson et al., 2002a,b), reduced (Jacobsen and Danneskiold-Samsøe, 1987, 1992; Bäckman et al., 1988; Mengshoel et al., 1990; Jacobsen et al., 1991; Lindh et al., 1994; Nørregaard et al., 1994, 1997; Vestergaard-Poulsen et al., 1995) and normal (Zidar et al., 1990; Stokes et al., 1993; Mengshoel et al., 1995; Miller et al., 1996; Häkkinen et al., 2000, 2001, 2002; Valkeinen et al., 2004) muscular activity has been found. However, the vast majority of studies are on voluntary muscle work and not on the muscular response to a mental stressor. A

Table 5
Subjective pain, tension and fatigue responses^a reported on a visual analogue scale (VAS) 0–100 mm and the number and percent of subjects who reported a pain response > 0

Response variable	Controls (<i>n</i> = 35)		Fibromyalgia (<i>n</i> = 23)		Shoulder/neck pain (<i>n</i> = 29)	
	Median VAS (Range)	Responses > 0 <i>n</i> (%)	Median VAS (Range)	Responses > 0 <i>n</i> (%)	Median VAS (Range)	Responses > 0 <i>n</i> (%)
Shoulder pain response	3.5 (0–39) ^e	21 (60%)	6.0 (–7 to 82)	14 (61%)	6.0 (–12 to 60) ^e	21 (75%)
Neck pain response	4.0 (–1 to 39) ^e	19 (54%)	11.5 (–6 to 57)	16 (70%)	12.0 (–18 to 65) ^e	22 (79%)
Temples pain response ^c	0 (–1 to 38)	11 (31%)	6.5 (–3 to 47)	16 (70%) ^{d,f}	1.0 (0–47)	15 (54%)
Forehead pain response	0 (0–30)	14 (40%)	5.5 (–7 to 45)	14 (61%)	0 (–3 to 43)	13 (46%)
Maximal pain response ^b	10.0 (0–57)	24 (69%)	21.0 (0–88)	22 (96%) ^{d,f}	23.0 (0–67)	25 (89%)
Fatigue response	22.0 (–2 to 78)	30 (86%)	20.0 (–11 to 89)	19 (83%)	27.0 (–18 to 73)	20 (71%)
Tension response	19.0 (–5 to 83)	31 (89%)	26.0 (–3 to 82)	22 (96%)	23.0 (–6 to 70)	22 (79%)

All responses are significant ($p < 0.003$; Wilcoxon intra group comparison).

^a Responses are defined as the difference between the maximal level during test and the level before test. The localized pain responses corresponds to electromyography recording sites (mean of left and right side).

^b The maximal pain response is the highest response irrespective of location.

^c Different between groups (χ^2 tests in 3×2 tables $p \leq 0.025$).

^d Different from controls (χ^2 tests with Yates' correction in 2×2 tables $p \leq 0.031$).

^e Different from forehead values, $p < 0.05$ (Wilcoxon intra group comparison).

^f FMS vs age-matched control subgroup (χ^2 test with Yates correction $p < 0.05$).

recent editorial article with a short review of the literature on FMS and muscle pathology concludes that there is a defect not seen at rest or submaximal load, but evident under maximal load and static contraction (Bengtsson, 2002).

Development of musculoskeletal pain during stress was not related to muscular activity for either FMS patients, SNP patients or controls. Bansevicius et al. (2001) investigated fibromyalgia patients and found a generalised pain response unrelated to SEMG in all investigated muscle groups except for the trapezius muscle. It must be noted that it is the low trapezius SEMG activity among the controls in the study of Bansevicius et al. that is the main difference from the present results, and the correlation between pain development and trapezius SEMG in FMS found by Bansevicius et al. was weak. The differing results may be explained by the fact that Bansevicius et al. (2001) used median SEMG values in the analysis while we have used mean SEMG values. Furthermore, in the study of Bansevicius et al. the investigator was not blinded to the diagnosis of the subjects. Thus we conclude that the pain which develops in FMS and SNP patients during a stressful task is generally not related to the simultaneously observed muscle activity.

Various models for a causal relationship between muscle activity and musculoskeletal pain have been hypothesised. For example, Johansson and Sojka (1991) proposed a model for a vicious circle where metabolites and low pH from muscle activity cause increasing muscle activity by sensitising muscle spindles (Johansson and Sojka, 1991). However, as concluded in several reviews (Simms, 1996; Westgaard, 1999; Knardahl, 2002) and further corroborated by the results of the present study, it is difficult to find support for a potential causal relationship between stress-related musculoskeletal pain and surface recorded low-grade muscle activity. Still, the possibility exists that exhaustion of small groups of motor units, too small to be detected by SEMG recordings (Hägg, 1991) or dysfunction in the pattern of motor unit recruitment and de-recruitment (Westad et al., 2003), may serve as mechanisms for musculoskeletal pain. However, several authors have proposed that more research effort should be directed to causal factors other than those related to muscle activity or muscle pathology (Lund et al., 1991; Simms, 1996; Rø, 2000; Knardahl, 2002).

Another objective of the present study was to relate subjective reports of fatigue and tension to muscular activity. Although we found the change in perceived tension during test (tension response) to be correlated with temporalis SEMG during test in the FMS group, the present study did not indicate that subjectively reported tension is generally associated with muscular activity. Earlier reports have shown equivocal associations between SEMG and subjectively reported tension (Vasseljen and Westgaard, 1996; Kendall et al., 2002;

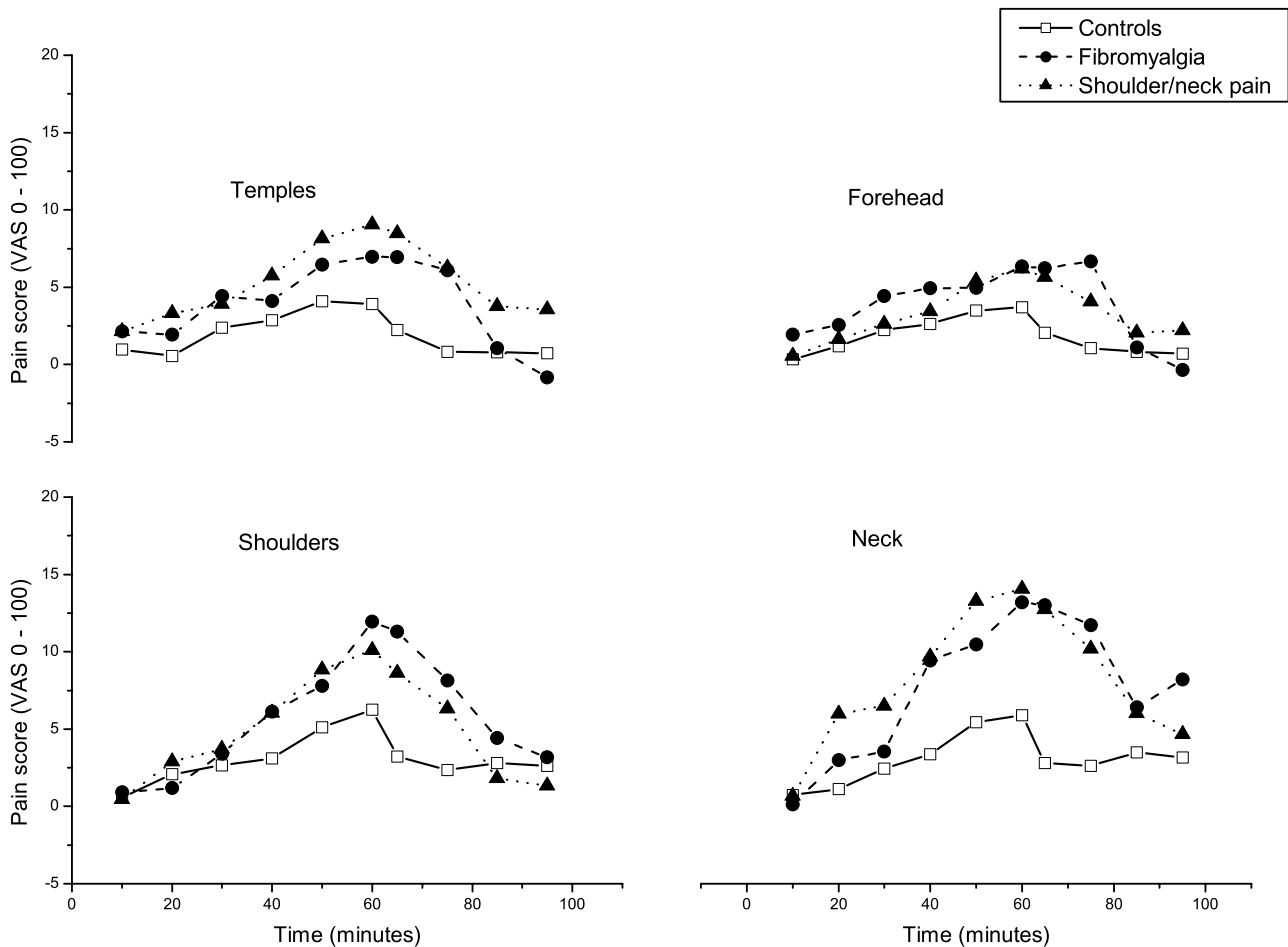


Fig. 4. Mean differential pain ratings. Pain reported at start (0 min) was subtracted from the pain scored during the stressful task and in the rest period. Pain was scored on a visual analogue scale (VAS) 0–100 mm, reported every 10th minute immediately before (0 min), during the stress period (10–60 min), after the venipuncture (65 min) and during the rest period (75–95 min). Note that both patient groups recovered more slowly than the healthy controls (from 60 min). For visual clarity the error bars are not shown.

Holte et al., 2003). Interestingly, a recent paper describes a higher trapezius SEMG activity during ordinary work in subjects who reported a feeling of muscular tension at least a few times per week the past month, compared to subjects who reported less muscular tension (Wahlström et al., 2003). Moreover, we found that the tension response was associated with development of pain, suggesting that in the present model perceived tension is more closely related to the mechanisms responsible for pain development than to muscle activity.

The groups did not differ regarding the perceived tension response. Although subjects did not report perceived stress explicitly, we believe the stress task was equally stressful for all groups as perceived tension has been reported to reflect perceived stress including both autonomic responses and the specific muscular response of perceived elevation of shoulders (Holte et al., 2003).

The fact that our FMS patients exercise more than the other groups is probably a result of our recruitment protocol (patients were referred from primary care and physiotherapists). TCA-users were excluded and the

FMS patient group is accordingly “selected” in this sense, probably representing a rather well-functioning FMS-subpopulation.

Performance of the stressful task (reaction time and/or the rate of correct answers) was not measured in the present study because we have previously observed that the level of performance does not influence the muscular response in this model unless a money-reward for high performance is promised (Wærsted et al., 1994). We cannot exclude that the level of performance affect perceived stress/tension or fatigue, but since the groups did neither differ in tension nor fatigue responses, both stress task and (most likely) stress load was probably similar between groups.

Although the second venipuncture had the potential to add some stress, reported tension were unchanged in both patients groups (from median VAS 31 to 30, $p = 0.51$ in FMS and from median VAS 24.5 to 23, $p = 0.15$ in SNP patients). The procedure was the same for all groups, and blood sampling was very short lasting compared to the rest of the experiment. Although

Table 6
Early (after 10 min rest) and late (after 30 min rest) pain recovery^a

	No recovery <i>n</i> (%)		
	Controls (<i>n</i> = 35)	Fibromyalgia (<i>n</i> = 23)	Shoulder/neck pain (<i>n</i> = 29)
<i>After 10 min rest (early recovery)</i>			
Shoulder ^c	9 (26%)	10 (43%)	17 (59%) ^d
Neck	13 (37%)	12 (52%)	19 (66%) ^d
Temples ^c	5 (14%)	12 (52%) ^{d,f}	12 (41%) ^d
Forehead ^c	6 (17%)	13 (57%) ^{d,f}	10 (34%)
Maximal pain location ^b	13 (37%)	14 (61%)	19 (66%) ^d
<i>After 30 min rest (late recovery)</i>			
Shoulder	11 (31%)	11 (52%)	12 (43%)
Neck	15 (43%)	15 (71%) ^{e,g}	17 (61%)
Temples	6 (17%)	9 (43%) ^e	10 (36%)
Forehead ^c	5 (14%)	10 (48%) ^{d,f}	11 (39%) ^d
Maximal pain location ^b	15 (43%)	16 (76%) ^{e,f}	19 (68%) ^e

Numbers and percents of subjects *not* recovering have been tabulated.

Two fibromyalgia patients and one shoulder/neck pain patient did not complete the rest period.

^a Recovery is defined as return to baseline values.

^b The number of subjects not recovering from the pain in the location with the highest pain response.

^c Different between groups (χ^2 tests in 3×2 tables, $p \leq 0.05$).

^d Significantly different from controls (χ^2 tests with Yates' correction in 2×2 tables, $p < 0.05$).

^e Trend towards difference from controls (χ^2 tests with Yates' correction in 2×2 tables, $0.05 \leq p < 0.085$).

^f FMS vs age-matched control subgroup (χ^2 test with Yates correction. $p < 0.05$).

^g FMS vs age-matched control subgroup (χ^2 test with Yates correction. $p < 0.10$).

we cannot exclude that a part of the response was modified by the blood test, this effect is probably small and short-lasting.

Bansevicius and co-workers (Bansevicius et al., 2001) found that the pain response to low-grade stress in FMS patients continued after termination of the stressful task, but did not analyse or discuss the phenomenon. In the present study, we analysed the recovery period more thoroughly and observed that both patient groups showed less pain recovery in the rest period than the control group. This observation may relate to the findings of prolonged aftersensations after windup of second pain in FMS patients by Staud et al. (2001, 2003, 2004), which have been interpreted as a sign of central sensitisation. Regardless of the reason for the sensitisation process (repetitive pain stimuli, stress, nerve damage, etc.) the present study indicate that also pain experienced in a situation simulating repetitive office-work show a pattern which may be compatible with central sensitisation. Further studies are needed to elucidate if pain induced by cognitive low-grade stress in musculo-skeletal pain patients exhibits other characteristics of central sensitisation (like hyperalgesia and allodynia) and to elucidate how low-grade stress of long duration affects pain modulation in humans. The possibility of attentional bias towards pain and somatic sensations (Brosschot, 2002) and sympathetically maintained pain should also be investigated further (Jänig and Häbler, 2000).

Pain recovery can be measured in different ways. Our choice of a categorical pain recovery variable (recovery: yes or no) is a conservative approach. This variable is in

our opinion less sensitive, but it is presumably more robust than a scaled variable (e.g. the absolute difference between pain at 75 min and pain at 0 min). Furthermore, it may be argued that pain change (response and recovery) should be evaluated on a logarithmic scale (or % change). This was not possible because many subjects (particularly controls) were without pain at baseline and after the recovery period.

We believe that the low-grade and long-lasting stress induced in the present study is comparable to work-related stress. However, it must be noted that laboratory experiments can never substitute real-life experiments. The fact that in the present study, both the laboratory investigations and the following data reduction were done without knowledge of the patient/control status of the participant strengthens the conclusions of the study.

In conclusion, with a blinded study design, FMS and SNP patients did not differ in muscular or subjective responses to low-grade mental stress of 60 min duration. Muscle activity measured by surface electromyography generally did not correlate with the induced pain, tension and fatigue during the stressful task for either group. Pain lasted longer in both FMS and SNP patients compared to healthy controls, possibly as a result of disease-related sensitisation in pain pathways.

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Paper III:

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Autonomic activation and pain in response to low-grade mental stress in fibromyalgia
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Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients

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Abstract

Objective: Psychosocial stress is a risk factor for musculoskeletal pain, but how stress affects musculoskeletal pain is poorly understood. We wanted to examine the relationship between low-grade autonomic activation and stress-related pain in patients with fibromyalgia and localised chronic shoulder/neck pain.

Methods: Twenty-three female patients with fibromyalgia, 29 female patients with chronic shoulder–neck pain, and 35 healthy women performed a stressful task lasting 60 min. With a blinded study design, we recorded continuous blood pressure, heart rate, finger skin blood flow and respiration frequency before (10 min), during (60 min) and after (30 min) the stressful task. The physiological responses were compared with subjective reports of pain.

Results: The increase in diastolic blood pressure and heart rate in response to the stressful task were smaller in fibromyalgia patients compared with the healthy controls. Furthermore, fibromyalgia patients had reduced finger skin blood flow at the end of the stressful task compared to healthy controls. We also found an inverse relationship between the heart rate response and development and recovery of the stress-related pain in fibromyalgia patients.

Conclusion: We found abnormal cardiovascular responses to a 60 min long stressful task in fibromyalgia patients. Furthermore, we found a negative association between the heart rate response and the pain which developed during the stressful task in the fibromyalgia group, possibly a result of reduced stress-induced analgesia for fibromyalgia patients.

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Keywords: Chronic pain; Sympathetic nervous system; SIA; Central sensitisation

1. Introduction

The pathophysiology for musculoskeletal pain disorders as fibromyalgia syndrome (FMS) and localised chronic shoulder/neck pain (SNP) has not been explained. It has been difficult to find a causal relation-

ship between pain development and muscle pathology or muscle activity in these disorders, and human models exploring hypotheses not related to muscle activation are wanted (Lund et al., 1991; Simms, 1996; Westgaard, 1999; Røe, 2000; Knardahl, 2002).

Psychosocial stress seems to be a risk factor for musculoskeletal pain (Linton, 2000; van der Windt et al., 2000; Ariëns et al., 2001; Bongers et al., 2002), but the mechanism by which stress is related to pain is poorly

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understood. Abnormalities in sympathetic nervous system function have been reported for FMS patients (e.g. van Denderen et al., 1992; Martínez-Lavín et al., 1997; Bou-Holaigah et al., 1997; Martínez-Lavín et al., 1998; Kelemen et al., 1998; Torpy et al., 2000; Cohen et al., 2000; Petzke and Clauw, 2000; Cohen et al., 2001). However, it is not known how sympathetic activation affects musculoskeletal pain during low-grade stress. In FMS patients, both a positive (Martínez-Lavín et al., 2002) and an inverse relationship (Okifuji and Turk, 2002) between sympathetic activity and pain has been hypothesised.

Chronic pain in the shoulder and neck region is highly prevalent (Picavet and Schouten, 2003). The pain distribution in SNP patients is by definition more localised than in FMS patients and a clear differentiating criterion. However, a noted similarity between the two patient groups is that pain is worsened by mental stress (Bansevicius et al., 2001; Holte and Westgaard, 2002; Van Houdenhove and Egle, 2004). In the present study we wanted to examine the relationship between mental stress-induced autonomic activation and pain in patients with FMS, in patients with chronic SNP and in healthy controls. We used a laboratory model with a low-grade stressful task previously proven to induce pain in healthy controls (Bansevicius et al., 1997) and patients with FMS (Bansevicius et al., 2001), tension type headache (Bansevicius et al., 1999), cervicogenic headache (Bansevicius and Sjaastad, 1996) and migraineurs (Leistad et al., 2006). Our intention was to establish a setting which is close to stressful and repetitive real office-work.

The following questions were addressed: (1) Is the sympathetic response to the low-grade stressful task in FMS patients and chronic SNP patients (a) different from healthy controls, and (b) different when comparing the two patient groups? (2) Can the response in the autonomic nervous system be related to (a) the pain response during the stressful task, or (b) the ability to recover from pain after the stressful task?

With a blinded study design we investigated autonomic responses together with development of pain during 60 min of low-grade stress, and in the following 30 min rest period, comparing FMS patients, SNP patients, and healthy controls. Physiological measurements included heart rate, continuous blood pressure, finger skin blood flow, and respiration frequency together with determination of catecholamine levels in venous blood before and after the stress period.

2. Methods

2.1. Subjects

Twenty-three female FMS patients (mean age 39.7 years, range 21–61 years), 29 female patients with chronic SNP (mean age 48.3 years, range 32–63 years) and 35

healthy women as controls (mean age 41.1 years, range 19–59 years) participated in the study ($F(2,86) = 4.7$, $p = 0.012$; posthoc: FMS/controls $p = 0.011$, SNP/controls $p = 0.85$, FMS/SNP $p = 0.053$). More detailed subject characteristics are presented elsewhere (Nilsen et al., 2006). Patients were mainly referred from primary care centres and physiotherapists. Controls were recruited from public institutions and private companies in Trondheim and they answered specific pain-related questions in a structured interview. Sporadic or situation-related minor headache and/or muscle aches were allowed in the control group because of the universal occurrence of such symptoms. Subjects who described their symptoms as unpleasant but not as bothersome pain were only excluded as healthy controls if two of the following three conditions were fulfilled: (1) symptoms occurred for more than one day per month, (2) the person had visited a physician for the complaint, and (3) usually took medication for the complaint. Subjects who considered their headache or pain to be more than “unpleasant” (i.e. bothersome pain) were not accepted as controls if at least one of the three conditions above was fulfilled.

Inclusion criteria for all participants were: (1) adults aged 18–65 years and (2) submitted written informed consent. FMS patients were included if they fulfilled the 1990 American College of Rheumatology Criteria (ACR criteria) for fibromyalgia (Wolfe et al., 1990). SNP patients were included if they reported chronic shoulder/neck pain (more than 3 months during the previous year) with local tenderness or triggerpoints. SNP patients were included even if they reported pain also from other body regions, but pain in the shoulder and neck region had to be their main problem. No SNP patients fulfilled the ACR criteria for fibromyalgia.

Patients were excluded if they had: (1) neoplastic disease; (2) high blood pressure or were taking anti-hypertensive medication; (3) infectious disease, including those who had caught a cold with fever, cough or muscle pain; (4) metabolic, endocrine or neuromuscular disease; (5) connective tissue disorder; (6) tendinitis or capsular affection of the shoulder joint; (7) recent accident or injury affecting function; (8) symptomatic heart disease or were taking medication for any vascular disease; (9) lung disease affecting function or were taking medication for such; (10) cerebrovascular disease; (11) chronic neurological disease; (12) or if headaches were a major part of the pain syndrome; (13) or if they were taking any medicament with a possible interaction on neural, vascular or muscular function (e.g. antiepileptics, β -blockers, or antidepressants).

2.2. Procedure

All subjects first went through a short telephone interview. Eligible patients went through a detailed interview and examination by one specialist in physical

medicine and rehabilitation (Magne Rø). Patients and controls not excluded by this initial screening received written information on the study background, and a questionnaire on background data, less than two weeks before the test day. After a short interview on the morning of the test day, venous blood was sampled from the right cubital fossa. Subjects emptied the bladder before starting the test. Brassieres were removed and subjects wore only a light shirt on the upper part of the body. The laboratory temperature was regulated to 24.5 ± 1 °C.

The subjects were seated in an office chair with the forearms resting on the table top before, during and after the test. Subjects got acquainted to the work-task by performing a mini-trial with instructions before the test started. The mini-trial was performed before introducing the stress-imposing feedback on reaction time and was used to determine the subjects' habitual, non-stressed reaction time. Short maximal voluntary contractions were performed on each pair of muscles twice (frontalis muscle – raising eyebrows, temporalis – clenching teeth, neck – pushing head back against resistance, trapezius – pushing extended arms upwards against resistance at 45° angle out from the body). In order to measure the subjects habitual level of physiological activation the laboratory experiment started with a 5 min period which served as a basis for the evaluation of physiological responses during the test and the subsequent rest period. The subjects were alone in the room and were not given any instructions other than to find a comfortable position with their arms resting on the table in front of them (uninstructed rest; "UIR"). A 5 min feedback ("FB") period with muscular activity visualised on a screen followed. The subject experienced how it was possible to influence the level of muscle activity by adopting different postures and thereafter concentrated on minimising any muscle activity. The stressful task (Westgaard and Bjørklund, 1987) was then presented: a two-choice reaction-time test on a monitor, lasting 1 h. An open ("frame") and a solid ("brick") quadrangle were placed in a square pattern, and a written suggestion on how to move the brick to superimpose on the frame was given. The subject responded by pressing one of two keys ("correct" or "wrong"), with the right middle or index finger. The test was to be carried out as quickly and correctly as possible. The PC program provided feedback on whether an answer was correct or wrong, and on the response time (very slow, slow, normal, fast, very fast), related to the subject's performance in the mini-trial carried out before the experiment started (Wærsted et al., 1994). Together with the feedback a new task was presented. After the end of the stressful task, all measurements continued for 30 min. The test person was instructed to sit still and relax during the rest period with unchanged posture; i.e. arms

resting on the table. Pain, tension and fatigue were reported every 10 min before, during, and after the test by scoring on a 100 mm visual analogue scale (VAS), with the endpoints marked no pain and worst imaginable pain. The subjects were asked to assess pain in the shoulders, neck, temples and forehead on both sides. The subjects were not allowed to see previous records when scoring.

A second blood sample was drawn immediately after the test, before the 30 min rest period. The laboratory personnel were blinded as to the diagnosis (control, FMS or SNP) of the subjects, and the subjects were instructed not to disclose their diagnostic status. All data reduction was made without knowledge of diagnostic status of the subjects.

2.3. Physiological recordings

Activity in the autonomic nervous system was assessed by measurements of continuous non-invasive finger blood pressure (Portapres, TNO Biomedical Instrumentation, Amsterdam, The Netherlands) (Imholz et al., 1993), finger skin blood flow with Laser-Doppler flowmetry (Moorlab, 4 channels, time constant 0.02 s, low-pass filter 22 kHz; Moor Instruments Ltd, Devon, England), and respiration with a thermistor (Embla S-AF-010, Flaga, Reykjavik, Iceland) below the nose with active elements in each nostril and in front of the mouth. The blood pressure cuffs were mounted on the intermediate phalanx of the left middle and ring fingers. Finger skin blood flow was measured bilaterally with the laser-doppler electrodes (fibre separation 0.5 mm) placed on the volar side of the distal phalanx (pulp) of the thumb. Signals were sampled at 200 Hz. Respiration frequency was calculated by the Chart 4.2 software (ADInstruments Pty Ltd, Sydney, Australia). Heart rate and blood pressure were calculated with the Beatscope 1.0 software (TNO, Amsterdam, the Netherlands) (Wesseling et al., 1993). Room temperature was measured every 10th minute with a logging thermometer with an accuracy of ± 0.2 °C (Digitron 2088 T, Digitron Instrumentation Ltd, Devon, England).

2.4. Biochemical analysis

Blood was collected into EDTA-vacutainers and immediately placed in ice-water or into vacutainers without an anti-coagulant. Non-coagulated blood was centrifuged within 10 min at 300g to obtain platelet-rich plasma (PRP). After withdrawing an adequate sample of PRP for catecholamine analysis and platelet counting, samples were centrifuged again for 10 min at 3000g to obtain platelet-poor plasma (PPP). Serum was collected after 30 min coagulation, by centrifugation at 1500g, 10 min, at room temperature. All samples

were stored at -80°C prior to analysis. Plasma catecholamines were extracted by adsorption to aluminium oxide (Smith et al., 1985) and analysed by HPLC (Merck Hitachi LaChrom system, Darm-Stadt, Germany) with electrochemical detection. Catecholamines were separated on a LiChroCART LiChrospher 100 RP-18 250-4 column (Merck, Darm-Stadt, Germany) using sodium acetate buffer (pH 4.8) and methanol (8.5 vol%) as eluents (Candito et al., 1996). Enzymatic degradation of adrenaline in platelet-rich plasma leading to lower values than in platelet-poor plasma (Pintar and Breakefield, 1982) could not be ruled out and the results are not reported here. Cortisol concentrations in serum samples were determined using a competitive enzyme immunoassay kit designed to measure cortisol in serum (R&D Systems, Abingdon, United Kingdom). Serum samples were diluted 8-fold, processed and analysed by absorbance reading at 405 nm, according to the manufacturer's procedure.

3. Analysis

Mean values for each 10-min period were calculated for all physiological recordings. The time-course of the physiological response to the stress was further characterised by three test – baseline summary-variables for each modality; early response (the difference between the mean of the first 10 min of the stressful task and the mean of the UIR period), late response (the difference between the mean of the last 10 min of the stressful task and the mean of the UIR period), and average response (the difference between the average of the whole stressful task and the mean of the UIR period). We found no side \times group effect for the finger skin blood flow neither when comparing the left and right side ($F_{11}(2, 82) = 1.78$ $p = 0.175$) or when comparing the most painful side with the contralateral side ($F_{11}(2, 66) = 3.19$, $p = 0.728$), and thus only the average values of the right and left side are reported.

Pain, tension and fatigue responses were defined as the difference between the maximal value during the 60 min stress period and the value reported immediately before starting the test (0 min). Regional pain responses were defined as the response on the most painful side in that region. The highest pain response irrespective of location was defined as the maximal pain response. The relationship between physiological responses and pain recovery was evaluated by categorizing in two subgroups; those subjects who did recover to baseline (0 min) pain after the 30 min rest period in the anatomic location with the highest pain response, and those who did not. Calculations of heart rate and blood pressure responses were not possible on two healthy controls and four SNP patients because of technical problems and the respiration signal was corrupted in seven

healthy controls, one FMS patient and two SNP patients.

3.1. Statistics

Between-group comparisons were done with the ANOVA repeated measurements technique with time as within-subject factor (eleven different time intervals) and patient groups as between-subjects factor (group) if not otherwise specified explicitly. To evaluate the response during the stressful task and the development in the recovery period more specifically we also performed ANOVA repeated measures with seven intervals (baseline and 0–60 min) and three intervals (65–95 min). When the group factor was significant we applied three two-group posthoc ANOVAS (controls vs. FMS, controls vs. SNP, FMS vs. SNP). The response to the stressful task was further evaluated with one-way ANOVA with posthoc Tukey test on the response variables (test – baseline). When analysing for side differences side was included as an additional within-subject factor. ANOVA repeated measures with pain recovery as between-subjects factor was also performed for each patient group.

The average age was higher for the FMS group than for SNP group and the controls (see subjects section), and therefore we corrected for age in all ANOVA models.

For within-subject comparisons of response magnitudes we used paired Student's *t*-test for normally distributed data (physiological variables) and Wilcoxon's signed rank test for non-normally distributed data (subjective variables). Correlation coefficients for the relationship between the physiological response variables and the pain response were calculated with Spearman's rank order correlation. Interval estimates (95% confidence intervals) of the correlation coefficients was calculated with StatXact 7 (Cytel Software Corporation). All other analysis was performed with SPSS 14. Two-tailed *p*-values less than 0.05 were considered to be significant.

4. Results

All physiological and biochemical measures are summarised in Table 1. Responses relative to baseline (UIR) are reported in Table 2 (physiological data) and in Table 3 (subjective data).

4.1. Baseline

When comparing the baseline values for the different physiological recordings the SNP group had a higher respiration frequency before test than the controls ($p = 0.031$, posthoc: SNP/controls $p = 0.035$; SNP/FMS $p = 0.10$, FMS/controls $p = 0.96$), but the groups

Table 1
Physiological and biochemical interval parameters

ANOVA test statistics ^a time × group interaction		Controls Mean (SD)	Fibromyalgia Mean (SD)	Shoulder/neck pain Mean (SD)
Heart rate (beats/min) $F_1(2, 77) = 0.55, p = 0.58$ $F_{11}(20, 730) = 2.86, p < 0.001$ $F_7(12, 450) = 3.09, p < 0.001$ $F_3(4, 156) = 0.51, p = 0.73$	Baseline	71 (9)	72 (6)	73 (10)
	Feedback	70 (9)	71 (6)	72 (10)
	0–10 min	75 (11)	73 (7)	74 (9)
	10–20 min	74 (10)	73 (6)	74 (9)
	20–30 min	73 (9)	73 (7)	73 (9)
	30–40 min	72 (9)	73 (6)	74 (9)
	40–50 min	72 (9)	72 (6)	74 (9)
	50–60 min	72 (9)	72 (6)	73 (10)
	65–75 min	69 (8)	71 (6)	72 (10)
	75–85 min	69 (8)	70 (6)	71 (10)
85–95 min	69 (8)	70 (6)	71 (9)	
Systolic blood pressure (mmHg) $F_1(2, 77) = 0.55, p = 0.58$ $F_{11}(20, 720) = 1.87, p = 0.26$ $F_7(12, 450) = 1.29, p = 0.22$ $F_3(4, 154) = 0.73, p = 0.57$	Baseline	111 (16)	109 (16)	109 (23)
	Feedback	112 (16)	109 (17)	110 (21)
	0–10 min	127 (18)	118 (18)	121 (22)
	10–20 min	123 (17)	118 (20)	119 (23)
	20–30 min	123 (16)	121 (22)	120 (22)
	30–40 min	124 (16)	122 (18)	121 (20)
	40–50 min	124 (15)	122 (20)	122 (20)
	50–60 min	125 (16)	124 (19)	125 (20)
	65–75 min	123 (15)	122 (16)	123 (18)
	75–85 min	122 (15)	119 (18)	121 (23)
85–95 min	124 (15)	121 (17)	126 (16)	
Diastolic blood pressure (mmHg) $F_1(2, 77) = 2.33, p = 0.10$ $F_{11}(20, 720) = 2.06, p = 0.004$ $F_7(12, 450) = 1.86, p = 0.037$ $F_3(4, 154) = 0.66, p = 0.62$	Baseline	63 (12)	58 (10)	60 (13)
	Feedback	64 (11)	60 (9)	62 (12)
	0–10 min	73 (14)	65 (12)	67 (12)
	10–20 min	71 (12)	64 (10)	67 (12)
	20–30 min	71 (11)	67 (11)	67 (13)
	30–40 min	72 (11)	68 (10)	69 (11)
	40–50 min	71 (10)	67 (9)	69 (11)
	50–60 min	72 (10)	68 (10)	70 (12)
	65–75 min	72 (9)	70 (9)	70 (10)
	75–85 min	70 (9)	67 (10)	68 (15)
85–95 min	72 (9)	69 (9)	72 (10)	
Respiration frequency (breaths/min) $F_1(2, 72) = 3.64, p = 0.031$ $F_{11}(20, 710) = 0.59, p = 0.92$ $F_7(12, 432) = 2.38, p = 0.99$ $F_3(4, 142) = 0.82, p = 0.51$	Baseline	15 (3)	15 (3)	17 (3)
	Feedback	15 (2)	16 (3)	17 (3)
	0–10 min	17 (3)	15 (3)	18 (4)
	10–20 min	16 (3)	15 (2)	18 (4)
	20–30 min	16 (2)	16 (3)	18 (4)
	30–40 min	16 (3)	16 (3)	18 (4)
	40–50 min	16 (3)	16 (3)	18 (4)
	50–60 min	16 (3)	15 (3)	18 (5)
	65–75 min	14 (2)	14 (3)	16 (4)
	75–85 min	14 (2)	14 (3)	16 (4)
85–95 min	14 (3)	15 (2)	17 (3)	
Finger skin blood flow (arbitrary units) $F_1(2, 83) = 0.14, p = 0.87$ $F_{11}(20, 810) = 1.11, p = 0.33$ $F_7(12, 498) = 2.02, p = 0.021$ $F_3(4, 162) = 2.42, p = 0.051$	Baseline	277 (122)	275 (95)	290 (100)
	Feedback	305 (128.1)	278 (91.8)	298 (91.5)
	0–10 min	238 (129)	230 (95)	253 (87)
	10–20 min	240 (140)	205 (99)	246 (100)
	20–30 min	241 (135)	188 (105)	236 (99)
	30–40 min	237 (134)	190 (106)	228 (111)
	40–50 min	226 (138)	177 (109)	221 (105)
	50–60 min	217 (128)	163 (103)	205 (93)
	65–75 min	203 (112)	194 (129)	211 (98)
	75–85 min	219 (119)	178 (105)	199 (92)
85–95 min	200 (113)	168 (104)	190 (93)	

(continued on next page)

Table 1 (continued)

ANOVA test statistics ^a time × group interaction		Controls Mean (SD)	Fibromyalgia Mean (SD)	Shoulder/neck pain Mean (SD)
Noradrenaline PPP (10 ⁻² nM) <i>F</i> ₂ (2, 65) = 1.26, <i>p</i> = 0.29	Baseline	175 (81)	165 (61)	153 (48)
	After 60 min	157.6 (50)	173 (62)	150 (40)
Noradrenaline PRP (10 ⁻² nM) <i>F</i> ₂ (2, 64) = 6.0, <i>p</i> = 0.004	Baseline	258 (88)	254 (81)	233 (57)
	After 60 min	254 (75)	284 (85)	219 (55)
Adrenaline PPP (10 ⁻² nM) <i>F</i> ₂ (2, 62) = 0.20, <i>p</i> = 0.82	Baseline	245 (97)	241 (67)	238 (113)
	After 60 min	217 (67)	209 (83)	218 (74)
Cortisol 10 ⁻¹ ng/ml <i>F</i> ₂ (2, 52) = 1.32, <i>p</i> = 0.28	Baseline	170 (47)	176 (66)	180 (42)
	After 60 min	109 (43)	107 (46)	138 (46)

Measured at baseline, during feedback aided relaxation, during mental stress (0–60 min) and during the recovery period (65–95 min).

PPP = platelet-poor plasma, PRP = platelet-rich plasma.

^a From repeated measures ANOVA models with diagnostic group as between-subjects factor: *F*₁₁: full model with 11 time intervals, *F*₇: model with seven intervals during the stressful task (baseline, 0–10 min, . . . , 50–60 min), *F*₃: model with three intervals during recovery (65–75 min, 75–85 min, 85–95 min), *F*₂: model with two time points for biochemical data (baseline, 60 min). *F*₁: One-way ANOVA comparing baseline values between groups. All models are corrected for age.

Table 2
Physiological responses to the stressful task

	Healthy controls Mean (SD)	Fibromyalgia Mean (SD)	Shoulder/neck pain Mean (SD)	ANOVA test statistics ^a
Heart rate (beats/min)				
Early	4.6 (6.1)	0.5 (3.9)	1.8 (4.5)	<i>F</i> (2, 77) = 5.47, <i>p</i> = 0.006
Average	2.8 (4.3)	0.1 (3.8)	1.3 (3.1)	<i>F</i> (2, 77) = 4.00, <i>p</i> = 0.022
Late	1.9 (4.2)	-0.6 (4.4)	0.8 (3.0)	<i>F</i> (2, 77) = 3.20, <i>p</i> = 0.046
Systolic blood pressure (mmHg)				
Early	15.5 (12.3)	9.8 (8.1)	13.3 (10.9)	<i>F</i> (2, 76) = 2.40, <i>p</i> = 0.10
Average	13.2 (7.3)	11.6 (10.0)	13.7 (8.3)	<i>F</i> (2, 77) = 0.75, <i>p</i> = 0.48
Late	14.2 (8.0)	14.4 (12.9)	17.4 (11.2)	<i>F</i> (2, 77) = 0.80, <i>p</i> = 0.45
Diastolic blood pressure (mmHg)				
Early	10.5 (8.5)	6.3 (6.3)	7.7 (6.3)	<i>F</i> (2, 76) = 2.44, <i>p</i> = 0.094
Average	9.1 (5.1)	8.2 (4.7)	8.5 (5.1)	<i>F</i> (2, 77) = 0.21, <i>p</i> = 0.81
Late	9.2 (5.6)	10.2 (6.1)	11.0 (7.7)	<i>F</i> (2, 77) = 0.61, <i>p</i> = 0.55
Respiration frequency (breaths/min)				
Early	1.7 (2.9)	0.5 (3.1)	1.4 (2.9)	<i>F</i> (2, 72) = 0.039, <i>p</i> = 0.96
Average	1.2 (2.7)	0.5 (2.0)	1.2 (2.5)	<i>F</i> (2, 72) = 0.082, <i>p</i> = 0.92
Late	0.8 (3.1)	0.2 (3.0)	0.9 (2.6)	<i>F</i> (2, 72) = 0.081, <i>p</i> = 0.092
Finger skin blood flow (arbitrary units)				
Early	-38.2 (58)	-44.4 (67)	-36.4 (64)	<i>F</i> (2, 83) = 0.25, <i>p</i> = 0.78
Average	-43.4 (59.0)	-82.3 (69.3)	-58.0 (69.9)	<i>F</i> (2, 83) = 2.59, <i>p</i> = 0.081
Late	-59.5 (74)	-111.7 (81)	-84.6 (73)	<i>F</i> (2, 83) = 3.30, <i>p</i> = 0.042

Early response = the difference between the mean of the first 10 min of stress and baseline. Baseline = mean of the UIR period. Late response = the difference between the mean of the last 10 min of the stressful task and baseline. Average response = the difference between the average of the whole stressful task and baseline. Bold values indicate responses significantly different from 0 (Student's *t*-test).

^a One-way ANOVA comparing groups, corrected for age.

were not different on baseline regarding the other physiological and biochemical variables (Table 1).

4.2. Response to the stressful task

Heart rate, blood pressure, finger skin blood flow and respiration frequency is illustrated in Fig. 1. ANOVA repeated measures analysis with all three groups

included revealed differences between groups in development (time × group factor) of diastolic blood pressure (*p* ≤ 0.037) and heart rate (*p* < 0.001; Table 1). When comparing two and two groups these time × group within-subjects effects (*F*₁₁ and *F*₇) were most clear when comparing the FMS patients to controls (diastolic blood pressure *F*_s ≥ 2.57, *p* ≤ 0.019, heart rate *F*_s ≥ 2.98, *p* ≤ 0.002) and more heterogenic when comparing the

Table 3

Subjective responses to the stressful task (maximal VAS value during the stressful task – baseline value)

	Controls Mean (SD)	Fibromyalgia Mean (SD)	Shoulder/neck pain Mean (SD)	ANOVA test statistics ^a
Maximal pain response	15 (16.1)	28 (24.8)	25 (20.0)	$F(2, 83) = 2.8, p = 0.067$
Shoulder pain response	10 (12.6)	19 (23.9)	17 (16.9)	$F(2, 83) = 1.30, p = 0.28$
Neck pain response	9 (11.1)	21 (19.6)	20 (20.3)	$F(2, 83) = 3.99, p = 0.022^b$
Temples pain response	7 (14.0)	15 (17.8)	13 (17.0)	$F(2, 83) = 1.23, p = 0.30$
Forehead pain response	6 (11.9)	14 (16.4)	8 (13.0)	$F(2, 83) = 1.60, p = 0.21$
Tension response	23 (21.4)	28 (20.3)	24 (21.6)	$F(2, 82) = 0.044, p = 0.96$
Fatigue response	27 (24.3)	27 (26.3)	26 (25.1)	$F(2, 82) = 0.074, p = 0.93$

Regional responses refer to the most painful side. VAS range 0–100. All responses are significantly different from 0 (Wilcoxon paired test).

^a One-way ANOVA (F and p values) comparing groups, corrected for age.

^b Posthoc Tukey; FMS/controls $p = 0.025$, SNP/controls $p = 0.033$, FMS/SNP $p = 0.97$.

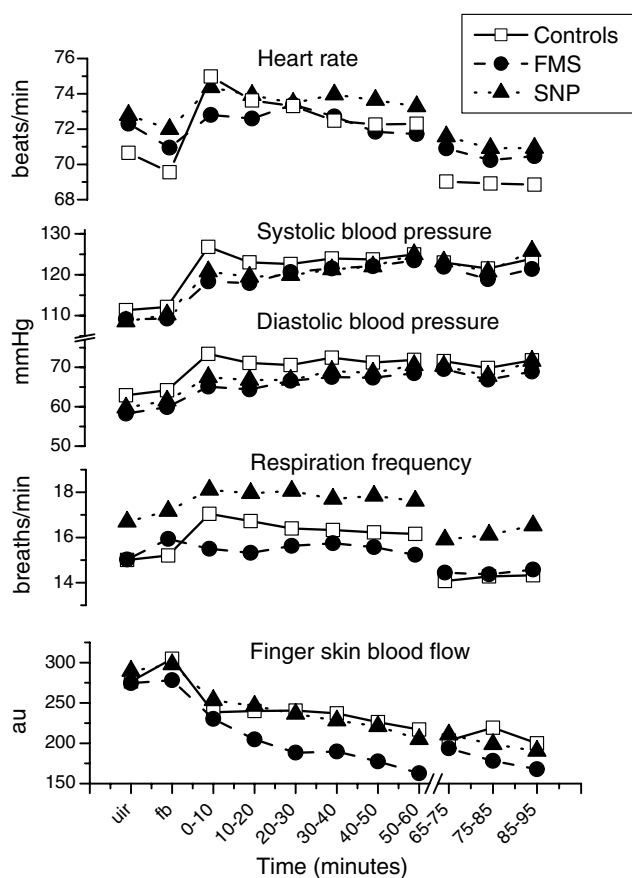


Fig. 1. Physiological recordings at baseline (UIR), during emg-feedback relaxation (fb), during the stressful task (0–60 min), and during recovery (65–75 min). Mean values for each 10 min period (UIR and FB = 5 min). The venepuncture is marked with a break in the horizontal axis. UIR = uninstructed rest period, FB = feedback period, au = arbitrary units.

SNP group to controls (diastolic blood pressure $F_s \geq 1.93, p \leq 0.075$, heart rate $F_s \geq 2.60, p \leq 0.018$). Differences were not evident when comparing the two patient groups except for a barely significantly difference when comparing the heart rate response during the stressful task ($F_7(2, 258) = 2.16, p = 0.047$), other $F_s \leq 1.14, p \geq 0.33$.

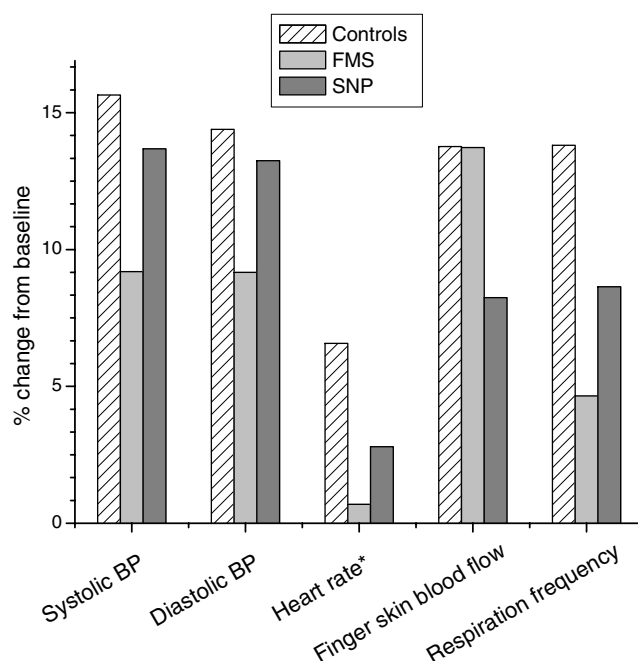


Fig. 2. Early responses illustrated as a percentage of baseline (UIR) values before test. Star indicate difference between groups for heart rate early response ($F(2, 77) = 5.47, p = 0.006$).

Further analysis of the physiological response to the stressful task was done by comparing the early, average, and late responses between groups (Table 2). The most evident result from this analysis was a significantly reduced early heart rate response in FMS patients compared to the healthy controls (Table 2, $p = 0.006$, posthoc FMS/controls $p = 0.01$; SNP/controls $p = 0.097$; SNP/FMS $p = 0.65$) and a trend towards reduced early diastolic blood pressure response (Table 2; $p = 0.094$, posthoc FMS/controls $p = 0.096$; SNP/controls $p = 0.34$; SNP/FMS $p = 0.77$), indicating a blunted early cardiovascular response to the stressful task in the FMS group (Fig. 2). One FMS patient responded with a large negative heart rate response (Fig. 3), however, the early heart rate response in the FMS group was still significantly different from the controls when

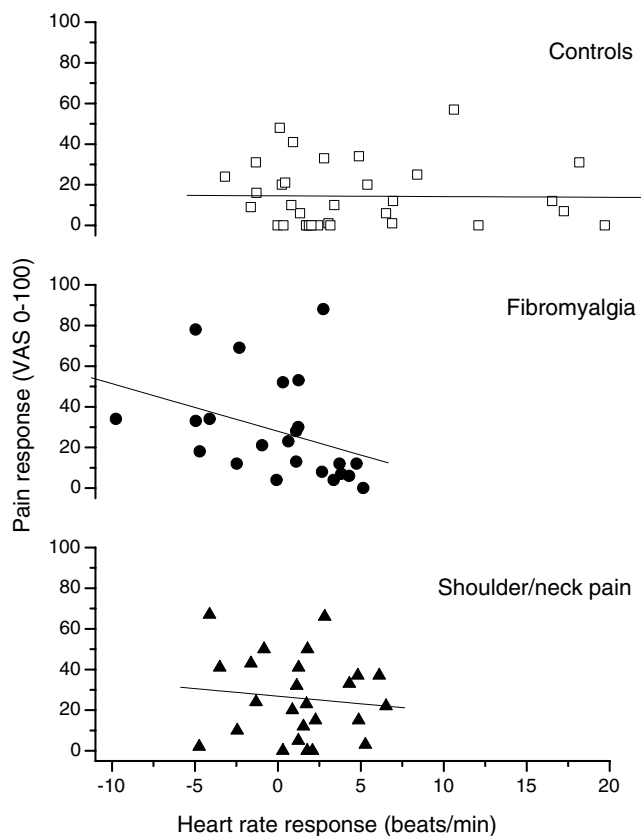


Fig. 3. Average heart rate response plotted against the maximal pain response with linear regression lines shown. The association is non-significant in the Control and the SNP group. The association is significant in the FMS group with ($r_s = -0.54$, $p = 0.009$) and without the outlier included ($r_s = -0.52$, $p = 0.014$).

this person was excluded from the analysis ($F(2, 76) = 4.77$, $p = 0.011$, posthoc FMS/controls $p = 0.026$; SNP/controls $p = 0.085$; FMS/SNP $p = 0.85$).

Furthermore, we found a higher respiration frequency in the SNP group (Table 1) compared to the two other groups (between-subject effect for group, all three groups in the model: $F_{11}(2, 71) = 4.71$, $p = 0.012$; posthoc two-group comparisons: SNP/controls $F_{11}(1, 51) = 7.89$, $p = 0.007$, SNP/FMS $F_{11}(1, 44) = 2.20$, $p = 0.15$, FMS/controls $F_{11}(1, 46) = 3.65$, $p = 0.062$). We did not find significant group effects with the ANOVA repeated measure analysis for other variables with non-significant time \times group interactions.

Analysis of the finger skin blood flow during the stressful task (baseline, 0–10 min, . . . , 50–60 min) reveals a significant time \times group interaction (Table 1; F_7 : $p = 0.021$). Further analysis with two and two groups revealed that it is the FMS group who differs from the controls with less finger skin blood flow during the stressful task (FMS/controls $F_7(6, 330) = 2.89$, $p = 0.009$; FMS/SNP = $F_7(6, 294) = 1.75$, $p = 0.11$; SNP/controls $F_7(6, 366) = 1.12$, $p = 0.35$). It is the late finger skin blood flow response which is different

between groups (Table 2; $p = 0.042$; posthoc: FMS/controls = 0.032, FMS/SNP $p = 0.41$, SNP/controls $p = 0.39$), indicating a slowly developing exaggerated sympathetic activity in vasoconstrictive sympathetic fibres in acral skin (Fig. 1).

The FMS group also differed from the other groups in the noradrenaline response (Table 1, $p = 0.004$), as noradrenaline in platelet-rich plasma increased during test in the FMS group ($t_{FMS}(16) = -2.2$, $p = 0.042$), but not in the other groups ($t_{controls}(24) = 0.46$, $p = 0.65$; $t_{SNP}(25) = 1.23$, $p = 0.23$). We found a higher level of noradrenaline in platelet-rich plasma after the stressful task in the FMS group compared to SNP patients ($F(2, 64) = 3.38$, $p = 0.040$; posthoc FMS/SNP $p = 0.012$; FMS/controls $p = 0.37$; SNP/controls $p = 0.19$) and a trend towards higher cortisol level after the stressful task for the SNP group compared to controls ($F(2, 52) = 3.33$, $p = 0.044$, posthoc SNP/controls $p = 0.092$; SNP/FMS $p = 0.12$; FMS/controls $p = 0.99$). Correlation analysis did not indicate any relation between the biochemical response variables and the physiologic response variables in Table 2.

Analysis of pain, tension and fatigue are reported in detail in another paper (Nilsen et al., 2006). In short, the FMS patients reported a higher baseline level of pain, tension and fatigue compared to healthy controls, with the SNP patients in an intermediate position. Although FMS patients reported pain more often than healthy controls, the analysis did not indicate higher pain responses in the patient groups. Furthermore, the number of subjects without pain recovery in the rest period was higher for both patient groups compared to controls.

Nevertheless, when looking at the most painful side in each region (possibly more clinically relevant than the mean of left and right as reported in the former study) we find a significant difference between groups regarding the neck pain response (Table 3, $p = 0.022$). However, ANOVA repeated measures analysis of the pain response (0 min, 10 min, . . . , 60 min) looking at the most painful side in each region did not indicate any difference in pain responses (time \times group factor) between groups for any region ($F_{7s}(12, 480-498) \leq 1.40$, $p \geq 0.16$, data not tabulated) as in the former study. Lastly, all subjects reported increased pain, tension and fatigue during the stressful task (Table 3).

4.3. Relation to pain development

We found an inverse relationship between the heart rate responses (Table 2) and the maximal pain response (Table 3) for the FMS group ($r_{sFMS} \leq -0.53$, $p \leq 0.009$) as opposed to the other groups ($r_{sSNP} \geq -0.12$, $p \geq 0.58$; $r_{scontrols} \geq -0.06$, $p \geq 0.46$), illustrated in Fig. 3. The correlations between pain in the different regions (Table 3) and the heart rate responses (Table

2) were also negative and significant for all four regions (shoulder, neck, temples, forehead: $r_s < -0.48$, $p < 0.021$). Omitting the outlier with negative heart rate response in the FMS group from the correlation analysis reduced the strength of the correlations slightly, but all the abovementioned correlation coefficients remained significant ($r_{s\text{FMS}} < -0.46$, $p < 0.034$).

The 95% confidence interval of the correlation coefficient between the average heart rate response and the maximal pain response was $(-0.202, 0.516)$ for the controls, $(-0.871, -0.208)$ for the FMS group, and $(-0.487, 0.326)$ for the SNP group. Between the early heart rate response and the maximal pain response the 95% confidence interval of the correlation coefficient

was $(-0.402, 0.283)$ for the controls, $(-0.839, -0.229)$ for the FMS group, and $(-0.476, 0.308)$ for the SNP group, and between the late heart rate response and the maximal pain response it was $(-0.242, 0.507)$ for the controls, $(-0.868, -0.300)$ for the FMS group, and $(-0.517, 0.283)$ for the SNP group. Thus, non-overlapping confidence intervals were observed for the comparison between the FMS group and controls for the correlation coefficients between the average heart rate response and the maximal pain response and between the late heart rate response and the maximal pain response.

Those FMS patients who did not recover from the pain in the following recovery period had lower heart

Table 4
Heart rate responses in subjects with and without pain recovery

ANOVA test statistics ^a time × group interaction		Heart rate responses (beats/min)	
		With pain recovery Mean (SD)	Without pain recovery Mean (SD)
Controls			
$F_1(1, 30) = 1.41$, $p = 0.25$	Baseline	69 (7.3)	73 (10.5)
$F_{11}(10, 300) = 0.47$, $p = 0.91$	Feedback	68 (7.6)	71 (9.7)
$F_7(6, 180) = 0.53$, $p = 0.79$	0–10 min	73 (7.6)	78 (14.1)
$F_3(2, 62) = 0.054$, $p = 0.95$	10–20 min	71 (7.8)	76 (11.5)
	20–30 min	71 (7.9)	76 (10.4)
	30–40 min	71 (7.5)	75 (10.0)
	40–50 min	71 (7.8)	74 (10.2)
	50–60 min	71 (7.3)	74 (10.0)
	65–75 min	68 (6.4)	71 (9.6)
	75–85 min	67 (6.6)	71 (9.9)
	85–95 min	67 (6.9)	71 (9.3)
Fibromyalgia			
$F_1(1, 20) = 2.71$, $p = 0.11$	Baseline	69 (7.8)	74 (4.6)
$F_{11}(10, 160) = 1.75$, $p = 0.075$	Feedback	70 (8.6)	71 (5.6)
$F_7(6, 108) = 4.00$, $p = 0.001$	0–10 min	72 (9.2)	73 (5.7)
$F_3(2, 36) = 1.28$, $p = 0.29$	10–20 min	71 (7.9)	73 (5.8)
	20–30 min	74 (9.2)	73 (5.9)
	30–40 min	74 (7.7)	72 (5.7)
	40–50 min	72 (6.8)	72 (5.5)
	50–60 min	73 (7.4)	71 (5.4)
	65–75 min	70 (7.3)	71 (6.1)
	75–85 min	69 (7.1)	71 (5.9)
	85–95 min	69 (6.3)	71 (6.1)
Shoulder/neck pain			
$F_1(1, 21) = 0.56$, $p = 0.46$	Baseline	73 (15.2)	73 (7.3)
$F_{11}(10, 210) = 0.23$, $p = 0.99$	Feedback	73 (15.7)	72 (7.0)
$F_7(6, 126) = 0.30$, $p = 0.94$	0–10 min	75 (13.3)	74 (7.0)
$F_3(2, 46) = 0.74$, $p = 0.48$	10–20 min	74 (13.7)	73 (7.4)
	20–30 min	74 (13.6)	73 (7.3)
	30–40 min	74 (14.0)	74 (7.5)
	40–50 min	74 (14.3)	73 (7.3)
	50–60 min	74 (14.6)	73 (7.8)
	65–75 min	73 (16.6)	71 (8.1)
	75–85 min	72 (14.7)	71 (7.7)
	85–95 min	71 (15.5)	71 (7.0)

Two FMS patients and one SNP patient did not complete the rest period. Eighteen controls recovered from the pain response, 15 did not. Seven FMS patients recovered from the pain response, 16 did not. Seven SNP patients recovered from the pain, 17 did not.

^a From repeated measures ANOVA models with diagnostic group as between-subjects factor. F_{11} : full model with 11 time intervals, F_7 : model with seven intervals during the stressful task (baseline, 0–10 min, . . . , 50–60 min), F_3 : model with three intervals during recovery (65–75 min, 75–85 min, 85–95 min), F_1 : One-way ANOVA comparing baseline values between groups. All models are corrected for age.

rate response to the stressful task (baseline, 0–10 min, . . . , 50–60 min) than those who recovered from the pain (Table 4, $F_7, p = 0.001$), a phenomenon not evident for the two other groups ($F_s < 0.53, p > 0.79$). There were no other physiological or biochemical differences when dividing the subjects in those with and without pain recovery.

In the SNP group we found a significant correlation between early finger skin blood flow response and the maximal pain response ($r_{s\text{SNP}} = 0.52, p = 0.004$; $r_{s\text{FMS}} = 0.05, p = 0.82$; $r_{s\text{controls}} = 0.06, p = 0.71$), i.e. less pain development for SNP subjects with more vasoconstriction during the first 10 min of the stressful task. The SNP group did however not differ from the other groups in finger skin blood flow response (see above).

No other physiological or biochemical responses correlated with the pain response for any of the groups.

5. Discussion

In the present study the cardiovascular response to low-grade stress was reduced in a group of female FMS patients compared to healthy controls. The FMS patients also had a larger finger skin blood flow response (blood flow decreased more, i.e. more vasoconstriction) during the 60 min stressful task compared to healthy controls. Furthermore, the present study demonstrated a negative association between the heart rate response and pain development and recovery for the FMS group, i.e. those FMS patients with a small heart rate response experienced more pain during the stressful task and did not recover from the induced pain in the rest period.

The 1-h stress provocation test used in the present study has in previous studies induced pain in the head and neck region both in healthy subjects (Bansevicius et al., 1997) and in patients with headache (Bansevicius and Sjaastad, 1996; Bansevicius et al., 1999; Leistad et al., 2006), and the test induces generalised pain in FMS patients (Bansevicius et al., 2001; Nilsen et al., 2006). However, the present study is the first where we compare activity in different parts of the autonomic nervous system with development of pain during low-grade mental stress.

A reduced heart rate response to stress in FMS patients has also been found by others (van Denderen et al., 1992; Martínez-Lavín et al., 1997, 1998; Bou-Holaigah et al., 1997; Kelemen et al., 1998; Cohen et al., 2000, 2001), and a review addressing the sympathetic nervous system function in FMS concluded that available data suggest an attenuated stress response in FMS patients (Petzke and Clauw, 2000). Others have postulated a possible connection between reports of a reduced stress response and the hyperalgesic state of the FMS patients (Clauw and Chrousos, 1997; Adler et al., 1999; Okifuji and Turk, 2002). A recent study

found an increased heart rate response (and normal blood pressure response) during static muscular contraction with no relation to pain development in FMS patients, but cognitive stress was not applied (Kadetoff and Kosek, 2007). We believe that the present study is the first report of a negative association between pain development and the heart rate response to a mentally demanding stressful task in FMS patients.

The diastolic blood pressure response to the stressful task was also reduced in the FMS group in the present study. Both normal and pathological blood pressure response to tilt-test in FMS patients has been reported by others (Bou-Holaigah et al., 1997; Furlan et al., 2005). An inverse relationship between pain sensitivity and resting blood pressure level (hypertension related hypoalgesia) has been reported (Maixner et al., 1997; Bruehl et al., 2002). This phenomenon might be relevant, but our data did not indicate that the blood pressure level correlated with the pain response neither for patients nor controls (correlation data not reported). However, it must be noted that the present study was not designed to investigate such a hypothesis.

One explanation for the low cardiovascular early response to the mental stress in the FMS group could be less engagement in the stressful task. If so, one could suspect that the patients had focused their attention towards potential pain and somatic sensations and not the stressful task. However, the development of fatigue and tension during the stressful task was not different between groups (Nilsen et al., 2006). Perceived tension (the Norwegian word “anspent”) has been reported to reflect perceived stress including the sensation of autonomic and muscular activation (Holte et al., 2003) and we used tension as an indirect measure of the level of stress. Thus the level of stress was assumed to be equal for all groups in the present study.

One potential confounding factor in the present study is room temperature, as skin blood flow is an integral part of temperature regulation. However, the room temperature in our laboratory was kept within very strict limits. Our analysis also indicates no differences between groups regarding room temperature ($F_{11}(2, 65) = 0.72, p = 0.49$, data not tabulated), and the increased finger skin blood flow response in the FMS group showed no correlation to room temperature ($r_s = 0.14, p = 0.53$). Moreover, the increase in finger skin blood flow seen in the first 10 min of the rest period indicates that the reduced finger skin blood flow in the FMS group is related to the stressful task, and not a temperature effect.

Our finding of both a low cardiovascular response and an enhanced finger skin vasoconstrictive response in the FMS patients may seem contradictory. However, because of the specificity and differential effect on different target organs of the autonomic nervous system (Sved et al., 2001; Jänig and Häbler, 2003; Gibbins et al., 2003), different magnitude and even different direction

of responses in different target organs are not surprising. Low-grade stress elicited different response patterns in different organs also in an extended analysis of the control group (unpublished data). Our results also suggest that in the fibromyalgia group the sympathoneural system (regulating skin blood flow) is de-coupled from the hypothalamo-pituitary-adrenocortical system and the adrenomedullary system because noradrenaline increased during the test while cortisol and adrenaline decreased in the fibromyalgia group.

Other studies investigating the skin blood flow response to stress in FMS patients have used briefer and more intense stress periods (Vaerøy et al., 1989; Qiao et al., 1991; Bennett et al., 1991; Lapossy et al., 1994; Jeschonnek et al., 2000) and not mental stress as a stimuli as in the present study. We believe this is the first study reporting increased acral skin vasoconstriction to mental stress in FMS patients.

We are furthermore not aware of any other reports of increased respiration frequency in this patient group.

The SNP patients seem to be in an intermediate position between the FMS patients and the controls both regarding the physiological responses and regarding the difference in heart rate response for those with and without pain recovery in the rest period. This may imply that the two patient groups share pathological mechanisms, but that FMS patients are more affected. On the other hand, if our findings are a result of chronic pain, the intermediate position of the SNP patients may simply imply that our FMS patients have experienced more pain than the SNP patients.

The results of the present study do not support findings of general hypocortisolism in FMS patients (McCain and Tilbe, 1989) or in persons with chronic shoulder/neck pain (for review see Heim et al., 2000). Cortisol levels were similar in the three groups before the test and were almost identical after test in FMS patients and controls. However, we found a trend towards higher cortisol after test in SNP patients as compared to controls, and according to the “intermediate” hypothesis discussed above, it is still possible that the results in FMS patients represent a relative hypoactivity compared to an earlier stage in disease progression (inverse U principle).

Regarding the possible mechanisms for the pain induced in our model with low-grade stress, we have earlier shown that muscle activity during stress does not correlate with the induced pain in patients with FMS and chronic shoulder/neck pain (Nilsen et al., 2006). Although speculative, at least two other different mechanisms may be relevant.

First, the autonomic nervous system may influence pain perception by a coupling between efferent sympathetic fibres and afferent nociceptive fibres named ‘sympathetically maintained pain’ (Jänig and Häbler, 2000; Baron et al., 2002). In a placebo-controlled study FMS

patients were more prone to develop pain after subcutaneously injected noradrenaline than rheumatoid arthritis patients and healthy controls (Martinez-Lavin et al., 2002). Pain worsening during a mentally demanding stressful task as in the present study may thus be hypothesised to be a direct result of efferent sympathetic activity. It is possible that this mechanism is partially relevant for the late part of the pain response in FMS patients because noradrenaline increased and acral skin blood flow decreased. On the other hand we found no correlation between finger skin blood flow and pain within the FMS group, and the association between pain response and vasoconstriction was negative in the SNP group. Sympathetic activation of muscle, not measured in our study could however be more important for stress-induced muscle pain.

Second, abnormalities in the central stress response network may include or affect central pathways for pain modulation (Clauw and Chrousos, 1997). One form of central endogenous pain modulation, diffuse noxious inhibitory control (DNIC) (Villanueva and Le Bars, 1995), has been shown to be deficient in FMS patients (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997). Different FMS patients may thus have different causes of peripheral nociception, although they may have a common defect in the physiological reaction to stress leading to a hyperalgesic state where non-painful stimuli may be interpreted as painful (i.e. allodynia).

Stress-induced analgesia (SIA) is a similar mechanism for pain modulation (Willer et al., 1981). Our finding of an inverse relationship between pain development and the heart rate response in the FMS group suggest reduced SIA for the FMS patients. Because reduced pain recovery suggest central sensitisation of pain (Gottrup et al., 2003), our finding of a reduced heart rate response among those FMS patients who did not recover from the induced pain suggest a relationship between reduced SIA and increased central sensitisation of pain.

Furthermore, our finding of an inverse relationship between pain development and the heart rate response in the FMS group bridges earlier reports of reduced sympathetic response to stress (Petzke and Clauw, 2000) with reports of reduced endogenous pain inhibition (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997) and increased central sensitisation (Sörensen et al., 1998; Staud et al., 2001, 2003, 2004) in FMS patients.

We did neither include a control task without cognitive stress nor different levels of task difficulty because we did not aim to disentangle the relative impact of the different aspects of a stressful task (i.e. position, movement, task type etc.). Our intention was to compare these different groups in a setting which is as close as possible to stressful and repetitive office-work. Adding a second “sham” test on a separate day or an extension of the time in the laboratory with another

90 min was not feasible. The abrupt change in physiological values and subjective ratings shortly after test onset suggest that the task is much more relevant than e.g. the sitting position. Motor activity in this test is minimal and we believe that task-related mental stress is the likely significant factor. It would be interesting to investigate the effects of task type and task difficulty in a future study.

In conclusion, FMS patients had a smaller cardiovascular response, but a larger finger skin vasoconstrictive response to 1 h low-grade stress, compared to healthy controls. SNP patients seem to be in an intermediate position between the FMS patients and the controls regarding the physiological responses. A smaller heart rate response to the stressful task was associated with a higher and longer lasting pain response for the fibromyalgia group, suggesting that a reduced autonomic response to mental stress is associated with increased central sensitisation of pain in FMS patients, possibly a result of reduced stress-induced analgesia.

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Paper IV:

Nilsen KB, Sand T, Borchgrevink P, Leistad RB, Rø M, Westgaard RH. A unilateral sympathetic blockade does not affect stress-related pain and muscle activity in patients with chronic musculoskeletal pain. (submitted)

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