# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities




WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 3

# Autonomic Regulation in Musculoskeletal Pain

David M. Hallman and Eugene Lyskov

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/51086

## 1. Introduction

A large number of people suffer from musculoskeletal disorders (MSDs), including regional pain in the neck-shoulder region, lower back and the upper extremities, or more widespread pain, e.g., fibromyalgia (Lindell et al. 2000; Côté et al. 2009). The 12-month prevalence for neck pain typically ranges between 30% and 50% in the general population (Hogg-Johnson et al. 2009). Chronic pain is reported by 19% of the adult European population (Breivik et al. 2006), affecting more females than men.

Chronic MSDs are characterized by a localized, regional or widespread sensation of pain affecting muscles, joints, tendons or ligaments, accompanied by symptoms such as fatigue, tenderness at palpation and muscle stiffness. Diagnoses are often based on self-reported symptoms, as adequate objective markers are difficult to obtain at an individual level (Larsson et al. 2007). Many of these disorders are thus commonly referred to as non-specific myalgias, e.g., trapezius myalgia, tension neck, cervicalgia and cervico-brachial syndrome according to the international classification for diseases (ICD). Regional pain conditions, such as neck-shoulder pain, may be accompanied by diffuse symptoms that can progressively develop into more widespread pain, e.g., fibromyalgia (Sjörs et al. 2011; Larsson et al. 2012). Research indicates the involvement of both peripheral and central mechanisms in the pathogenesis of MSDs (Arendt-Nielsen and Graven-Nielsen 2003; Johansson et al. 2003). Furthering our understanding of core mechanisms could improve prevention, diagnostics and treatment of chronic MSDs.

## 2. Stress-related muscle pain

The aetiology of MSDs is multifactorial, involving the interactions of physiological, psychological, behavioural and external mechanical factors. During recent years, increased attention has been directed towards the impact of psychosocial factors on musculoskeletal health. Epidemiological studies have shown an association between MSDs and a wide range

INTECH
open science | open minds

© 2012 Hallman and Lyskov, licensee InTech. This is an open access chapter distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

of stress-related exposures, including time pressure, lack of control and influence, low social support and high perceived stress (Torp et al. 2001; Bongers et al. 2006; Christensen and Knardahl 2011). It is well established that perceived stress can be manifested in various physiological disease indicators, such as increased heart rate, elevated blood pressure, and sustained muscle activity (Lundberg et al. 1994; Vrijkotte et al. 2000). Thus, exposures that induce perceived stress seem to play an important role in both the development and perpetuation of chronic muscle pain (Linton 2000; Keijsers et al. 2010). Recent data even suggest that cardiovascular disorders are risk factors for developing chronic musculoskeletal pain (Nolet et al. 2012).

Stress can been be defined as a state in which homeostasis (maintenance of balance in the internal milieu) is- , or is perceived to be, threatened (Chrousos 2009). These threats or challenges, also termed stressors, can be of different natures, e.g., psychological, physical, and physiological, but all can trigger adaptive physiological changes in order to actively preserve homeostasis (i.e., allostasis) (McEwen 2000). The adaptive physiological stress response is coordinated by the central nervous system, resulting in an orchestrated cascade of events in the periphery (Ulrich-Lai and Herman 2009).

On the other hand, chronic or frequently repeated stress without sufficient recovery can lead to an allostatic load, the price of adaptation resulting in disease (McEwen 1998). According to McEwen, there are four different scenarios that contribute to allostatic load. First, frequently repeated exposure to multiple stressors; second, lack of adaptation (e.g., when repeated stressors elicit similar response amplitudes); third, a prolonged response due to delayed shut-down of the stress systems; and fourth, an inadequate response that leads to compensatory hyperactivity of other mediators (McEwen 2007).

Thus, both over-activity or under-activity in physiological stress systems, such as the hypothalamic-pituitary-adrenal (HPA) axis or the autonomic nervous system (ANS), which are normally involved in adaptation to different challenges, may cause significant health problems (McEwen 1998). The ANS acts as a bridge between the central nervous system and the peripheral organs, and ANS activation in response to stressors is a key element in nociceptive and anti-nociceptive mechanisms (Schlereth and Birklein 2008). Pain itself is considered a powerful stressor, and intense, chronic pain may thus cause further adaptive or maladaptive changes in the ANS or other stress systems. Within this context, muscle pain can be viewed as a stress-related disorder.

In the following sections, we will analyse the possible link between ANS regulation and chronic muscle pain.

## 3. The autonomic nervous system

Physical (e.g., mechanical) or psychological stressors can facilitate chronic pain due to their effects on physiological stress systems (Kalezic et al. 2003). In particular, research has paid attention to the involvement of the ANS in the initiation and maintenance of chronic muscle pain. The ANS is a key stress response system in the body and helps to maintain internal

balance via rapid activation during physical and mental load. ANS regulation involves a close and harmonious interplay between its two anatomically separated divisions: the sympathetic nervous system and the parasympathetic nervous system. The sympathetic system is generally considered an excitatory system associated with energy mobilization in situations requiring high physical or mental effort, while the parasympathetic system is activated during routine activities and rest, allowing for restoration of bodily resources.

ANS effects on different target organs

- **Sympathetic activation:** increases heart rate and blood pressure; generates peripheral vasoconstriction (muscle vasodilatation) and relaxation of bronchi; stimulates secretion of adrenaline and noradrenalin from the adrenal medulla.
- **Parasympathetic activation:** reduces heart rate; contracts bronchial muscles; stimulates digestive glands and the secretion of saliva.

Although some peripheral target organs (e.g., peripheral blood vessels, kidney, and liver) react mainly to one of these autonomic systems, many organs respond to both systems, often with each system eliciting opposite effects. For example, the sinus node of the heart is affected by both the sympathetic and parasympathetic (vagal) systems. Resting heart rate is under tonic parasympathetic inhibition, which reduces heart rate from its intrinsic value as driven by the sinus node. In different conditions, heart rate can increase instantaneously with reduced parasympathetic activation, with further increases above the intrinsic state resulting mainly from sympathetic activation. It is important to note that even in low heart rate conditions, autonomic regulation involves both sympathetic and parasympathetic components, and their complex interplay leads to continuous fluctuations in beat-to-beat heart rate. These variations are termed heart rate variability (HRV), and characterize a healthy autonomic state.

A predominance of sympathetic activity, either due reduced parasympathetic tone or excessive sympathetic activation, reduces the dynamic flexibility of the ANS and results in poor adaptation to altered internal or external demands. Thus, an autonomic imbalance or dysfunction may have detrimental consequences in terms of pathological conditions (Thayer et al. 2010).

Various structures at multiple levels of the central nervous system are involved in coordinating the stress responses, which affect the periphery. The ANS does not function independently, but rather constitutes an important part of a multi-stress system that is highly integrative and involves sophisticated co-activation and interaction between different homeostatic processes, and the immune and endocrine systems, including the HPA and the sympatho-adrenomedullary axis (Ulrich-Lai and Herman 2009). In this sense, an autonomic imbalance may also reflect altered regulation of the entire stress response system.

Further, basic physiological processes, for example, muscle circulation, muscle contractility, inflammatory processes, and sensory motor control, that have been linked to chronic MSDs are influenced by autonomic reflexes (Passatore and Roatta 2006; Visser and van Dieën 2006). Although autonomic nerves do not usually modulate nociceptor activation, this may change with chronic muscle pain (Martinez-Lavin 2007).

## 4. Autonomic regulation in acute and chronic pain

At the central level there is a strong connection between autonomic activation and nociception (Jänig 2003; Schlereth and Birklein 2008). Studies based on brain imaging techniques show a close anatomical and functional overlap between cortical and sub-cortical structures involved in pain processing and those controlling autonomic regulation. These include, but are not limited to, the periaqueductal grey matter and rostral ventrolateral medulla located in the brainstem, thalamus, hypothalamus, and insular, anterior cingulate, prefrontal and somatosensory cortices, and the amygdala (Critchley et al. 2000; Price 2000; Apkarian et al. 2005; Thunberg et al. 2005; Benarroch 2006) as illustrated in figure 1.

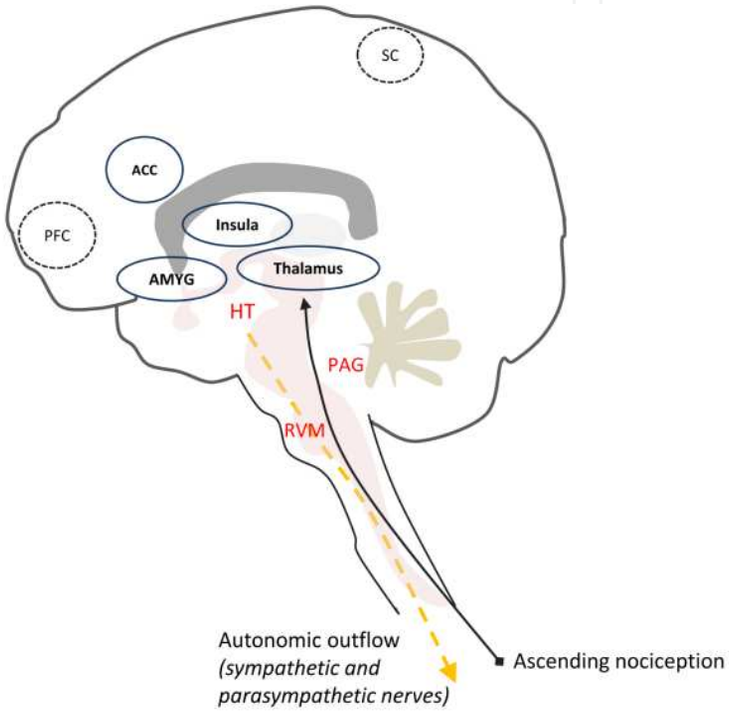



**Figure 1.** Simplified scheme of brain regions involved in pain processing and autonomic control, including brainstem: the periaqueductal grey matter (PAG) and rostral ventrolateral medulla (RVM), and cortical regions: thalamus, hypothalamus (HT), amygdala (AMYG) and the insular, anterior cingulate (ACC), prefrontal (PFC) and somatosensory (SC) cortices.

Studies indicate that autonomic responses to pain induced by electrical stimulation or heat are associated with brain activity in the cingulate and insular cortices (Dubé et al. 2009; Piché et al. 2010). Interestingly, higher brain activity in these brain regions has also been observed in patients with chronic pain, a condition previously assumed to be related to altered autonomic activity (Malinen et al. 2010).

Pain has a strong emotional component. This is manifested centrally via the involvement of the amygdala, which integrates polymodal information from different levels of the pain neuraxis, and attaches emotional significance to nociceptive stimuli. In turn, the amygdala projects to the hypothalamus, which is responsible for autonomic and neuroendocrine responses, and to the brainstem areas involved in endogenous pain modulation (Neugebauer et al. 2004; Rouwette et al. 2011).

The interactions between the ANS and pain are markedly different in acute and chronic pain conditions. In a healthy state, acute pain induces sympathetic arousal. Sympathetic arousal alleviates pain, which serves an adaptive stress response. The amplitude of pain-induced sympathetic reactivity depends on the intensity of the stimulus rather than on the state of wakefulness (sleep-wake) (Chouchou et al. 2011). Repeated painful stimulation over time may result in habituation with reduced perceived pain intensity and increased pain threshold (Bingel et al. 2007); the opposite may also occur. During acute physical or psychological stress, pain is normally suppressed via the activation of the descending anti-nociceptive pathways, involving opioid-dependent and noradrenalin-dependent mechanisms (Benarroch 2006; Schlereth and Birklein 2008).

With chronic musculoskeletal pain, and also with chronic stress, the interaction between the nociceptive and autonomic systems appears to become maladapted (Bruehl and Chung 2004; Schlereth and Birklein 2008). Chronic neck-shoulder pain is associated with increased local pain intensity, and reduced pain thresholds in response to sympathetic stimulation (Ge et al. 2006). Moreover, elevated blood pressure is normally associated with greater pain inhibition, but the opposite is observed in persons with chronic low back pain, and higher blood pressure is associated with increased sensitivity to pain (Bruehl and Chung 2004). The studies suggest that this inverse relationship results from altered function of the baro-receptors, which regulate blood pressure through changes in sympathetic outflow. Another study showed that elevated resting baroreflex sensitivity was associated with hypoalgesia in healthy normotensive subjects, but not in chronic low back pain patients (Chung et al 2008), and that an alfa-2 adrenergic blockade normalized the baroreceptor-pain association among the pain afflicted subjects. Additional studies supporting this model in chronic neck-shoulder pain are still lacking.

Under certain circumstances chronic pain may also be dependent on sympathetic neuronal activity, i.e., sympathetically maintained pain (Jänig 2003; Martinez-Lavin 2012). In such circumstances, sympathetic hyperactivity may activate nociceptive afferents, contributing to widespread pain, increased sensitivity to painful (hyperalgesia) and non-painful (allodynia) stimuli, and may be associated with additional symptoms, including fatigue and sleep disorders (Martinez-Lavin 2012). Different pain conditions may be affected in different ways, either directly (e.g., sympathetic-nociceptor activation) or indirectly (e.g., vasoconstriction-vasodilatation imbalance).

Taken together, it is possible that chronic muscle pain could be maintained and intensified due to pain-induced alterations in ANS regulation, particularly through the sympathetic branch of the ANS. In the next section, we will highlight some potential mechanisms for chronic neck-shoulder pain.

## 5. The sympathetic nervous system in musculoskeletal pain

Different explanatory models for MSDs have focused on ANS involvement in the pathogenesis of chronic pain. Autonomic activity, particularly of its sympathetic division, can modulate muscle function and pain via several mechanisms (see figure 2). These

mechanisms are not considered mutually exclusive and may interact and play different roles depending on the time course and severity of the pain.

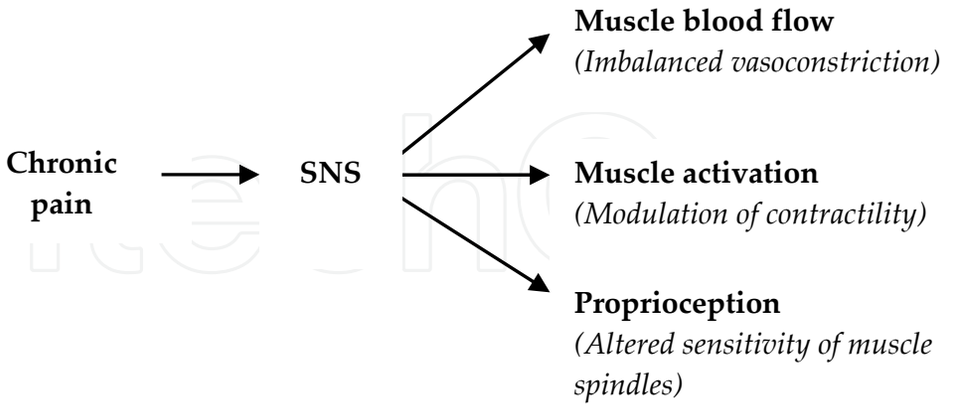



**Figure 2.** Local effects of sympathetic nervous system (SNS) activation induced by chronic pain

## 5.1. Sympathetic control of muscle blood flow

The neural control of blood flow in working muscles involves sympathetic and somatomotor interactions (Thomas and Segal 2004). Static contractions, often used in experimental protocols to assess systemic and local hemodynamics, induce sympathetic activation, which increases in proportion to the intensity and duration of muscular contractions (Saito et al. 1986). During exercise, sympathetic activation leads to vasoconstriction in skeletal muscles, and blood flow is re-directed to facilitate adequate oxygenation of working muscles. Somatomotor nerve activity leads to contraction of skeletal muscle, which generates the release of metabolites causing vasodilatation and functional hyperemia (Thomas and Segal 2004). Although other factors are also involved (e.g., central command, systemic blood pressure, and local factors), optimal regulation of muscle blood flow is highly dependent on these major components. Sympathetic reduction of blood flow in active and passive muscles has been demonstrated at different contraction intensities (Saito et al. 1986; Joyner et al. 1992; Buckwalter et al. 1997). Blood flow can also be influenced by mental stress via enhanced adrenaline secretion from the adrenal medulla into the circulating blood, resulting in ß2-adrenoreceptor mediated vasodilatation in contracting muscles (Larsson et al. 1995).

### *5.1.1. Insufficient blood flow regulation in chronic muscle pain*

Impaired blood flow to the pain region has been observed in persons with both chronic regional and widespread pain during various provocations, e.g., cold water, needle stimulation by acupuncture, and static or dynamic contractions (Acero et al. 1999; Larsson et al. 1999; Sandberg et al. 2005; Elvin et al. 2006; Hallman et al. 2011); for comprehensive reviews on this topic see Passatore and Roatta (2006) and Vierck (2006).

In these pain conditions, it has been argued that enhanced sympathetic activity may contribute to impaired blood flow and nociceptive muscle pain due to an imbalance

between vasoconstriction and vasodilatation (Passatore and Roatta 2006). When the oxygen demands are not adequately met, the muscles become ischemic and the local accumulation of metabolites may result in nociceptor activation, which, in turn, can enhance sympathetic outflow (Passatore and Roatta 2006; Vierck 2006). Hence, excessive sympathetic activation may play an important role in generation of muscle pain by mediating the response to various kinds of physical and psychological stressors. Once pain has become chronic, additional effects on ANS regulation can also be expected. First, amplification of afferent nociceptive signals may activate the sympathetic system through somato-sympathetic reflexes (Sato and Schmidt 1973); this occurs at a central level. This activation may result in further intensification of pain due to sensitization occurring at both the peripheral and central levels. Second, chronic pain is a strong psychological stressor that also activates the sympathetic system. As such, it seems possible that chronic pain can be maintained through a self-perpetuating (vicious) cycle.

Empirical support for this model is gained from studies examining widespread pain (fibromyalgia). Bengtsson and Bengtsson (1988) demonstrated that blocking the sympathetic stellate ganglions relieved pain in fibromyalgia patients, and they hypothesized that this was due to improved microcirculation. More recently, it was found, in a randomized controlled trial, that injections of norepinephrine (noradrenalin) evoked pain in fibromyalgia patients (Martinez-Lavin et al. 2002).

An alternative explanation for blunted blood flow response to stress in people with chronic muscle pain, proposed by Maekawa et al. (2002), is ß2-receptor down regulation due to prolonged sympathetic activation . This would also explain a blunted blood flow response to stress, owing to a lack of vasodilatation. Further experimental and clinical studies are needed to elucidate the possible relationships between sympathetic function, impaired blood flow regulation and nociceptive sensitization in pathogenesis of chronic muscle pain.

## 5.2. Sustained muscle activity in chronic muscle pain

It is known that the sympathetic nervous system influences muscle contractility mechanisms (Roatta and Farina 2010). Sympathetic effects on muscle activity and motor-unit discharge rate have been observed in human experiments during fatiguing contractions and painful stimulation with cold water (Seals and Enoka 1989; Roatta et al. 2008). During acute stress exposure, skeletal muscles are activated to enable a `fight-or-flight´ response involving extreme physical efforts or movements. Although this is a protective response, it may also result in sustained muscle activation or inadequate muscle relaxation, which plays an important role in the development of chronic MSDs

Studies on chronic neck pain have shown a different pattern of muscle activity as determined from electromyography (EMG) recordings, manifested in reduced muscle rest and increased activation of the neck-shoulder muscles in response to various functional tasks (Lundberg et al. 1999; Thorn et al. 2007; Johnston et al. 2008). We recently investigated autonomic and muscular responses, in subjects with chronic neck-shoulder pain and healthy controls, to sustained muscle contraction and a cold stimulation, known to provoke

sympathetic activation (Hallman et al. 2011). We found that the pain group had significantly higher muscle activity during the rest period following the static contraction task, and during cold stimulation, than the control group did. The muscle activity increase in the cold condition was also correlated with pain intensity in the pain group. These findings suggest an augmented muscle response to sympathetic activation among those with chronic muscle pain. However, as we did not assess changes in muscle sympathetic nerve activity, the direct influence of sympathetic activation on muscle contractility could not be tested.

The neck-shoulder muscles are particularly susceptible to develop MSDs due to their high sensitivity to physical and mental stressors (Wang et al. 2011). For example, the trapezius muscle has been shown to be uniquely lacking in adaptation capacities to repeated stress exposures. In a recent study on healthy volunteers, the activity of different muscles was recorded by EMG during repeated exposure to mental stress (Stroop colour-word interference tests). All muscles showed lower reactivity during the second exposure except the trapezius muscles (Willmann and Bolmont 2012).

### *5.2.1. Stress induced muscle activity*

Experimental studies have shown that mental stress can induce increased muscle activity that is unexplained by physical loads (Lundberg et al. 1994; Larsson et al. 1995). One hypothesis to explain such observations proposes that so-called low-threshold "Cinderella" motor units, which are recruited at all levels of contraction, may be especially affected by low-level mechanical loads and psychological stressors (Sjøgaard et al. 2000; Hägg 2003). In occupational settings with incorporated stress, this may result in increased low-level muscle activity and inadequate muscle relaxation, even in pauses between physical work bouts. In this way, these particular muscle fibres could become overused, and muscle fatigue and pain could develop.

Occupational tasks typically involve both physical and cognitive components. Research combining physical and mental tasks indicates a synergistic effect on trapezius muscle activity (Mehta and Agnew 2011). Further, Larsman et al. (2009) found that perceived work-related stress was positively associated with increased trapezius muscle activity and lower muscular rest during a combined mental stress and typing task. This relationship was more prominent among subjects with neck-shoulder pain (Larsman et al. 2009). However, not all studies have confirmed such effects. For instance, psychosocial exposures induced during breaks from computer keying work did not result in increased trapezius muscle activation (Blangsted et al. 2004). The interactions between physical (e.g., mechanical) and psychological exposures are complex and likely depend on many factors, including the type, duration and intensity of exposures, as well as the time pattern of alternation between work and rest. Muscle activity induced by mental or physical stress tests was also found to be correlated with cardiovascular indicators of sympathetic arousal (Lundberg et al. 1994; Krantz et al. 2004). These results may be interpreted as a `central effect´ that co-activates both the somatic and sympathetic nervous systems. In contrast, a peripheral sympathetic block did not affect pain and muscle activity in response to a stressful task (Nilsen et al. 2008).

### 5.3. Sympathetic nervous system involvement in sensory-motor control

Aberrant motor control has been identified as a potential factor in the continuation of chronic MSDs (Visser and van Dieën 2006). The transition from acute to chronic pain may be accompanied by alterations in motor variability. Chronic neck-shoulder pain was associated with reduced motor variability during a repetitive timing task (Madeleine et al. 2008). Chronic nociceptive stimuli may affect motor output via several mechanisms, including inhibition of motor neurons, reduced motor unit discharge rate, and compensatory activation of new motor units to maintain force production. In addition, increased sympathetic outflow induced by chronic pain, or psychological stress, can influence motor output, leading to reduced efficiency and precision of movements (Nijs et al. 2012). Studies also suggest that increased sympathetic tone may affect sensory-motor control through modulation of sensory receptors (i.e., muscle spindles) involved in afferent transmission of proprioceptive information (Johansson et al. 2003; Passatore and Roatta 2006; Nijs et al. 2012); this theory is, however, currently largely based on evidence from animal experiments.

In conclusion, an increase in sympathetic activity induced by chronic pain may contribute to pain sensitization at peripheral and central levels.

## 6. The parasympathetic nervous system in musculoskeletal pain

While research has mainly focused on the connection between the sympathetic nervous system and muscular pain, the involvement of the parasympathetic nervous system must also be considered. Studies have shown that parasympathetic withdrawal can facilitate sympathetic dominance of the ANS response and thus contribute to inadequate stress responses and cardiovascular adjustments during recovery following exercise, or during sleep (Gockel et al. 1995; Kingsley et al. 2009; Lerma et al. 2011).

It is known that conditions of psychological stress or pain can result in reduced parasympathetic (vagal) activity, a state that is associated with increased morbidity and all-cause mortality (Thayer et al. 2010). For instance, reduced heart rate variability (HRV) reflected diminished parasympathetic (vagal) activity in workers who reported high levels of perceived stress (Vrijkotte et al. 2000) and in people afflicted with chronic muscle pain (Martinez-Lavin 2007).

### 6.1. Inflammation

Studies show that inflammatory processes are modulated by the parasympathetic nervous system (Tracey 2002). During acute stress, activation of sympathetic and vagal nerves provides local and systemic anti-inflammatory effects without affecting the heart. The cholinergic anti-inflammatory pathway consists of the efferent vagus nerve and the secretion of acetylcholine. The afferent vagus provides information about the state of peripheral inflammation to the brain, resulting in compensatory vagal activation to attenuate pro-inflammatory cytokine production by the release of acetylcholine (Rosas-Ballina and Tracey 2009). Such anti-inflammatory effects have been demonstrated in

response to electrical stimulation of the vagus nerve (Borovikova et al. 2000). In contrast, acute systemic inflammation may temporarily alter parasympathetic function in healthy subjects (Jae et al. 2010). In injury, or excessive overload, local inflammation may play a significant role in development of MSDs, especially in early stages (Barbe and Barr 2006). However, the possible role of the ANS as a mediator of this relationship is still unknown.

### 6.2. Sleep

Night time sleep is generally considered highly restorative when it is adequate. Not surprisingly, insufficient (non-restorative) sleep negatively impacts physical and mental health. Studies examining self-reports and objective measures by polysomnography report disturbed sleep as a common symptom in chronic muscle pain (Spaeth et al. 2011); this would partly explain why these individuals may experience general fatigue and tiredness (Fishbain et al. 2004). Even occasional nights with poor sleep may affect pain perception in the following days (Edwards et al. 2008). The mechanisms responsible for sleep disturbances in chronic MSDs, however, are not fully understood, and may in part be related to co-morbidity of psychological stress, depression or a reduction in physical activity. Pain is also a possible factor for sleep alterations in MSDs due to its effects on cortical and autonomic arousals (Chouchou et al. 2011).

Diurnal variations or 24-hour day-night patterns in cardiovascular autonomic regulation show higher sympathetic day-time activation, and reduced activity during sleep (non-rapid eye movement). The enhancement of parasympathetic (vagal) activation during sleep is dependent on a variety of factors, for example changes in physical activity and light, circadian biological rhythms, and coupling between sleep mechanisms and cardiovascular regulation (Trinder et al. 2012). The relationship between sleep and autonomic activity is bi-directional. During normal sleep, the cardiovascular system can exhibit brief periods of distinct activation, i.e., arousals, reflecting changes in autonomic regulation. However, poor sleep may result in a higher frequency and amplitude of nocturnal arousals, and *vice versa*, and in such circumstances, altered autonomic balance can be expected (Trinder et al. 2012).

## 7. Autonomic aberrations in chronic neck-shoulder pain: recent findings

Findings from clinical and applied studies show that chronic muscle pain is associated with peripheral ANS aberrations at both systemic and local levels. ANS dysfunctions have been extensively studied in patients with widespread chronic pain (Martínez-Lavín et al. 1998; Haley et al. 2004; Martinez-Lavin 2007; Reyes del Paso et al. 2010; Lerma et al. 2011) often by using ECG-based methods, e.g., heart rate variability (HRV) analyses. In general, at a group level these patients show autonomic imbalance in terms of high sympathetic activation and low parasympathetic tone at rest and blunted sympathetic response to various types of stressors (Martinez-Lavin 2007).

Our research group has recently shown similar findings among persons with regional chronic pain, as compared to symptom-free controls. In subjects with chronic low back pain, assessment of ANS regulation during a rest condition revealed higher heart rate,

electrodermal activity and low frequency HRV in the pain group, indicating increased basal sympathetic activity (Kalezic et al. 2007). Individuals with whiplash-associated disorders had increased heart rate and arterial blood pressure in response to a chewing test, as compared to healthy controls (Kalezic et al. 2010).

We recently investigated autonomic responses to a battery of functional tests in persons with chronic trapezius myalgia and in healthy controls. After a 15 minute resting condition subjects performed a hand grip test, a cold pressor test and a deep breathing test, interspaced by 5 minute rest periods. Autonomic regulation was assessed using HRV, arterial blood pressure, local trapezius muscle blood (photoplethysmography) and muscle activity (electromyography). During the initial rest condition, persons with chronic pain showed reduced HRV in comparison with controls. In response to the static contraction, blunted trapezius blood flow and arterial blood pressure with simultaneous increased HRV were observed in the pain group compared with the controls (Hallman et al. 2011), reflecting aberrations in ANS regulation at both systemic and local levels. Similar results were obtained from 24-hour ambulatory monitoring of ECG in persons with chronic neck-shoulder pain and in healthy controls. Increased heart rate and diminished HRV were found during sleep, which indicated increased sympathetic and reduced parasympathetic activity among the pain afflicted individuals, in comparison with controls (Hallman and Lyskov 2010). Overall, these results indicate that regional chronic muscle pain is associated with ANS imbalance at rest, and with altered sympathetic nervous system response to laboratory stressors.

These findings were in line with an earlier observation of altered sympathetic function in persons with regional neck-shoulder symptoms, as observed from cardiovascular variables (Gockel et al. 1995). However, contradictory findings have also been reported. For example, altered cardiovascular responses to low-grade mental stress were found in fibromyalgia patients, whereas a group of subjects with neck-shoulder pain did not react significantly differently than healthy controls (Nilsen et al. 2007). More recently, a study of individuals with trapezius myalgia showed an elevated heart rate at rest but no differences in stress responses compared with controls (Sjörs et al. 2009).

Our results on local muscle blood flow were in concert with previous findings, which generally reflected insufficient muscle circulation in people with chronic neck-shoulder pain. In a series of studies, Larsson and colleagues investigated local microcirculation using laser Doppler flowmetry in patients with chronic neck pain. During static contractions, reduced microcirculation was observed in painful muscles among patients (Larsson et al. 1994). In addition, a greater reduction in blood flow was associated with a higher pain intensity and mitochondrial changes in patients (Larsson et al. 1990). Similar findings were later observed using noninvasive techniques. Acero et al. (1999) used near-infrared spectroscopy (NIRS) to assess blood volume during a cold pressor test, known to induce pain and sympathetic activation, in persons with chronic neck pain. During cold stimulation, blood volume was found to be lower in the pain group; this was interpreted as a lack of vasodilatation, possibly induced by chronic stress. In a recent study in trapezius myalgia, NIRS recordings on patients reflected reduced oxygenation of relaxed

trapezius muscle in response to cycling (Andersen et al. 2010). Similar results have been shown by photoplethysmography recordings of changes in local blood flow during acupuncture (Sandberg et al. 2005). Although muscular contractions at lower intensities induced normal, or slightly aberrant, responses in subjects with neck-shoulder pain, trapezius blood flow remained increased in these patients after simulated office work (Strøm et al. 2009) and repetitive low-force exercise (Rosendal et al. 2004). Hence, a different mechanism may be involved when the physical work induces distinct sympathetic activation, which possibly did not occur in the latter studies applying low-intensity mechanical loads.

Doppler ultrasound has been used to assess vascular responses to muscular work in patients with diffuse forearm pain. Vasoconstriction of the radial artery and lack of a vasodilatory response to exercise were found in patients (Pritchard et al. 1999). Further, changes in skin temperature determined by thermography (i.e., far infrared images) showed reduced temperature in the afflicted region among patients with forearm pain, possibly reflecting sympathetic dysfunction (Sharma et al. 1997; Gold et al. 2009).

Although aberrations in autonomic regulation are relatively small and have not always been seen at the individual level, the cross-sectional findings outlined above provide convincing support for autonomic involvement at both the systemic and local levels in chronic neck-shoulder pain. Given the lack of prospective studies to date, the causal relations still remain unclear.

## 7.1. Difficulties in interpreting stress reactivity

Studies generally show a wide spectrum of physiological reactions to laboratory stressors, which are not easily interpreted in terms of ANS hypo- or hyper-reactivity. There are, however, several explenations that may account for this. First, there could be methodological issues related to discrepancies in application of stress stimuli (e.g., different types, intensities and durations of stressors) and varied diagnosis or exclusion criteria for patient groups. Furthermore, it is possible that there exist sub-groups of pain patients with different aetiologies and underlying mechanisms. Also, co-morbidity factors (including depression, chronic fatigue, and posttraumatic stress syndromes, frequent usage of medication) affecting autonomic function may also play significant roles in ANS reactions as similar signs of cardiovascular system aberrations are observed across a variety of stress-related disorders (Cohen et al. 2000; Newton et al. 2011; Kemp et al. 2012). Alternatively, physiological variables could be insensitive and unspecific regarding discrimination between pain and control groups, consequently masking group differences.

A second explanation for the heterogeneous results to date is the inconsistency in symptom duration, severity, and anatomical spread in pain-group participants. It has been suggested that regional chronic pain may represent an earlier stage of widespread pain (Riva et al. 2012). This may account for observations of cardiovascular hypo-reactivity in patients with fibromyalgia, and the less consistent observations among persons with chronic neck-shoulder pain. This theory is in line with the allostatic load model of chronic stress (McEwen

1998), where a hyper-reactive stress system, i.e., regional neck-shoulder pain, might progress into hypo-reactivity, i.e., widespread chronic pain, due to beta receptor down regulation (Martinez-Lavin 2007). Although this is an intriguing idea, it still needs to be verified by prospective studies.

### 7.2. Predictive value of heart rate variability

Measures of HRV, especially when derived from 24-h ambulatory recordings including night time sleep, are valuable predictors of mortality from cardiovascular diseases (Kleiger et al. 2005). Also, individual differences in HRV seem to be associated with pain variables (Campbell et al. 2003).

In a recent animal study (Oliveira et al. 2012), chronic widespread pain was induced in rats by two injections of acidic saline, administered five days apart. One day after the second injection, HRV spectral power had shifted towards lower frequency ranges indicating a change in cardiac autonomic regulation in terms of increased sympathetic predominance. These findings support the theory that chronic pain may alter autonomic balance. In a study on patients with chronic regional pain or fibromyalgia, it was found, across both pain conditions, that age, gender, pain sensation, pain anxiety and physical functioning could all predict resting HRV (Mostoufi et al. 2012). In an ambulatory study, nocturnal HRV was similarly shown to be a strong predictor of widespread pain (Lerma et al. 2011). Further, increased baroreflex sensitivity was associated with higher pain tolerance and lower pain intensity in patients with widespread pain (Reyes del Paso et al. 2011). Thus, a bi-directional relationship likely exists with chronic pain affecting ANS regulation and *vice versa*. Studies on regional pain conditions have shown contradictory results. For instance, a study on chronic low back pain (Gockel et al. 2008) found no association between perceived pain intensity and autonomic function assessed by HRV among patients, while functional disability was associated with impaired autonomic function in the same sample.

It is not yet clear whether lower HRV among persons with chronic regional muscle pain is specific to pain or whether it reflects poor health in general. Physical activity is another recognized factor that may influence HRV, and because altered activity patterns have been found in chronic muscle pain (Griffin et al. 2012), this possible relationship should be taken into account in forthcoming studies.

## 8. A hypothetical model of ANS involvement in chronic muscle pain

In the present hypothetical model of possible ANS involvement in chronic pain, it is assumed that the causal relations look different depending on the progression of symptoms, i.e., development or maintenance of pain (see figure 3). The current model is centred on:

- the acute response to external exposures, which may become maladaptive and lead to initiation of muscle pain if it is extended for a long period of time or frequently repeated without recovery

- the prolonged response induced by chronic pain, which is characterized by a basal state of ANS imbalance and by altered reactivity to stressors, which may eventually lead to worsening of symptoms.

It is hypothesized that long-term exposure to mechanical (e.g., low-level repetitive work) and/or psychological (e.g., time pressure) stressors may give rise to an unfavourable physiological response, including sustained muscle activity and lack of muscle rest, inadequate circulation, and altered sensory-motor control, via activation of the sympathetic nervous system, resulting in local accumulation of noxious substances that activate afferent nociceptors, producing local or regional pain. The latter may result in further sympathetic activation that acts back to the periphery. In chronic pain, alterations between (anti)nociceptive mechanisms and ANS regulation may contribute to maintenance of pain, and sensitization, via a self-perpetuating (vicious) cycle, which adds an additional loading on the allostatic stress systems via involvement of positive feedback loops. ANS imbalance, resulting from pain, in terms of sympathetic hyperactivity and diminished parasympathetic tone, may eventually lead to sympathoadrenal hyporeactivity (beta-receptor down regulation) to stressors. This may also be expressed in additional subjective symptoms, including sleep disorders, fatigue, and psychological stress, as well as reduced physical activity.

A variety of individual predisposing factors, such as age, gender, anthropometrics, and genetics/epigenetics, should also be taken into account in attempts to understand individual differences in susceptibility to chronic pain. Among other factors, perceived stress is assumed to play a mediating role at different levels of the model, both in the initiation and continuation of pain, by inducing inadequate ANS reactions. In chronic pain states, accumulated symptoms, which may be accompanied by perceived stress, fatigue and physical inactivity (reduced cardio-respiratory fitness), may all worsen the state of allostatic load (see figure 3).

## 9. Complexity in assessment of autonomic regulation of MSDs

Various methods exist for assessing ANS regulation; these, however, are individually suitable for experimental application depending on the specific circumstances. Here, relevant methods and tests for characterizing different aspects of ANS activity will be briefly summarized. We will focus on relevant physiological measures and tests applicable to patients with chronic MSDs.

### 9.1. Measures of autonomic regulation at systemic and local levels

Heart rate variability (HRV) analysis has emerged as a reliable instrument for assessment of autonomic regulation. Heart rhythm is inconstant and varies in a complex and seemingly chaotic way due to efferent sympathetic and parasympathetic modulation of the sinus node of the heart; in general, increased variability reflects healthy ANS regulation. Time series of beat-to-beat RR intervals can be derived from continuous ECG recordings, and variability assessed.

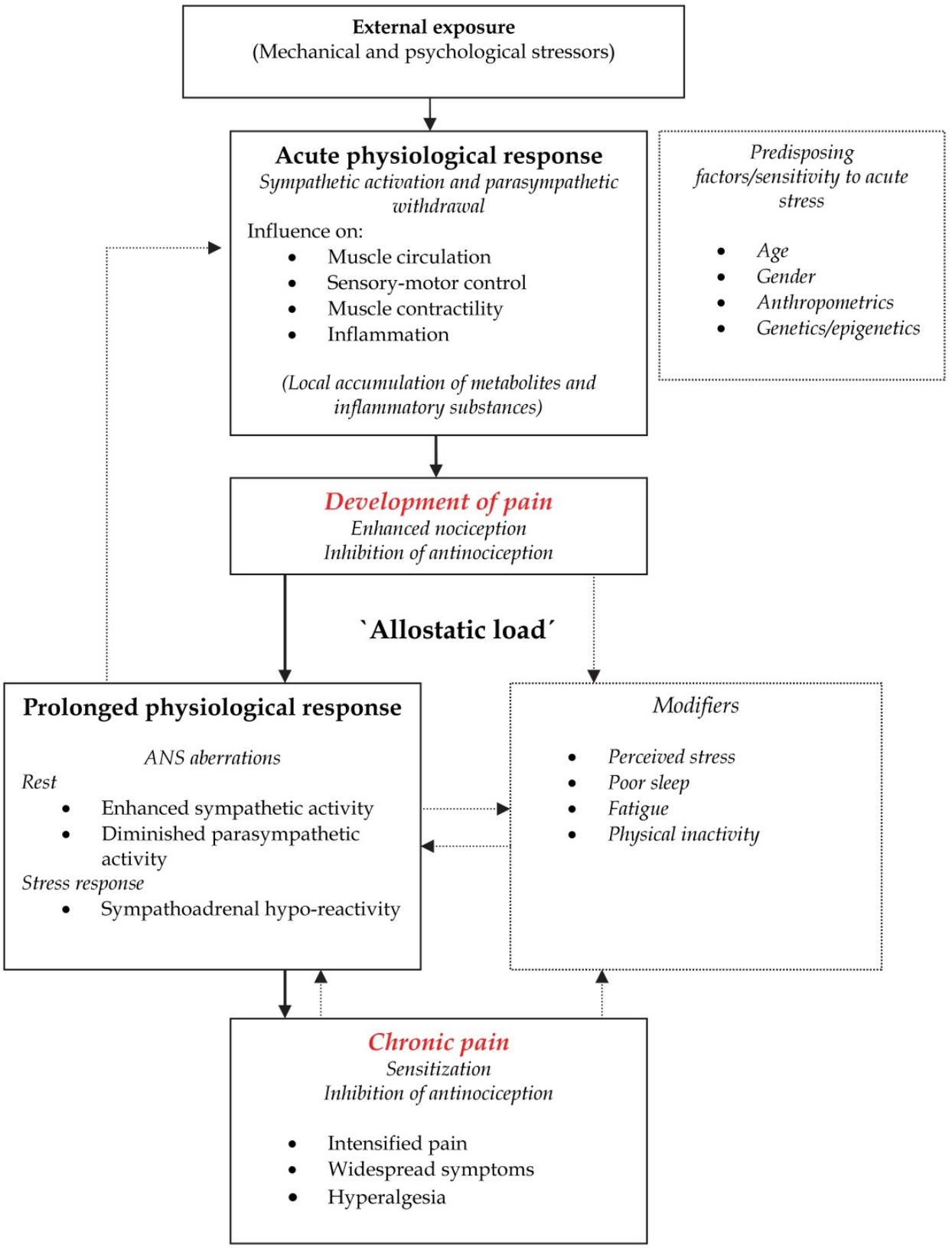



**Figure 3.** The autonomic nervous system (ANS) involvement in the pathogenesis of chronic musculoskeletal pain

Based on time series of RR intervals, HRV can be analysed in the time domain in units of milliseconds. The standard deviation of all RR-intervals is a measure of ANS regulation, while other measures of short-term variability, for example the root mean square of successive differences between adjacent pairs of RR intervals, are closely related to parasympathetic (vagal) activity as mediated through breathing mechanisms (i.e., respiratory sinus arrhythmia). Frequency domain measures of HRV, via analysis of spectral power density in various frequency ranges, can be informative regarding both the sympathetic and parasympathetic contributions to ANS regulation and balance. The RR interval power spectra contains a low frequency peak between 0.04-0.15 Hz, reflecting baroreceptor modulation with a combination of sympathetic and parasympathetic influences, and a high frequency peak (0.15-0.4 Hz), which predominantly reflects parasympathetic influences, according to Task force standards (1996). Short-term HRV, usually derived over 5 minute ECG segments, is suitable for laboratory experiments, and can be analysed under rest conditions or in response to different sympathetic or parasympathetic manoeuvres. Long-term 24-hour recordings may provide useful information about circadian rhythms (Bilan et al. 2005) and autonomic balance during sleep (Hallman and Lyskov 2010).

Arterial blood pressure is another important cardiovascular characteristic of ANS regulation, which can be easily monitored continuously by non-invasive techniques. Also assessment of sudomotor parameters (e.g., skin conductance and sweat) and temperature changes are common indicators of sympathetic arousal. These variables seem to be rather far removed from local muscle processes, although they may provide relevant information regarding the autonomic state at rest or in response to laboratory, or real-life, stressors in individuals with musculoskeletal pain.

Moreover, indicators of local circulation (blood flow, blood volume, and oxygenation) are relevant measures of sympathetic influences on vasoconstriction, and they can be used reliably in experimental assessment of regional MSDs, such as neck-shoulder pain, or widespread pain conditions, without acting disturbing. Changes in muscle blood flow or blood volume can be derived from different non-invasive methods, including NIRS, photoplethysmography, and doppler ultrasound.

Muscle sympathetic nerve activity, although an invasive method, can be directly recorded from human peripheral nerves using microneurography. Quantification of spontaneous sympathetic bursts gives information regarding efferent sympathetic neural activity to skeletal muscle, and its effects on muscle circulation.

Muscle activity, assessed using surface EMG, has been widely used in exposure assessment as an adequate indicator of muscle fatigue. EMG characteristics may also add information about individual differences in stress reactivity, with a relatively clear connection to ANS function (Lundberg et al. 1994).

In conclusion, ANS testing in chronic MSDs may include a combination of these measures, as well as other methods not mentioned here, for adequate assessment of autonomic reactions. Some methods are preferably used in the laboratory setting, while others can be used in both lab and field studies.

## 9.2. Laboratory tests and ambulatory monitoring

Laboratory tests assessing systemic and local cardiovascular reactions are valuable tools for characterizing ANS function at the group level for persons afflicted with chronic MSDs, although they are more often applied in evaluation of autonomic neuropathies, and risk assessment for cardiovascular disease. Autonomic provocations should preferably be standardized, non-invasive and target specific reflex pathways. In preparation, it is important to avoid substances that may affect ANS regulation, such as beta blocker drugs, and to be fully recovered from any acute illnesses. Furthermore, subjects should avoid caffeine, nicotine, large meals, and extensive physical activity at the day of testing (Weimer 2010). Commonly used tests include: sustained hand grip, cold pressor, deep breathing, orthostatic, and mental stress tests.

The sustained (static) hand grip test can be used to assess sympathetic nervous function, so long as the subject is able to perform a proper calibration contraction close to their maximal voluntary effort. The static test consists of pressing a dynamometer with the hand at 30% of maximal voluntary contraction for duration of approximately 3 minutes. The hand grip test activates mechanical and chemically sensitive muscle receptors that tend to give rise to a distinct cardiovascular response due to an initial reduction of parasympathetic (vagal) activity followed by an increase in sympathetic tone, i.e., the exercise pressor reflex (Khurana and Setty 1996; Smith et al. 2006). Static contractions have been applied in several studies to differentiate between chronic MSDs and healthy subject groups (Gockel et al. 1995; Hallman et al. 2011).

The cold pressor test is also frequently used to test autonomic function, and is based on submersion of the hand or foot in cold water (between 1 and 5 degrees Celsius). This test activates nociceptive afferents, which in turn activate the efferent sympathetic nervous system, and inhibit vagal modulation of the heart, which is associated with increases in heart rate, arterial blood pressure and muscle sympathetic nerve activity (Victor et al. 1987). Previous studies have demonstrated its applicability in cases of chronic MSDs (Vaeroy et al. 1989; Acero et al. 1999). Due to pain intolerance, a maximum of 3 minute test duration can be recommended for assessment of this population.

Orthostatic stressors are widely excepted tests for reliable assessment of sympathetic (adrenergic) function by recording blood pressure and heart rate changes in response to head-upright tilt (i.e., passive orthostatic test) or standing up from a supine position (i.e., active orthostatic test). These procedures induce a sequence of cardiovascular reflexes controlled by the sympathetic nervous system, mainly characterized by increases in heart rate and diastolic blood pressure, to maintain adequate perfusion to the brain (Weimer 2010). Signs of orthostatic intolerance have been found among fibromyalgia patients, with reduced blood pressure during upright standing indicating impaired sympathetic function (Bou-Holaigah et al. 1997; Furlan et al. 2005; El-Sawy et al. In press)

A multitude of mental stressors, such as the colour-word interference test, mental arithmetic, public speech, and the social trial stress test have been used in experiments for assessment of sympathetic reactions at local and systemic levels. The physiological

responses induced by mental stressors may vary to greatly axross individuals, as well as between different types of tasks (Fechir et al. 2008), and are largely dependent on cognitive and behavioural processes. Increased sympathetic reactivity to mental stress is correlated with subjective stress ratings, and is associated with a wide range of pathological conditions, including chronic MSDs (Lundberg 2006).

Deep breathing by following a paced stimulus (e.g., 5 breaths per minute) is a strong parasympathetic provocation, and it induces large oscillations in beat-to-beat heart rate. This test can thus be used for assessment of parasympathetic cardiac regulation, as derived by computing the mean difference between the shortest RR interval at inhalation and the longest RR interval at exhalation.

To ensure the quality of the results obtained using any of the above tests, it is essential to control for possible confounding factors, that is, factors that influence both the independent variable and the outcome variable. For example, if the purpose is to investigate the effect of gender on resting blood pressure, a possible confounder is psychological stress. Stress may be more prevalent in females than males, and may thus result in elevated female blood pressure. One advantage of performing tests in a laboratory setting is that it is possible to control for many potential confounders that can have a direct influence on ANS regulation, including temperature, noise, body position, prior food and medication intake. However, it is also important to account for other behavioural (physical activity, sleep), psychological (depression, anxiety, stress) and physiological (various diseases, circadian rhythms) factors, which may influence autonomic regulation, leading to erroneous results.

One must also consider, however, whether the results obtained under experimental conditions can be generalized to real life conditions. How well do laboratory stressors used in the lab match those occurring in a real working environment with regard to type, intensity and duration? Ambulatory monitoring can, therefore, be used as an effective complement to laboratory testing, as it allows assessment of many physiological variables under real-life conditions. Due to the fast development of ambulatory devices and their accompanying signal processing software, ambulatory monitoring is mainly non-invasive, and relatively easy to wear under periods of several days. Thus, such methods can be used in research, by clinicians, and for coaching (e.g., in sports and exercise).

## 10. ANS involvement in chronic MSDs, implications for treatment

The above studies suggest that deviations in ANS regulation constitute an important element of the pathogenesis of chronic muscle pain. Chronic MSDs are considered to be a state of allostatic load, including continuation of pain due to maladaptive ANS regulation of anti-nociceptive and nociceptive processes. It is thus hypothesized that treatment of chronic MSDs will benefit from restoring ANS balance.

How do individuals recover from this complex vicious cycle? Although the external exposures, such as those mechanical and psychological strains people may encounter at work, could be partly avoided by staying at home or by changing to another occupation, it is

not possible to just switch off the internal exposure: increased sympathetic activity due to nociception.

It does not seem to be a coincidence that effective treatments of chronic MSDs are also beneficial for ANS balance, particularly for improving cardiovascular control. A variety of forms of physical activity and exercise are established strategies for treatment of muscle strength and function, perceived pain reduction , and for improving cardiovascular fitness and general health (Ylinen et al. 2003; Andersen et al. 2008). Physical activity may also reduce perceived stress and acts preventing against various chronic diseases (Warburton et al. 2006). Although increased physical activity is strongly associated with long-term effects on autonomic regulation, surprisingly little is known about this relationship regarding chronic MSDs. Considering the proposed model of ANS involvement in chronic musculoskeletal pain at local and systemic levels, we would expect that improvement of pain by increasing or adjusting the level of physical activity may be accompanied by restoration of ANS regulation. Relaxation techniques, for example by using individually based slow breathing (Hallman et al. 2011), or psychological treatments aiming at reducing perceived stress, may also be considered for improving ANS balance in people with musculoskeletal pain. Thus, combined strategies, including both adjustments of physical activity levels and psychological stress, may prove to be effective for prevention and treatment of chronic MSDs.

## 11. Conclusion

Studies indicate that the involvement of the ANS at both the systemic and local levels is an important element of the pathogenesis of chronic musculoskeletal pain. It is hypothesized that treatment of chronic MSDs will benefit from improving ANS balance. Future studies on chronic MSDs should look closer at the possible causal relations between the ANS and pain. There is also a need to consider many other factors that could affect this relationship.

## Author details

David M Hallman and Eugene Lyskov
*University of Gävle, Centre for Musculoskeletal Research, Sweden*

## 12. References

Acero, C. O., Kuboki, T., Maekawa, K., Yamashita, A. and Clark, G. T. (1999). Haemodynamic responses in chronically painful, human trapezius muscle to cold pressor stimulation. *Archives of Oral Biology* 44(10): 805-812.

Andersen, L., Blangsted, A., Nielsen, P., Hansen, L., Vedsted, P., Sjøgaard, G., et al. (2010). Effect of cycling on oxygenation of relaxed neck/shoulder muscles in women with and without chronic pain. *European Journal of Applied Physiology* 110(2): 389-394.

Andersen, L. L., Jørgensen, M. B., Blangsted, A. K., Pedersen, M. T., Hansen, E. A. and Sjøgaard, G. (2008). A Randomized Controlled Intervention Trial to Relieve and Prevent

Neck/Shoulder Pain. *Medicine & Science in Sports & Exercise* 40(6): 983-990 910.1249/MSS.1240b1013e3181676640.

Apkarian, A. V., Bushnell, M. C., Treede, R.-D. and Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain* 9(4): 463-463.

Arendt-Nielsen, L. and Graven-Nielsen, T. (2003). Central sensitization in fibromyalgia and other musculoskeletal disorders. *Current Pain and Headache Reports* 7(5): 355-361.

Barbe, M. F. and Barr, A. E. (2006). Inflammation and the pathophysiology of work-related musculoskeletal disorders. *Brain, Behavior, and Immunity* 20(5): 423-429.

Benarroch, E. (2006). Pain-autonomic interactions. *Neurological Sciences* 27(0): s130-s133.

Bilan, A., Witczak, A., Palusinski, R., Myslinski, W. and Hanzlik, J. (2005). Circadian rhythm of spectral indices of heart rate variability in healthy subjects. *Journal of Electrocardiology* 38(3): 239-243.

Bingel, U., Schoell, E., Herken, W., Büchel, C. and May, A. (2007). Habituation to painful stimulation involves the antinociceptive system. *Pain* 131(1–2): 21-30.

Blangsted, A., Søgaard, K., Christensen, H. and Sjøgaard, G. (2004). The effect of physical and psychosocial loads on the trapezius muscle activity during computer keying tasks and rest periods. *European Journal of Applied Physiology* 91(2): 253-258.

Bongers, P., Ijmker, S., van den Heuvel, S. and Blatter, B. (2006). Epidemiology of work related neck and upper limb problems: Psychosocial and personal risk factors (Part I) and effective interventions from a bio behavioural perspective (Part II). *Journal of Occupational Rehabilitation* 16(3): 272-295.

Borovikova, L. V., Ivanova, S., Zhang, M., Yang, H., Botchkina, G. I., Watkins, L. R., et al. (2000). Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405(6785): 458-462.

Bou-Holaigah, I., Calkins, H., Flynn, J. A., Tunin, C., Chang, H. C., Kan, J. S., et al. (1997). Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. *Clinical and experimental rheumatology* 15(3): 239-246.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R. and Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain* 10(4): 287-333.

Bruehl, S. and Chung, O. Y. (2004). Interactions between the cardiovascular and pain regulatory systems: an updated review of mechanisms and possible alterations in chronic pain. *Neuroscience & Biobehavioral Reviews* 28(4): 395-414.

Buckwalter, J. B., Mueller, P. J. and Clifford, P. S. (1997). Sympathetic vasoconstriction in active skeletal muscles during dynamic exercise. *J Appl Physiol* 83(5): 1575-1580.

Campbell, T. S., Ditto, B., Séguin, J. R., Sinray, S. and Tremblay, R. E. (2003). Adolescent Pain Sensitivity Is Associated With Cardiac Autonomic Function and Blood Pressure Over 8 Years. *Hypertension* 41(6): 1228-1233.

Chouchou, F., Pichot, V., Perchet, C., Legrain, V., Garcia-Larrea, L., Roche, F., et al. (2011). Autonomic pain responses during sleep: A study of heart rate variability. *European Journal of Pain* 15(6): 554-560.

Christensen, J. O. and Knardahl, S. (2011). Work and neck pain: A prospective study of psychological, social, and mechanical risk factors. *Pain* 151(1): 162-173.

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology* 5(7): 374-381.

Cohen, H., Benjamin, J., Geva, A. B., Matar, M. A., Kaplan, Z. and Kotler, M. (2000). Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Research* 96(1): 1-13.

Côté, P., van der Velde, G., Cassidy, J. D., Carroll, L. J., Hogg-Johnson, S., Holm, L. W., et al. (2009). The Burden and Determinants of Neck Pain in Workers: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Journal of Manipulative and Physiological Therapeutics* 32(2, Supplement 1): S70-S86.

Critchley, H. D., Corfield, D. R., Chandler, M. P., Mathias, C. J. and Dolan, R. J. (2000). Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *The Journal of Physiology* 523(1): 259-270.

Dubé, A.-A., Duquette, M., Roy, M., Lepore, F., Duncan, G. and Rainville, P. (2009). Brain activity associated with the electrodermal reactivity to acute heat pain. *NeuroImage* 45(1): 169-180.

Edwards, R. R., Almeida, D. M., Klick, B., Haythornthwaite, J. A. and Smith, M. T. (2008). Duration of sleep contributes to next-day pain report in the general population. *Pain* 137(1): 202-207.

El-Sawy, N., El-Tantawi, G., Achmawi, G. A. H., Sultan, H. and Younis, S. (In press). Autonomic changes in fibromyalgia: Clinical and electrophysiological study. *Alexandria Journal of Medicine*.

Elvin, A., Siösteen, A.-K., Nilsson, A. and Kosek, E. (2006). Decreased muscle blood flow in fibromyalgia patients during standardised muscle exercise: A contrast media enhanced colour doppler study. *European Journal of Pain* 10(2): 137-144.

Fechir, M., Schlereth, T., Purat, T., Kritzmann, S., Geber, C., Eberle, T., et al. (2008). Patterns of sympathetic responses induced by different stress tasks. *Open Neurobiology Journal* 2: 25-31.

Fishbain, D. A., Cutler, R. B., Cole, B., Lewis, J., Smets, E., Rosomoff, H. L., et al. (2004). Are Patients with Chronic Low Back Pain or Chronic Neck Pain Fatigued? 5: 187-195.

Furlan, R., Colombo, S., Perego, F., Atzeni, F., Diana, A., Barbic, F., et al. (2005). Abnormalities of cardiovascular neural control and reduced orthostatic tolerance in patients with primary fibromyalgia. *The Journal of Rheumatology* 32(9): 1787-1793.

Ge, H.-Y., Fernández-de-las-Peñas, C. and Arendt-Nielsen, L. (2006). Sympathetic facilitation of hyperalgesia evoked from myofascial tender and trigger points in patients with unilateral shoulder pain. *Clinical Neurophysiology* 117(7): 1545-1550.

Gockel, M., Lindholm, H., Alaranta, H., Viljanen, A., Lindquist, A. and Lindholm, T. (1995). Cardiovascular functional disorder and stress among patients having neck-shoulder symptoms. *Annals of the Rheumatic Diseases* 54(6): 494-497.

Gockel, M., Lindholm, H., Niemist, L. and Hurri, H. (2008). Perceived Disability but Not Pain is Connected with Autonomic Nervous Function Among Patients with Chronic Low Back Pain. *Journal of Rehabilitation Medicine* 40: 355-358.

Gold, J., Cherniack, M., Hanlon, A., Dennerlein, J. and Dropkin, J. (2009). Skin temperature in the dorsal hand of office workers and severity of upper extremity musculoskeletal disorders. *International Archives of Occupational and Environmental Health* 82(10): 1281-1292.

Griffin, D. W., Harmon, D. C. and Kennedy, N. M. (2012). Do patients with chronic low back pain have an altered level and/or pattern of physical activity compared to healthy individuals? A systematic review of the literature. *Physiotherapy* 98(1): 13-23.

Haley, R. W., Vongpatanasin, W., Wolfe, G. I., Bryan, W. W., Armitage, R., Hoffmann, R. F., et al. (2004). Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome. *The American Journal of Medicine* 117(7): 469-478.

Hallman, D., Lindberg, L.-G., Arnetz, B. and Lyskov, E. (2011). Effects of static contraction and cold stimulation on cardiovascular autonomic indices, trapezius blood flow and muscle activity in chronic neck–shoulder pain. *European Journal of Applied Physiology* 111(8): 1725-1735.

Hallman, D. and Lyskov, E. (2010). Monitoring of heart rate variability, physical activity and percieved stress and energy in daily life among persons suffering from neck-shoulder pain. Nordic Conference Odense, Danmark, University of Southern Danmark: 57.

Hallman, D., Olsson, E., von Schéele, B., Melin, L. and Lyskov, E. (2011). Effects of Heart Rate Variability Biofeedback in Subjects with Stress-Related Chronic Neck Pain: A Pilot Study. *Applied Psychophysiology and Biofeedback* 36(2): 71-80.

Hogg-Johnson, S., van der Velde, G., Carroll, L. J., Holm, L. W., Cassidy, J. D., Guzman, J., et al. (2009). The Burden and Determinants of Neck Pain in the General Population: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Journal of Manipulative and Physiological Therapeutics* 32(2, Supplement 1): S46-S60.

Hägg, G. M. (2003). The Cinderella hypothesis. 127-132.

Jae, S., Heffernan, K., Park, S.-H., Jung, S.-H., Yoon, E., Kim, E., et al. (2010). Does an acute inflammatory response temporarily attenuate parasympathetic reactivation? *Clinical Autonomic Research* 20(4): 229-233.

Johansson, H., Windhorst, U., Djupsjöbacka, M. and Passatore, M., Eds. (2003). *Chronic Work-Related Myalgia. Neuromuscular Mechanisms behind Work-Related Chronic Muscle Pain Syndromes*. Gävle, Gävle University Press.

Johnston, V., Jull, G., Darnell, R., Jimmieson, N. and Souvlis, T. (2008). Alterations in cervical muscle activity in functional and stressful tasks in female office workers with neck pain. *European Journal of Applied Physiology* 103(3): 253-264.

Joyner, M. J., Nauss, L. A., Warner, M. A. and Warner, D. O. (1992). Sympathetic modulation of blood flow and O2 uptake in rhythmically contracting human forearm muscles. *American Journal of Physiology - Heart and Circulatory Physiology* 263(4): H1078-H1083.

Jänig, W. (2003). Relationship Between Pain and Autonomic Phenomena in Headache and Other Pain Conditions. *Cephalalgia* 23(1 suppl): 43-48.

Kalezic, N., Noborisaka, Y., Nakata, M., Crenshaw, A. G., Karlsson, S., Lyskov, E., et al. (2010). Cardiovascular and muscle activity during chewing in whiplash-associated disorders (WAD). *Archives of Oral Biology* 55(6): 447-453.

Kalezic, N., Roatta, S., Lyskov, E. and Johansson, H. (2003). Stress - An Introductory Overview. *Chronic Work-related Myalgia. Neuromuscular Mechanisms behind Work-related Chronic Muscle pain Syndromes*. H. Johansson, U. Windhorst, M. Djupsjöbacka and M. Passatore. Gävle, Gävle University press: 57-71.

Kalezic, N., Åsell, M., Kerschbaumer, H. and Lyskov, E. (2007). Physiological Reactivity to Functional Tests in Patients with Chronic Low Back Pain. *Journal Of Musculoskeletal Pain* 15(1): 29 - 40.

Keijsers, E., Feleus, A., Miedema, H. S., Koes, B. W. and Bierma-Zeinstra, S. M. A. (2010). Psychosocial factors predicted nonrecovery in both specific and nonspecific diagnoses at arm, neck, and shoulder. *Journal of Clinical Epidemiology* 63(12): 1370-1379.

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S. and Jelinek, H. F. (2012). Depression, Comorbid Anxiety Disorders, and Heart Rate Variability in Physically Healthy, Unmedicated Patients: Implications for Cardiovascular Risk. *PLoS ONE* 7(2): e30777.

Khurana, R. and Setty, A. (1996). The value of the isometric hand-grip test-studies in various autonomic disorders. *Clinical Autonomic Research* 6(4): 211-218.

Kingsley, J. D., Panton, L. B., McMillan, V. and Figueroa, A. (2009). Cardiovascular Autonomic Modulation After Acute Resistance Exercise in Women With Fibromyalgia. *Archives of Physical Medicine and Rehabilitation* 90(9): 1628-1634.

Kleiger, R. E., Stein, P. K. and Bigger, J. T. (2005). Heart Rate Variability: Measurement and Clinical Utility. *The Annals of Noninvasive Electrocardiology* 10(1): 88-101.

Krantz, G., Forsman, M. and Lundberg, U. (2004). Consistency in physiological stress responses and electromyographic activity during induced stress exposure in women and men. *Integrative Physiological and Behavioral Science* 39(2): 105-118.

Larsman, P., Thorn, S., Søgaard, K., Sandsjö, L., Sjøgaard, G. and Kadefors, R. (2009). Work related perceived stress and muscle activity during standardized computer work among female computer users. *Work: A Journal of Prevention, Assessment and Rehabilitation* 32(2): 189-199.

Larsson, B., Björk, J., Börsbo, B. and Gerdle, B. (2012). A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. *European Journal of Pain*: n/a-n/a. (In press).

Larsson, B., Søgaard, K. and Rosendal, L. (2007). Work related neck-shoulder pain: a review on magnitude, risk factors, biochemical characteristics, clinical picture and preventive interventions. *Best Practice & Research Clinical Rheumatology* 21(3): 447-463.

Larsson, R., Öberg, P. A. and Larsson, S. E. (1999). Changes of trapezius muscle blood flow and electromyography in chronic neck pain due to trapezius myalgia. *Pain* 79: 45-50.

Larsson, S. E., Bodegård, L., Henriksson, K. G. and Öberg, P. Å. (1990). Chronic trapezius myalgia. Morphology and blood flow studied in 17 patients. *Acta Orthopaedica Scandinavica* 61: 394-398.

Larsson, S. E., Larsson, R., Zhang, Q., Cai, H. and Öberg, P. Å. (1995). Effects of psychophysiological stress on trapezius muscles blood flow and electromyography during static load. *European Journal of Applied Physiology and Occupational Physiology* 71: 493-498.

Larsson, S. E., Ålund, M., Cai, H. and Öberg, P. Å. (1994). Chronic pain after soft-tissue injury of the cervical spine: trapezius muscle blood flow and electromyography at static loads and fatigue. *Pain*. 57: 173-180.

Lerma, C., Martinez, A., Ruiz, N., Vargas, A., Infante, O. and Martinez-Lavin, M. (2011). Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. *Arthritis Research & Therapy* 13(6): R185.

Lindell, L., Bergman, S., Petersson, I. F., Jacobsson, L. T. H. and Herrström, P. (2000). Prevalence of fibromyalgia and chronic widespread pain. *Scandinavian Journal of Primary Health Care* 18(3): 149-153.

Linton, S. J. (2000). A Review of Psychological Risk Factors in Back and Neck Pain. *Spine* 25(9): 1148-1156.

Lundberg, U. (2006). Stress, subjective and objective health. *International Journal of Social Welfare* 15: S41-S48.

Lundberg, U., Elfsberg Dohns, I., Melin, B., Sandsjö, L., Palmerud, G., Kadefors, R., et al. (1999). Psychophysiological stress responses, muscle tension, and neck and shoulder pain among supermarket cashiers. *Journal of Occupational Health Psychology* 4(3): 245-255.

Lundberg, U., Kadefors, R., Melin, B., Palmerud, G., Hassmén, P., Engström, M., et al. (1994). Psychophysiological stress and emg activity of the trapezius muscle. *International Journal of Behavioral Medicine* 1(4): 354-370.

Madeleine, P., Mathiassen, S. and Arendt-Nielsen, L. (2008). Changes in the degree of motor variability associated with experimental and chronic neck–shoulder pain during a standardised repetitive arm movement. *Experimental Brain Research* 185(4): 689-698.

Maekawa, K., Clark, G. T. and Kuboki, T. (2002). Intramuscular hypoperfusion, adrenergic receptors, and chronic muscle pain. *The Journal of Pain* 3(4): 251-260.

Malik, M. (1996). Task force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart Rate Variability : Standards of Measurement, Physiological Interpretation, and Clinical Use. *European Heart Journal* 93(5): 1043-1065.

Malinen, S., Vartiainen, N., Hlushchuk, Y., Koskinen, M., Ramkumar, P., Forss, N., et al. (2010). Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proceedings of the National Academy of Sciences* 107(14): 6493-6497.

Martinez-Lavin, M. (2007). Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Research & Therapy* 9(4): 216.

Martinez-Lavin, M. (2012). Fibromyalgia: When Distress Becomes (Un)sympathetic Pain. *Pain Research and Treatment* 2012.

Martínez-Lavín, M., Hermosillo, A. G., Rosas, M. and Soto, M. E. (1998). Circadian studies of autonomic nervous balance in patients with fibromyalgia: A heart rate variability analysis. *Arthritis & Rheumatism* 41(11): 1966-1971.

Martinez-Lavin, M., Vidal, M., Barbosa, R.-E., Pineda, C., Casanova, J.-M. and Nava, A. (2002). Norepinephrine-evoked pain in fibromyalgia. A randomized pilot study [ISRCTN70707830]. *BMC Musculoskeletal Disorders* 3(1): 2.

McEwen, B. S. (1998). Stress, Adaptation, and Disease: Allostasis and Allostatic Load. *Annals of the New York Academy of Sciences* 840(1): 33-44.

McEwen, B. S. (2000). The neurobiology of stress: from serendipity to clinical relevance. *Brain Research* 886(1-2): 172-189.

McEwen, B. S. (2007). Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. *Physiological Reviews* 87(3): 873-904.

Mehta, R. K. and Agnew, M. J. (2011). Effects of concurrent physical and mental demands for a short duration static task. *International Journal of Industrial Ergonomics* 41(5): 488-493.

Mostoufi, S. M., Afari, N., Ahumada, S. M., Reis, V. and Wetherell, J. L. (2012). Health and distress predictors of heart rate variability in fibromyalgia and other forms of chronic pain. *Journal of Psychosomatic Research* 72(1): 39-44.

Neugebauer, V., Li, W., Bird, G. C. and Han, J. S. (2004). The Amygdala and Persistent Pain. *The Neuroscientist* 10(3): 221-234.

Newton, J. L., Pairman, J., Hallsworth, K., Moore, S., Plotz, T. and Trenell, M. I. (2011). Physical activity intensity but not sedentary activity is reduced in chronic fatigue syndrome and is associated with autonomic regulation. *QJM*. vol, issue, pages: 104(8):681-687

Nijs, J., Daenen, L., Cras, P., Struyf, F., Roussel, N. and Oostendorp, R. A. B. (2012). Nociception Affects Motor Output: A Review on Sensory-motor Interaction With Focus on Clinical Implications. *The Clinical Journal of Pain* 28(2): 175-181 110.1097/AJP.1090b1013e318225daf318223.

Nilsen, K. B., Sand, T., Borchgrevink, P., Leistad, R. B., Rø, M. and Westgaard, R. H. (2008). A unilateral sympathetic blockade does not affect stress-related pain and muscle activity in patients with chronic musculoskeletal pain. *Scandinavian Journal of Rheumatology* 37(1): 53-61.

Nilsen, K. B., Sand, T., Westgaard, R. H., Stovner, L. J., White, L. R., Bang Leistad, R., et al. (2007). Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. *European Journal of Pain* 11(7): 743-755.

Nolet, P. S., Côté, P., Cassidy, J. D. and Carroll, L. J. (2012). The Association Between Self-Reported Cardiovascular Disorders and Troublesome Neck Pain: A Population-Based Cohort Study. *Journal of Manipulative and Physiological Therapeutics* 35(3):176-183.

Oliveira, L. R., de Melo, V. U., Macedo, F. N., Barreto, A. S., Badaue-Passos Jr, D., Viana dos Santos, M. R., et al. (2012). Induction of chronic non-inflammatory widespread pain increases cardiac sympathetic modulation in rats. *Autonomic Neuroscience* 167(1): 45-49.

Passatore, M. and Roatta, S. (2006). Influence of sympathetic nervous system on sensorimotor function: whiplash associated disorders (WAD) as a model. *European Journal of Applied Physiology* 98(5): 423-449.

Piché, M., Arsenault, M. and Rainville, P. (2010). Dissection of perceptual, motor and autonomic components of brain activity evoked by noxious stimulation. *Pain* 149(3): 453-462.

Price, D. D. (2000). Psychological and Neural Mechanisms of the Affective Dimension of Pain. *Science* 288(5472): 1769-1772.

Pritchard, M., Pugh, N., Wright, I. and Brownlee, M. (1999). A vascular basis for repetitive strain injury. *Rheumatology* 38(7): 636-639.

Reyes del Paso, G. A., Garrido, S., Pulgar, Á. and Duschek, S. (2011). Autonomic cardiovascular control and responses to experimental pain stimulation in fibromyalgia syndrome. *Journal of Psychosomatic Research* 70: 125-134.

Reyes del Paso, G. A., Garrido, S., Pulgar, Á., Martín-Vázquez, M. and Duschek, S. (2010). Aberrances in Autonomic Cardiovascular Regulation in Fibromyalgia Syndrome and Their Relevance for Clinical Pain Reports. *Psychosomatic Medicine* 72(5): 462-470.

Riva, R., Mork, P. J., Westgaard, R. H. and Lundberg, U. (2012). Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. *Psychoneuroendocrinology* 37(2): 299-306.

Roatta, S., Arendt-Nielsen, L. and Farina, D. (2008). Sympathetic-induced changes in discharge rate and spike-triggered average twitch torque of low-threshold motor units in humans. *The Journal of Physiology* 586(22): 5561-5574.

Roatta, S. and Farina, D. (2010). Sympathetic actions on the skeletal muscle. *Exerc Sport Sci Rev* 38(1): 31-35.

Rosas-Ballina, M. and Tracey, K. J. (2009). Cholinergic control of inflammation. *Journal of Internal Medicine* 265(6): 663-679.

Rosendal, L., Larsson, B., Kristiansen, J., Peolsson, M., Søgaard, K., Kjær, M., et al. (2004). Increase in muscle nociceptive substances and anaerobic metabolism in patients with trapezius myalgia: microdialysis in rest and during exercise. *Pain* 112(3): 324-334.

Rouwette, T., Vanelderen, P., Roubos, E. W., Kozicz, T. and Vissers, K. (2011). The amygdala, a relay station for switching on and off pain. *European Journal of Pain*: 16(6):782-792.

Saito, M., Mano, T., Abe, H. and Iwase, S. (1986). Responses in muscle sympathetic nerve activity to sustained hand-grips of different tensions in humans. *European Journal of Applied Physiology and Occupational Physiology* 55(5): 493-498.

Sandberg, M., Larsson, B., Lindberg, L.-G. and Gerdle, B. (2005). Different patterns of blood flow response in the trapezius muscle following needle stimulation (acupuncture) between healthy subjects and patients with fibromyalgia and work-related trapezius myalgia. *European Journal of Pain* 9(5): 497-510.

Sato, A. and Schmidt, R. F. (1973). Somatosympathetic Reflexes: Afferent Fibers, Central Pathways, Discharge Characteristics. *Physiological Reviews* 53(4): 916-947.

Schlereth, T. and Birklein, F. (2008). The Sympathetic Nervous System and Pain. *NeuroMolecular Medicine* 10(3): 141-147.

Seals, D. R. and Enoka, R. M. (1989). Sympathetic activation is associated with increases in EMG during fatiguing exercise. *Journal of Applied Physiology* 66(1): 88-95.

Sharma, S. D., Smith, E. M., Hazleman, B. L. and Jenner, J. R. (1997). Thermographic changes in keyboard operators with chronic forearm pain. *BMJ* 314(7074): 118-.

Sjøgaard, G., Lundberg, U. and Kadefors, R. (2000). The role of muscle activity and mental load in the development of pain and degenerative processes at the muscle cell level during computer work. *European Journal of Applied Physiology* 83(2): 99-105.

Sjörs, A., Larsson, B., Dahlman, J., Falkmer, T. and Gerdle, B. (2009). Physiological responses to low-force work and psychosocial stress in women with chronic trapezius myalgia. *BMC Musculoskeletal Disorders* 10(1): 63.

Sjörs, A., Larsson, B., Persson, A. and Gerdle, B. (2011). An increased response to experimental muscle pain is related to psychological status in women with chronic non-traumatic neck-shoulder pain. *BMC Musculoskeletal Disorders* 12(1): 230.

Smith, S. A., Mitchell, J. H. and Garry, M. G. (2006). The mammalian exercise pressor reflex in health and disease. *Experimental Physiology* 91(1): 89-102.

Spaeth, M., Rizzi, M. and Sarzi-Puttini, P. (2011). Fibromyalgia and Sleep. *Best Practice & Research Clinical Rheumatology* 25(2): 227-239.

Strøm, V., Røe, C. and Knardahl, S. (2009). Work-induced pain, trapezius blood flux, and muscle activity in workers with chronic shoulder and neck pain. *Pain* 144(1-2): 147-155.

Thayer, J. F., Yamamoto, S. S. and Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology* 141(2): 122-131.

Thomas, G. D. and Segal, S. S. (2004). Neural control of muscle blood flow during exercise. *J Appl Physiol* 97(2): 731-738.

Thorn, S., Søgaard, K., Kallenberg, L. A. C., Sandsjö, L., Sjøgaard, G., Hermens, H. J., et al. (2007). Trapezius muscle rest time during standardised computer work – A comparison of female computer users with and without self-reported neck/shoulder complaints. *Journal of Electromyography and Kinesiology* 17(4): 420-427.

Thunberg, J., Lyskov, E., Korotkov, A., Ljubisavljevic, M., Pakhomov, S., Katayeva, G., et al. (2005). Brain processing of tonic muscle pain induced by infusion of hypertonic saline. *European Journal of Pain* 9(2): 185-194.

Torp, S., Riise, T. and Moen, B. E. (2001). The Impact of Psychosocial Work Factors on Musculoskeletal Pain: A Prospective Study. *Journal of Occupational and Environmental Medicine* 43(2): 120-126.

Tracey, K. J. (2002). The inflammatory reflex. *Nature* 420(6917): 853-859.

Trinder, J., Waloszek, J., Woods, M. and Jordan, A. (2012). Sleep and cardiovascular regulation. *Pflügers Archiv European Journal of Physiology* 463(1): 161-168.

Ulrich-Lai, Y. M. and Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 10(6): 397-409.

Vaeroy, H., Qiao, Z. G., Morkrid, L. and Forre, O. (1989). Altered sympathetic nervous system response in patients with fibromyalgia (fibrositis syndrome). *The Journal of rheumatology* 16(11): 1460-1465.

Wang, Y., Szeto, G. and Chan, C. (2011). Effects of physical and mental task demands on cervical and upper limb muscle activity and physiological responses during computer tasks and recovery periods. *European Journal of Applied Physiology* 111(11): 2791-2803.

Warburton, D. E. R., Nicol, C. W. and Bredin, S. S. D. (2006). Health benefits of physical activity: the evidence. *CMAJ* 174(6): 801-809.

Weimer, L. H. (2010). Autonomic Testing: Common Techniques and Clinical Applications. *The Neurologist* 16(4): 215-222

Victor, R., Leimbach, W., Seals, D., Wallin, B. and Mark, A. (1987). Effects of the cold pressor test on muscle sympathetic nerve activity in humans. *Hypertension* 9(5): 429-436.

Vierck, J. C. J. (2006). Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain* 124(3): 242-263.

Willmann, M. and Bolmont, B. (2012). The trapezius muscle uniquely lacks adaptive process in response to a repeated moderate cognitive stressor. *Neuroscience Letters* 506(1): 166-169.

Visser, B. and van Dieën, J. H. (2006). Pathophysiology of upper extremity muscle disorders. *Journal of Electromyography and Kinesiology* 16(1): 1-16.

Vrijkotte, T. G. M., van Doornen, L. J. P. and de Geus, E. J. C. (2000). Effects of Work Stress on Ambulatory Blood Pressure, Heart Rate, and Heart Rate Variability. *Hypertension* 35(4): 880-886.

Ylinen, J., Takala, E.-P., Nykänen, M., Häkkinen, A., Mälkiä, E., Pohjolainen, T., et al. (2003). Active Neck Muscle Training in the Treatment of Chronic Neck Pain in Women. *JAMA: The Journal of the American Medical Association* 289(19): 2509-2516.

IntechOpen