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Non-Specific Chronic Musculoskeletal Pain
Prevalence, Spatial Extent of Pain, Mental Comorbidities, and
Psychophysiological Patterns

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Publications for the cumulative dissertation

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2. Gerhardt, A., Hartmann, M., Schuller-Roma, B., Blumenstiel, K., Bieber, C., Eich, W., & Steffen, S. (2011). The prevalence and type of Axis-I and Axis-II mental disorders in subjects with non-specific chronic back pain: Results from a population-based study. *Pain Medicine, 12,* 1231-1240.

3. Blumenstiel, K[*]., Gerhardt, A[*]., Rolke, R., Bieber, C., Tesarz, J., Friederich, H.-C., Eich, W., & Treede, R.-D. (2011). Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clinical Journal of Pain, 27,* 682-690. [*]both authors contributed equally to the study

4. Tesarz, J., Gerhardt, A., Schommer, K., Treede, R.-D., & Eich, W. (2013). Alterations in endogenous pain modulation of endurance athletes: An experimental study using quantitative sensory testing and the cold pressor task. *Pain, in press*.

5. Gerhardt, A., Hartmann, M., Tesarz, J., Janke, S., Leisner, S., Seidler, G., & Eich, W. (2012). Subgroups of musculoskeletal pain patients and their psychobiological patterns – The LOGIN study protocol. *BMC Musculoskeletal Disorders, 13*, 136.

1. Introduction

Pain is ubiquitous and serves an important protective function. However, pain also causes a burden both to the patient and to society (Krismer & van Tulder, 2007; Wenig, Schmidt, Kohlmann, & Schweikert, 2009). Musculoskeletal disorders, especially back pain (BP), are responsible for more days of sick leave than any other illness (DAK-Gesundheit, 2012; Techniker-Krankenkasse, 2012). Almost every person experiences BP at least once in their life (Schmidt et al., 2007), and the average prevalence of current chronic back pain (CBP) is 10-27% (Freburger et al., 2009; Picavet & Schouten, 2003; B. H. Smith, Elliott, Hannaford, Chambers, & Smith, 2004).

The most common type of CBP, non-specific CBP (Deyo, Rainville, & Kent, 1992), is the focus of this dissertation thesis. Although the word "chronic" implies that this pain cannot be healed, the ability to ameliorate this pain through treatment also seems to be low (Keller, Hayden, Bombardier, & van Tulder, 2007; Machado, Kamper, Herbert, Maher, & McAuley, 2009; Stein, Reinecke, & Sorgatz, 2010). Therefore, research is necessary to decrease the burden of CBP for both patients and society.

One important limitation of previous research is related to the methodologies used in these studies. Many studies have investigated highly selective clinical samples or very heterogeneous samples and used non-validated instruments. This hampers the generalization of their results. Therefore, there is not only a need for more research in general but also for research with high methodological quality in particular.

This research must consider that CBP seems to be a complex condition that usually involves further symptoms in addition to pain in the back. Furthermore, the group of patients with CBP is reportedly heterogeneous (Natvig, Bruusgaard, & Eriksen, 2001; A. Raspe, Matthis, Héon-Klin, & Raspe, 2003). Therefore, CBP is best described by a bio-psychosocial model (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Kikuchi, 2008). Application of such a model has been neglected; this is a second limitation of prior research. Therefore, a comprehensive assessment of psychosocial aspects and further co-morbidities is necessary to account for the complexity of CBP.

Although mechanism-based approaches were introduced long ago (Woolf et al., 1998), they have been neglected in research. The lack of specific mechanism-based treatment options might explain the current insufficiency of treatment. Thus, potential pathophysiological mechanisms should be studied and linked with clinical variables.

In summary, there is a need for research with high methodological quality that accounts for the complexity of CBP and links clinical manifestations with pathophysiological findings. The five studies encompassed by this dissertation thesis will contribute to a better understanding of CBP and foster the development of new treatment options and diagnostic markers.

In the first study, we determined the prevalence of non-specific CBP in a representative population-based sample in Germany to address the lack of valid recent information on this topic. Moreover, we considered the spatial extent of the pain and the bio-psychosocial model to verify that the group of CBP patients is heterogeneous. In the second study, we estimated the type and the prevalence of mental co-morbidities in the same sample. Previous studies may have overestimated the prevalence of mental disorders in CBP due to their use of highly selected clinical samples that might be especially burdened by their pain. In the third study, we examined the psychophysiological heterogeneity of CBP patients because it has been suggested that CBP patients also differ in neurobiological aspects. In the fourth study, we considered psychophysiological aspects of physical activity. Physical activity is a part of most CBP treatment programs, but the pathophysiological mechanisms underlying the effectiveness of physical activity remain largely unclear. In the fifth manuscript, we combined the results of the previous four studies and introduced a new study designed based on them and the most recent findings in regard to CBP. The study aims to identify mechanism-based subgroups of CBP patients and subsequently develop subgroup-specific treatment options.

In conclusion, the author has aimed to foster CBP research by combining the methodological advantages of population-based studies and clinical methods. Thereby, clinical data collected with validated instruments will be brought together with psychophysiological patterns. This will account for the heterogeneity of CBP patients and stimulate the development of new subgroup-specific treatment options.

2.0 Background

## 2.1 Musculoskeletal pain: definition and classification

According to the definition accepted by the International Association for the Study of Pain (IASP), pain is an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Mersky, 1979). This definition highlights the subjective aspects of pain that must be considered in research.

Musculoskeletal pain is pain of the bones, joints, muscles, or surrounding structures. The most common location of musculoskeletal pain is the back, which accounts for 22% to 48% of all musculoskeletal pain (Chung & Wong, 2007; Gureje, Von Korff, Simon, & Gater, 1998). Low BP, the most common type of BP, is defined as pain localized between the 12th rib and the inferior gluteal folds, with or without leg pain (Airaksinen et al., 2006). With regard to the pathology associated with BP, only 5% to 10% of BP cases are associated with a pathophysiological correlate (e.g., an inflammatory or degenerative disease such as spinal stenosis, fracture, disc hernia, ankylosing spondylitis, or rheumatoid arthritis). In most cases (>90%), the BP is non-specific (Deyo et al., 1992). This is a diagnosis of exclusion, meaning that no cause or structure responsible for the pain can be determined with currently available evaluation and/or diagnostic tools (S. S. Weiner & Nordin, 2010).

BP patients are categorized as acute, sub-acute, or chronic cases according to the duration of the pain. Acute BP occurs suddenly and lasts for less than 6 weeks. Pain that persists for more than 6 weeks but less than 3 months is classified as sub-acute. Pain with duration of more than 3 months is usually classified as chronic (Krismer & van Tulder, 2007). The focus of this dissertation thesis is non-specific chronic low BP. For simplicity, this entity will be referred to as CBP.

One important concept in CBP is the spatial extent of the pain, which is usually captured using a pain drawing. A pain drawing is a diagram of the body. Patients are usually asked to mark all areas in which they experience pain on the pain drawing (Figure 1a). It is possible to classify patients in different categories of pain extent based on these pain drawings. The commonly used categories are "chronic local pain" (CLP) and "chronic widespread pain"

(CWP). CWP is defined as axial pain (cervical, thoracic, lumbar, or sacral spine) with contralateral limb pain, whereas CLP is defined as all non-CWP (Wolfe et al., 1990). A transparent template can be used to facilitate the classification of CLP and CWP (Figure 1b). However, the spatial extent of the pain is a neglected aspect of CBP, and the designations of CLP and CWP might not fully describe the heterogeneity of CBP patients. Therefore, research that links pain extent with clinical variables and neurobiological correlates is necessary.
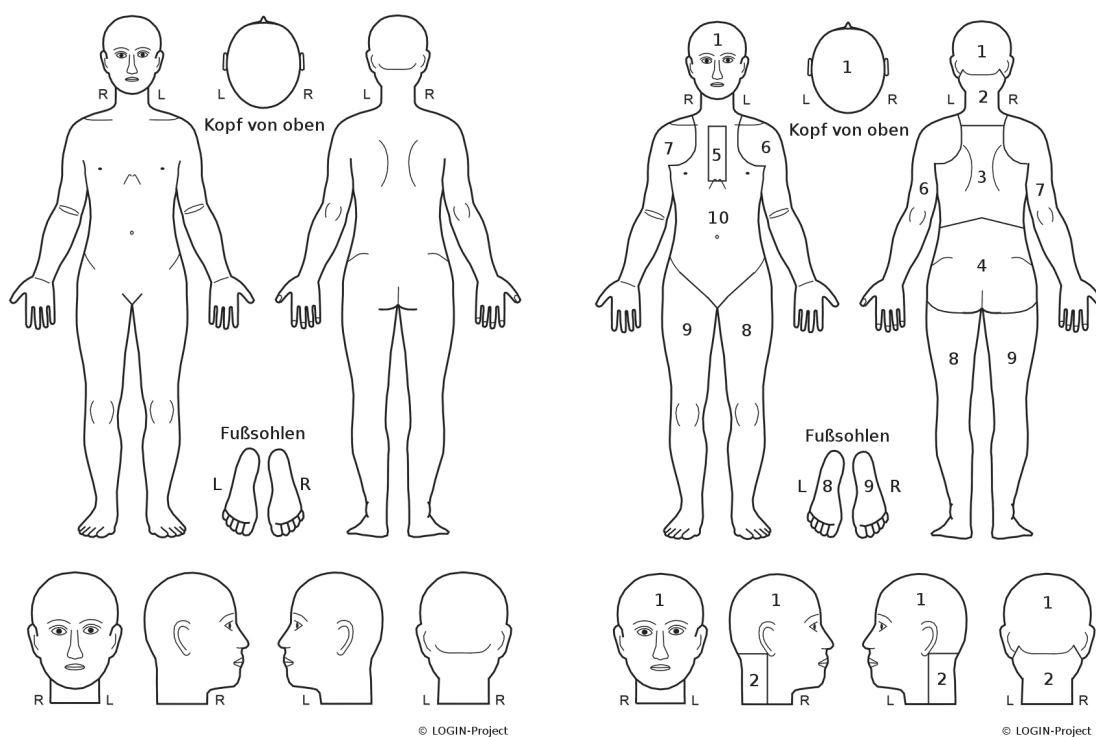
Figure 1a. Patients are asked to indicate all areas of their body in which they experience pain.

Figure 1b. The transparent template indicates the boundaries of each body region. It is placed over the drawings to assist in analysis.

2.2 Epidemiology of chronic musculoskeletal pain

Epidemiology is the study of the distribution and patterns of diseases or health-related variables and their causes or influences in well-defined populations. Thus, risk factors for diseases and targets for preventive approaches can be identified. One important concept in epidemiology is prevalence. Prevalence is defined as the proportion of cases in a population that satisfy the criteria for a respective disease (or e.g., a behavior or risk factor) at a given

time point. Thus, it is possible to estimate how common a risk factor is in the population over a certain period of time (Gordis, 2009). In CBP research, the time periods are usually defined as "in the moment" (point-prevalence/current prevalence rate), "within the last year" (one-year prevalence rate), or "once in your life" (lifetime prevalence rate; Hoy et al., 2012).

Chronic pain of the musculoskeletal system is common. Studies report current prevalence rates from 13.5% to 47%, with a mean prevalence of approximately 30% (Cimmino, Ferrone, & Cutolo, 2011). Lifetime prevalence for BP varies between 48% and 84% (G. B. J. Andersson, 1999; McBeth & Jones, 2007). These values are consistent with those of a recent German study that reported a current prevalence of 37.1%, a 1-year prevalence of 76%, and a lifetime prevalence of 85.5% for BP (Schmidt et al., 2007). However, this study did not report prevalence values for CBP.

With regard to chronic conditions, the average current prevalence rates are 10-27% for CBP (Freburger et al., 2009; Picavet & Schouten, 2003; B. H. Smith et al., 2004) and 7-13% for CWP (Gran, 2003; Staud, 2009). The wide range of prevalence rates likely reflects differences in the geographical areas, case definitions, methodologies, and investigated samples used in different studies (Dionne et al., 2008; Hoy et al., 2012; McBeth & Jones, 2007; H. Raspe, Matthis, Croft, & O'Neill, 2004; Tsang et al., 2008). In addition, the prevalence of BP and CBP (Harkness, Macfarlane, Silman, & McBeth, 2005; D. K. Weiner, Kim, Bonino, & Wang, 2006) and the demand for consultation and treatment are increasing (H. I. Andersson, Ejlertsson, Leden, & Scherstén, 1999; Freburger et al., 2009). The increases in prevalence might be due to the aging of the population (Ahacic & Kåreholt, 2010; Hoy et al., 2012). However, there are many other factors that might account for this increase, such as increased reporting behavior, higher awareness of pain, or more/higher risk factors for reporting, such as psychological distress, the possibility of receiving compensation claims, etc. (Harkness et al., 2005; H. Raspe & Kohlmann, 1994).

Chronic pain is characterized by its high persistence. Studies with 1- to 12-year follow-up periods showed that 75% to 90% of patients with chronic pain as well as patients with CBP had persistent pain. Higher severity, higher distress, and higher pain extent were associated

with lower recovery rates (H. I. Andersson, 2004; Bergman, Herrström, Jacobsson, & Petersson, 2002; McBeth, Macfarlane, Hunt, & Silman, 2001). Moreover, many variables have been identified as associated with the onset, chronicity and spread of pain. Several variables that are consistently observed are age, female sex, education, and the spatial extent of the pain (H. I. Andersson, 2004; Cimmino et al., 2011; Hoy et al., 2012). Therefore, research on the prevalence of CBP in Germany using comprehensive approaches is necessary. This research should also account for psychological distress (H. Raspe, Hüppe, & Matthis, 2003) because mental co-morbidities are associated with the onset and persistence of pain (Gureje, Simon, & Von Korff, 2001; McBeth et al., 2001).

2.3 Chronic musculoskeletal pain and mental disorders

Studies of mental co-morbidity in patients with CBP performed in the 1980s were an important first step in demonstrating a strong relationship between chronic pain and psychological factors (Fishbain, Goldberg, Labbe, Steele, & Rosomoff, 1988; Katon, Egan, & Miller, 1985; Reich, Rosenblatt, & Tupin, 1983). Subsequent research confirmed the reported association. For example, it was suggested that approximately 65% of patients with depression have pain symptoms, and 18-85% of patients with pain have depression (depending on the pain condition and the study population; Bair, Robinson, Katon, & Kroenke, 2003).

Chronic musculoskeletal pain has also been found to be associated with a higher prevalence of mental disorders in general. Patients with CBP (Demyttenaere et al., 2007; Patten, Williams, & Wang, 2006) and CWP (Benjamin, Morris, McBeth, Macfarlane, & Silman, 2000) suffer from mental disorders significantly more frequently than pain-free controls. The prevalences of current Axis-I mental disorders ranged from approximately 30% to 75% in CBP patients compared to approximately 20% in the general population (Jacobi et al., 2004; Wittchen et al., 2011), excluding somatoform pain disorder (Härter et al., 2002; Thieme, Turk, & Flor, 2004). The most common mental co-morbidities are mood disorders, anxiety disorders and substance-related disorders (Härter et al., 2002; Knaster, Karlsson, Estlander,

& Kalso, 2012), consistent with data from the general population (Jacobi et al., 2004; Wittchen et al., 2011).

In a group of musculoskeletal pain patients, the current prevalence rates of anxiety, mood, and substance-related disorders (excluding nicotine dependence) were 15%, 10.7%, and 2%, respectively (Härter et al., 2002; general population: 9%, 6%, and 3%, respectively; Jacobi et al., 2004). Life-time prevalence rates were reported as 33.5%, 32.5%, and 9%, respectively (Härter et al., 2002; general population: >14.5%, 18.6%, and 10%, respectively: Jacobi et al., 2004). The frequency of Axis-II personality disorders in chronic pain patients are inconsistent (Dersh, Polatin, & Gatchel, 2002) with reported prevalence rates ranging from approximately 9% to 60% (Kinney, Gatchel, Polatin, Fogarty, & Mayer, 1993; Thieme et al., 2004).

The association of CBP and mental co-morbidities also has clinical implications. Co-morbid depression is associated with more pain complaints, more frequent pain episodes, a longer duration of pain, more intense pain, more days out of work, higher hospitalization rates and greater health care utilization (Bair et al., 2003).

Furthermore, mental disorders are also of interest in the transition from (sub-acute) BP to CBP. First-onset BP is more likely to progress to CBP in men who have been diagnosed with major depression, GAD, or PTSD at some time in their lives (OR = 4.99, 2.45, and 3.23, respectively; Shaw et al., 2010). Moreover, the current and lifetime prevalence rates of depression and anxiety disorders are higher in CBP patients than in sub-acute BP patients (Kinney et al., 1993).

Mental co-morbidity is also of interest in the spread and generalization of CBP. The odds ratio for psychiatric disorders in CWP compared to non-CWP patients is 3.18 (Benjamin et al., 2000), and the current prevalence rates for psychiatric disorders are 16.9% in CWP compared to 6.5% in CLP (Benjamin et al., 2000). Conversely, pain characteristics also influence mental co-morbidity. Current pain intensity was associated with higher odds of mental disorders (Knaster et al., 2012). These findings suggest that mental disorders are specifically associated with chronic pain and that research should target this association. It is

of special interest to determine whether this association also holds in non-selective, population-based samples. The complex association of CBP and mental co-morbidity demands mechanism-based approaches that might account for this complexity.

2.4 Mechanism-based theories of chronic musculoskeletal pain

The etiology and pathogenesis of chronic musculoskeletal pain are still mainly unknown. Moreover, there is evidence suggesting that subgroups of CBP patients may differ in terms of etiopathology, clinical symptomatology, and psychophysiological patterns. The heterogeneity of CBP patients (Natvig et al., 2001; A. Raspe et al., 2003) is supported by the finding that the same disease can arise from various pathophysiological mechanisms. Conversely, the same pathophysiological mechanism may be relevant to distinct diseases (C. Maier et al., 2010). This could explain differences in responses to the same treatments in patients with the same disease (C. Maier et al., 2010; Woolf & Mannion, 1999). Consequently, these subgroups should be treated with specific mechanism-based approaches, but to date, they have been treated with the same non-specific multimodal treatment programs, which often have only minor success (Karjalainen et al., 2009; Machado et al., 2009; O'Brien et al., 2010).

One of the most promising approaches to understanding CBP pathogenesis addresses the role of the central nervous system (CNS). Many techniques have been applied to detect abnormalities in the CNS, including quantitative sensory testing (QST; Dadabhoy, Crofford, Spaeth, Russell, & Clauw, 2008). QST is a method used to assess somatosensory function. A comprehensive QST protocol permits the determination of pain and detection thresholds and the discrimination of local vs. generalized and peripheral vs. central nervous mechanisms (Rolke et al., 2006). QST aberrations including signs of abnormal central nervous pathway function have been found in CBP. For example, studies have reported low pain thresholds and pain tolerance values in patients with CBP (Flor, Diers, & Birbaumer, 2004). Another aspect of the psychobiology of pain is descending pain inhibition. It was found that pain inhibition is deficient in patients with different pain conditions (King et al.,

2009; Leonard et al., 2009; Normand et al., 2011). Both somatosensory processing and pain inhibition might also be influenced by mental disorders (de Souza, Potvin, Goffaux, Charest, & Marchand, 2009; Klauenberg et al., 2008; Moeller-Bertram, Keltner, & Strigo, 2012).

One important variable that has been associated with pain processing and pain inhibition is physical activity. Physical activity represents an important therapeutic concept in chronic pain (Hassett & Williams, 2011; Hayden, van Tulder, Malmivaara, & Koes, 2011) and is a part of most pain treatment programs (Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), & Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2010; Themenheft, 2012). Different mechanisms underlying physical activities effects on pain have been proposed to be involved (Koltyn, 2000; Koltyn & Umeda, 2006). There is consistent evidence that pain perception is reduced for a limited period of time following an episode of intense exercise (so-called "acute exercise-induced analgesia"; Koltyn, 2000; Kosek & Lundberg, 2003). It has been theorized that physical activity activates some generalized endogenous pain-modulatory mechanisms, such as conditioned pain modulation (CPM; formerly termed "diffuse-noxious-inhibitory-control"; Boecker et al., 2008; Koltyn, 2000). Moreover, a deficit in this system is associated with chronic widespread pain (CWP; Normand et al., 2011). However, the mechanisms of long-term changes in pain processing due to physical activity remain unclear.

The major hypothesis underlying the mechanism-based diagnosis in chronic pain syndromes is that defined symptoms and signs reflect possible underlying neurobiological mechanisms (Jensen & Baron, 2003; Woolf & Mannion, 1999). Therefore, the psychobiological assessment of CBP may detect common underlying pathophysiological changes. This might foster the development of mechanism-based treatment options and will impact the medical care of pain patients. Therefore, the assessment of chronic pain and research to identify factors associated with the development, maintenance, and spread of chronic pain, including their neurobiological correlates, is highly relevant. For example, this research may include studies of differences and commonalities of different subgroups of patients with CBP and the effects of preventative and therapeutic treatments such as regular physical activity.

3. Publications

3.1 Study 1: The prevalence of chronic non-specific musculoskeletal pain and the role of the spatial extent of the pain

<u>Gerhardt, A.</u>, Hartmann, M., Blumenstiel. K., Tesarz, J., & Eich, W. (in review)

Two major problems arise when CBP research is discussed. First, much of the information about BP has been gathered in clinical studies and is thus applicable only to a highly selected population. The authors therefore conclude that there is an urgent need for surveys on CBP in a representative population-based sample. Second, in most cases, CBP is only one aspect of a more complex syndrome that consists of additional pain and other symptoms (Natvig et al., 2001; A. Raspe et al., 2003). This is consistent with the bio-psychosocial perspective, which proposes that BP is associated with other pain and somatic symptoms as well as with social and psychological factors (Gatchel et al., 2007; Hancock, Maher, Laslett, Hay, & Koes, 2011; Kikuchi, 2008; H. Raspe et al., 2003). Therefore, it is important to consider the extent of pain and co-morbidities as well as correlates of chronic musculoskeletal pain conditions.

Population-based data on CBP in general is available, but these data are typically based on questionnaire results. Thus, it is not possible to determine whether patients suffer from specific causes of CBP or from non-specific pain. Moreover, there is a lack of current data on the prevalence of CBP in representative population-based samples in Germany.

The aim of our study was therefore to determine the prevalence of non-specific CBP in the general population of southwest Germany. Because the group of chronic musculoskeletal pain patients is reported to be heterogeneous (Natvig et al., 2001; A. Raspe et al., 2003), we also consider variables that might be associated with pain extent. Therefore, we combined the advantages of a population-based approach with those of clinical examination-based studies to enhance the validity of our findings and to overcome the limitations of prior research (Gerhardt, Hartmann, Blumenstiel, Tesarz, & Eich, in review).

We contacted 4000 representative inhabitants of southwest Germany by mail. Of the responders, 427 subjects suffered from CBP. With respect to the general population of southwest Germany, the age- and sex-adjusted prevalence rates for CBP and chronic widespread pain (CWP) were 17.7% and 6.7%, respectively. Other studies have reported prevalence rates for CBP ranging from 10% (Freburger et al., 2009) to 27% (Picavet & Schouten, 2003; B. H. Smith et al., 2004). Thus, the prevalence of CBP found in our study ranks in the middle of the previously reported range. The prevalence of CWP found in our study was relatively low (Gran, 2003; Staud, 2009; Wolfe, Ross, Anderson, Russell, & Hebert, 1995) compared with those in previous reports. The differences in the reported prevalence rates can be explained by the different definitions of CBP and methodologies used in different studies.

Our data corroborates the assumption that the group of chronic pain patients is heterogeneous in terms of pain extent (Natvig et al., 2001). For example, persons referred to as having CLP can have pain in a single circumscribed area or pain affecting one entire half of the body. Therefore, the commonly used categorization of CLP vs. CWP is inadequate. We developed a pain drawing classification system to measure the extent of pain from a clinical point of view in a standardized manner to address this neglected issue. We subdivided the CLP and CWP groups into two groups each, depending on the extent of pain affecting the spine and the limbs (see caption of Figure 2.). Only 19.6% of those with CBP were categorized as having strict local pain (SLP), 42.1% reported chronic regional pain (CRP), 24.3% reported common chronic widespread pain (CoCWP), and 13.9% reported extreme chronic widespread pain (ExCWP).

This finding has clinical implications. CBP is typically treated as a distinct disease. This approach seems artificial because almost 40% of the CBP subjects fulfilled the criteria for CWP, and only 19.6% had pain in the back only. This might contribute to the low treatment success. That most patients report pain in more than one body location is in line with the results of other studies (Carnes et al., 2007; Natvig et al., 2001; Picavet & Schouten, 2003), although extremely extensive pain is rare (Carnes et al., 2007). Thus, results that refer to

CBP must be interpreted with caution when observed in isolation from concomitant symptoms.

Instead, bio-psychosocial models that account for the amplification of CBP into a broader syndrome that involves pain elsewhere, other somatic symptoms, psychological factors, and social and occupational context seem to be more appropriate (Hancock et al., 2011; Kikuchi, 2008; H. Raspe et al., 2003).

To account for the bio-psychosocial model we evaluated the associations of our four pain extent groups with sociodemographic variables and overall clinical context. Our findings are consistent with those of other studies, which have shown that increased pain extent is associated with female gender (Gran, 2003; Staud, 2009; Wolfe et al., 1995), a higher rate of applications for disability pensions (Kamaleri, Natvig, Ihlebaek, & Bruusgaard, 2009), higher pain severity, and greater impairment (Carnes et al., 2007; Wenngren & Stålnacke, 2009). Moreover, greater extents of pain were associated with more medical consultations and greater pain medication use.

In conclusion, our data show that CBP is prevalent and that pain is not restricted to the back in most individuals with CBP. This challenges the concept of CBP as a distinct entity. Our proposed four-group classification system that links the extent of pain with sociodemographic and clinical variables was able to subdivide the patients in distinct groups. This underscores the utility of classifying pain patients according to pain extent. Clinically, the developed classification system can be used to identify highly distressed/burdened subjects that might be responsible for a large share of the costs associated with CBP. In addition, physicians should pay closer attention to clinical variables other than pain extent, especially in patients with more extensive spread of pain. As we showed, this group has also higher rates of mental co-morbidity. Due to the high prevalence of mental disorders in chronic pain patients, as was observed in our sample, we decided to use the SCID as the gold standard for the assessment of mental disorders in the second study. Due to the observed heterogeneity of sociodemographic variables and clinical profiles of these CBP patients, we tested whether there is also psychophysiological heterogeneity within the CBP group in the third study.
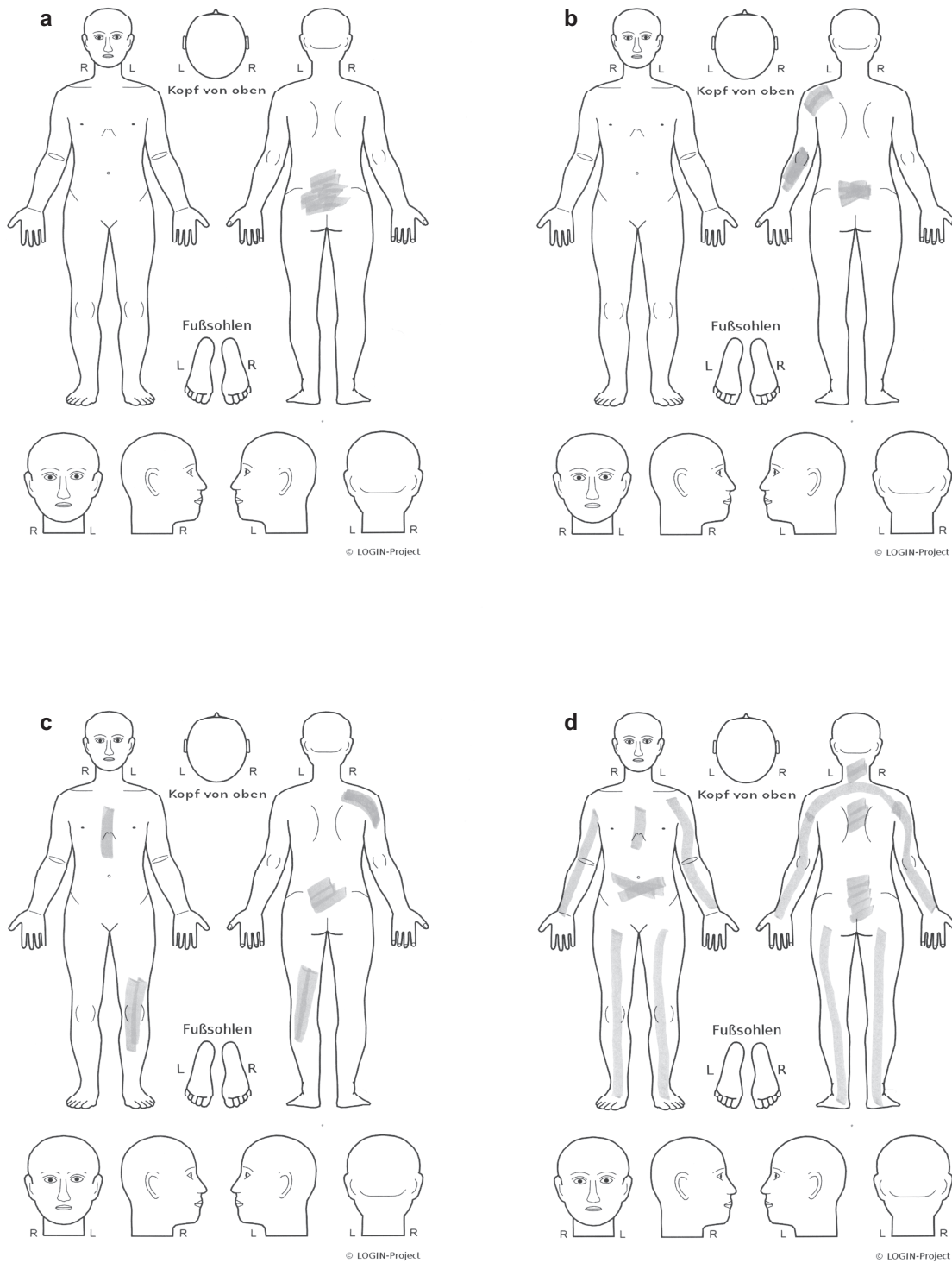
Figure 2. The four classes of pain extent in the new suggested classification system. Chronic local pain (CLP) and chronic widespread pain (CWP; for classification see Figure 1) were each subdivided. **a)** Strict back pain: pain in 1 to 3 spinal areas, no further pain. **b)** Chronic regional pain: pain in the spinal area plus additional pain, but criteria for CWP not fulfilled. **c)** Common CWP: pain in the spinal area plus at least two contralateral limbs but not all four limbs. **d)** Extreme CWP: all spinal areas and all four limbs.

3.2 Study 2: Chronic non-specific musculoskeletal pain and mental disorders

Gerhardt, A., Hartmann, M., Schuller-Roma, B., Blumenstiel, K., Bieber, C., Eich, W., & Steffen, S. (2011).

Patients with CBP are more likely to suffer from mental disorders than are pain-free individuals (Demyttenaere et al., 2007; Uguz et al., 2010). However, the prevalence of mental co-morbidities is sample dependent (Bair et al., 2003), and few data related to the prevalence of mental co-morbidities in CBP patients in Germany are available. Moreover, mental co-morbidity in CBP is often assessed through questionnaires. This limits the validity of the results because most questionnaires include both somatic and vegetative signs (Fishbain, Cutler, Rosomoff, & Rosomoff, 1997). Thus, diagnoses of many disorders and chronic pain might be confounded.

The aim of this study was to investigate the prevalence and types of mental co-morbidities in a well-characterized, representative population-based sample of subjects with non-specific CBP (Gerhardt et al., 2011). The main advantage of our approach was that individuals with CBP were drawn from the general population rather than from a specific clinical setting. The second strength was the simultaneous assessment of Axis-I and -II disorders in a validated clinical interview. The third advantage was the use of a physical examination to ensure that the diagnosis of non-specific CBP was not based on patient self-reports, as is common.

In our population-based sample of 4000 inhabitants of the Rhein-Neckar-Kreis (see study 1), we randomly selected 50% of the subjects for a Structured Clinical Interview for DSM-IV (SCID). The SCID-I + II was used to assess current (within the previous four weeks) mental co-morbidity and was completed by 110 subjects with non-specific CBP.

Of the subjects with CBP, 39 (35.5%) received at least one current Axis-I diagnosis, excluding somatoform pain disorders. Anxiety disorders (20.9%) and affective disorders (12.7%) were the most frequent diagnoses, followed by substance-related disorders (7.3%) and eating disorders (5.5%).

The prevalence of at least one Axis-II personality disorder (PD) was 15.5%. The most frequent diagnoses were obsessive-compulsive and avoidant PD (4.5% each), followed by borderline PD (3.6%), paranoid PD (2.7%) and narcissistic PD (0.9%). Thus, diagnoses in Cluster C (anxious or fearful disorders) were the most prominent and were found in 9.1% of subjects.

When the psychopathological aspects of both Axes are considered together, a consistent tendency towards vulnerability to anxiety, fear and avoidance was observed among our subjects, as reported elsewhere (Malmgren-Olsson & Bergdahl, 2006). Sensitivity to anxiety can be viewed as a precursor to pain-related fear or depression; avoidance behavior or disability is thought to be a response to pain (Alschuler, Theisen-Goodvich, Haig, & Geisser, 2008; Murphy, Lindsay, & De C Williams, 1997; Vlaeyen & Linton, 2000). Furthermore, avoidance may contribute to the maintenance or exacerbation of chronic pain and produce a number of additional negative physical and psychological symptoms. Fearful people are more conscious of possible threatening signals and are therefore less able to shift their attention away from pain-related information (Vlaeyen & Linton, 2000). Additional longitudinal studies are needed to better characterize the role of anxiety in chronic pain.

The prevalence rates found here rank at the lower end of the previously reported range of mental co-morbidity rates in subjects with CBP (Atkinson, Slater, Patterson, Grant, & Garfin, 1991; Dersh, Gatchel, Polatin, & Mayer, 2002; Katon et al., 1985; Polatin, Kinney, Gatchel, Lillo, & Mayer, 1993). However, the prevalence of Axis-I disorders remains significantly elevated compared to that in the general population (OR 2.23, p < 0.001; Jacobi et al., 2004). The prevalence of Axis-II disorders is comparable to that found in the general population (W. Maier, Lichtermann, Klingler, Heun, & Hallmayer, 1992). Other studies are consistent with our findings of a significantly higher, albeit still moderate, prevalence of mental co-morbidity in patients with CBP (31%-38%; Härter et al., 2002; Joukamaa, 1991; Mayr, Högler, Ghedina, & Berek, 2003; Von Korff et al., 2005).

The most frequent mental co-morbidities that we reported were anxiety disorders (20.9%). In contrast, others have reported that affective disorders are the most frequent mental co-

morbidities in patients suffering from pain (Kinney et al., 1993; Polatin et al., 1993). The finding that anxiety disorders were the most prevalent might be due to our population-based setting, as confirmed by other population-based studies (McWilliams, Cox, & Enns, 2003; Stang et al., 2006; Von Korff et al., 2005) and consistent with data from the general population (Jacobi et al., 2004). It can be hypothesized that depressed patients tend to be identified more easily in the medical system than are patients with anxiety disorders because patients with depression are more likely to seek help than are patients with anxiety disorders (Essau, Conradt, & Petermann, 2000; Henderson, Pollard, Jacobi, & Merkel, 1992).

The recognition of anxiety, fear and avoidance may be well established in research literature and in specialized pain centers. However, our population-based setting also captures patients with low to moderate pain intensity and those with low help-seeking behavior. These patients also suffer from mental co-morbidities, and failing to recognize this fact may foster chronification. Moreover, rehabilitation may be compromised if concurrent psychiatric disorders are not recognized and adequately treated (Dersh et al., 2007; Gatchel, 1996).

Therefore, we recommend that a standardized screening for and assessment of mental disorders be implemented in conjunction with the initial pain assessment and at regular intervals. This should also be conducted in primary care settings, not only in research or specialized pain centers. This might help to reduce the high number of untreated patients who may be reluctant to seek help in overcoming pain due to their anxiety disorder.

3.3 Study 3: Somatosensory (mechanism-based) aspects of chronic non-specific musculoskeletal pain

Blumenstiel, K., Gerhardt, A., Rolke, R., Bieber, C., Tesarz, J., Friederich, H.-C., Eich, W., & Treede, R.-D. (2011).

Due to the observed heterogeneity of CBP patients (e.g., in study 1) and insufficient treatment success, we tested whether there are also psychophysiological differences

between distinct subgroups of CBP patients (Blumenstiel et al., 2011). Such findings might have implications for treatment and potentially improve treatment success.

Research has revealed certain alterations in the central nervous system that lead to greater pain sensitivity in both CBP and fibromyalgia syndrome (FMS; CWP plus tenderness in specified regions; Arendt-Nielsen & Graven-Nielsen, 2003; Desmeules et al., 2003). However, it is unclear whether CBP and FMS subjects show the same or different alterations. Therefore, the aim of this study was to identify commonalities and differences in the pathophysiologies of CBP and FMS.

We used the German Research Network on Neuropathic Pain (DFNS) QST protocol to obtain comprehensive profiles of somatosensory function. The protocol comprised thermal and mechanical detection and pain thresholds, vibration thresholds, and pain sensitivity to sharp and blunt mechanical stimuli (Rolke et al., 2006). We studied 21 FMS patients, 23 CBP subjects, and 20 healthy controls (HC). Each subject underwent the battery of tests on the back (pain site) and on the dorsal hand (pain-free control site).

The FMS group showed significantly increased mechanical and thermal pain sensitivity (with the exception of HPT over the hand dorsum) compared to the CBP and HC groups, whereas detection sensitivity was not increased. Our sensory profile suggests that hyperalgesia in FMS may involve all nociceptive submodalities. Moreover, pain sensitivity was increased over the back and hand dorsum (parallel profiles for back and hand; Figure 3a). Thus, the increased sensitivity in FMS is generalized in space (superficial and deep pain, back and hand) and across nociceptive submodalities, but not to other somatosensory functions.

The best possible explanation for such generalized hyperalgesia is a deficiency in the pain inhibitory system (Villanueva & Le Bars, 1995). The term "central sensitization", often used in the context of FMS (Desmeules et al., 2003; Price & Staud, 2005), does not sufficiently describe the clinical picture. This term implies an increased excitability of the central neurons, but its effects are restricted in space to the receptive fields and often limited to mechanical test stimuli (Treede, Handwerker, Baumgärtner, Meyer, & Magerl, 2004; Treede, Meyer, Raja, & Campbell, 1992). Disinhibition, in contrast, strikes the entire body and may be
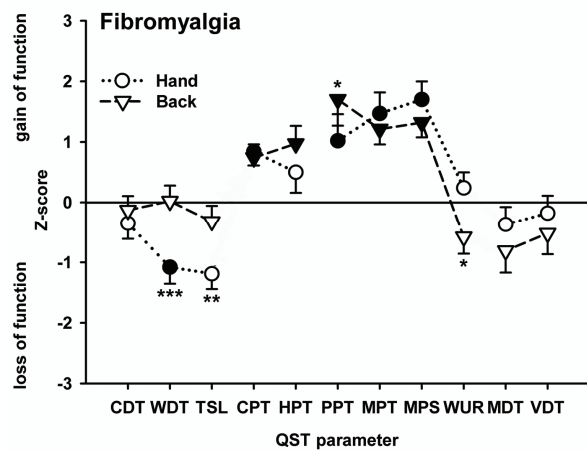
Figure 3a. QST profiles in fibromyalgia syndrome patients. Circles: hand, triangles: back. Filled symbols: significant difference from healthy controls (open symbols: n.s.; t test). *P < 0.05, **P < 0.01, ***P < 0.001, paired t test of hand versus back. Parallel profiles between hand and back indicate generalized sensory changes. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio; values are mean±SEM.
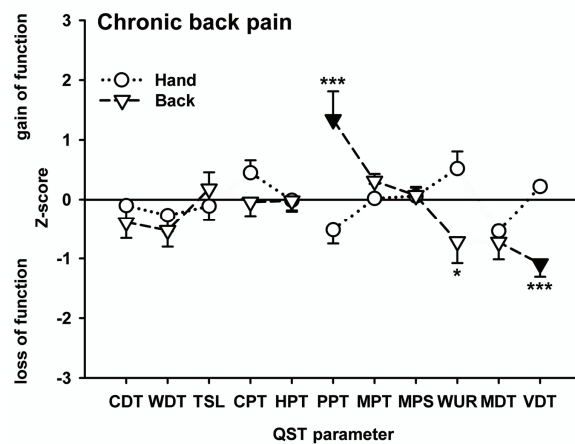
Figure 3b. QST profiles in chronic back pain patients. Circles: hand, triangles: back. Filled symbols: significant difference from healthy controls (open symbols: n.s.; t tests). *P < 0.05, ***P < 0.001, paired t test hand versus back. Significant differences indicate that sensory changes are localized to the back. Abbreviations are defined in the legend to Figure 3a. Values are mean±SEM.

Figure 3 a and b: Reproduced from the Clinical Journal of Pain (volume 27, number 8, pages 682-690), with permission from Walters Kluwer Health.

adequate to explain a generalized pain syndrome such as FMS. Thus, the role of disinhibition should be addressed in future studies (Pud, Granovsky, & Yarnitsky, 2009; Yarnitsky et al., 2010).

We found an increased pressure pain sensitivity and lower vibration sensitivity on the back, but no significant differences in the dorsum of the hand, in sample of CBP subjects compared to HCs. Increased PPT sensitivity primarily reflects muscle nociception and peripheral sensitization (Kilo, Schmelz, Koltzenburg, & Handwerker, 1994; Kosek, Ekholm, & Hansson, 1999). The restriction of sensitization to the painful area in the back means that there were no signs of pain generalization (Figure 3b). These results suggest localized changes in the muscles and joints. There was no evidence for central sensitization or disinhibition in our sample of CBP subjects, indicating that chronic pain per se is not sufficient to indicate these abnormalities.

This finding is intriguing because other authors (Giesecke et al., 2004) have suggested that central sensitization is involved in both FMS and CBP. Because our CBP sample was drawn from the general population, widespread pain sensitivity observed in pain clinic patients may not be representative of all patients with CBP. Therefore, parameters other than chronic

ongoing nociceptive pain are likely to be predisposing factors for widespread pain and FMS. Such factors may include pain intensity, the subtype of CBP, and psychosocial factors, which were investigated in study 1 and 2.

In summary, FMS and CBP subjects exhibit distinct sensory profiles. This finding underscores that CBP patients are heterogeneous with regard to not only sociodemographic and clinical variables but also psychophysiological measures. This is consistent with the main hypothesis of a mechanism-based diagnosis in chronic pain syndromes, which proposes that defined symptoms and signs reflect possible underlying neurobiological pain mechanisms (Jensen & Baron, 2003; Woolf & Mannion, 1999). Based on these findings and the suggested role of the descending pain modulatory system in the observed alterations, we designed study 4. Study 4 addresses a protective/curative factor, physical activity. Physical activity is a major component of the treatment for chronic musculoskeletal pain, and descending pain modulation is discussed as a potential factor in its efficacy.

3.4 Study 4: Evaluation of physical activity as a mechanism-based concept

Tesarz, J., <u>Gerhardt, A.</u>, Schommer, K., Treede, R.-D., & Eich, W. (2013).

Regular physical activity is recommended in many chronic musculoskeletal pain treatment guidelines (BÄK, KBV, & AWMF, 2010; Themenheft, 2012). However, although there is consistent evidence that pain perception is reduced for a limited time period following an episode of intense exercise (Koltyn, 2000), the effect of regular physical activity on long-term changes in pain perception and pain processing at rest is inconsistent. A meta-analysis to which the author of this doctoral thesis contributed concluded that athletes possess higher pain tolerance than normally active controls, whereas the available data on pain threshold are less uniform (Tesarz, Schuster, Hartmann, Gerhardt, & Eich, 2012). However, there was a high heterogeneity between the included studies, possibly due to the different pain

induction methods and heterogeneous study groups used. Moreover, the underlying mechanisms remain largely unclear.

Therefore, we conducted a study to identify differences and commonalities in pain perception and pain processing at rest between athletes (n = 25) and normally active controls (n = 26). Our study is the first to assess pain perception in athletes using a comprehensive standardized and validated pain assessment protocol (QST) and an objective evaluation of physical fitness (VO$_2$max; Tesarz, Gerhardt, Schommer, Treede, & Eich, 2013). We also evaluated the endogenous pain modulating system to investigate a potential underlying mechanism (conditioned pain modulation, CPM; i.e., the diffuse-noxious-inhibitory-control-like effect). CPM was measured using two tonic heat pain stimuli separated by a 2-min cold pressor task (CPT; conditioning stimulus). The theory behind is that pain inhibits subsequent pain by activating the descending pain modulatory system (Le Bars, Dickenson, & Besson, 1979a, 1979b). CPM is quantified by subtracting the pain ratings given before the CPT from those given after the CPT. Negative values indicate CPM activity.

We observed an increased mechanical pain threshold and an increased sensitivity to vibration in the athletes. No significant differences were found for heat, cold or pressure pain thresholds or for temperature and mechanical detection thresholds.

These findings are consistent with previous work, which also showed no differences for heat (L. Smith, 2004; Sternberg, Bailin, Grant, & Gracely, 1998) or pressure pain thresholds between athletes and normally active controls (Manning & Fillingim, 2002; Ryan & Kovacic, 1966). The isolated loss of function for pinprick stimuli described in this study is particularly interesting because MPT by pinprick has not been tested previously in athletes. An increase in MPT can be caused by either denervation of the peripheral nociceptors or inhibition within the central nervous system (Treede & Magerl, 2000; Ziegler, Magerl, Meyer, & Treede, 1999). Even if only MPT and VDT differed significantly between the groups, it is worth noting that except for vibration, all QST parameters showed a general tendency toward a reduced sensitivity indicating a 'loss of function'.

The increased sensitivity to vibration is an interesting finding because the vibration detection

threshold was the only measure that exhibited a gain of function (more sensitive perception). There is evidence that vibration perception is associated with postural control (Kristinsdottir, Fransson, & Magnusson, 2001; Kristinsdottir, Jarnlo, & Magnusson, 1997). Postural control is an important feature of athletic competence, and enhanced vibration sensitivity may be the result of a well-trained locomotive system. However, this explanation is rather speculative, and further research is needed to better understand the underlying mechanisms.

Another important finding was that CPM was different in athletes and normally active controls. Interestingly, athletes were characterized by a significantly lower activation of the CPM by the CPT than were normally active controls. One possible explanation for this phenomenon may be an elevated activation level of the endogenous pain inhibitory system in athletes. This continuously heightened activation level of endogenous pain inhibition may impede additional activation by the CPT. This 'elevated activation-level hypothesis' to describe the inhibitory pain control in athletes is consistent with our observation that all QST parameters, except VDT, showed a general trend of reduced sensitivity in the athletes. However, there are also other promising explanations, such as a shift in the activation threshold of the endogenous pain inhibitory system in athletes. The 'threshold hypothesis' postulates that the pain inhibitory system in athletes requires stronger stimuli for activation or that – using fixed stimulus intensity – the same stimulus will result in a lower activation of the pain inhibitory system in these subjects.

The specific mechanism underlying alterations of pain perception at rest in athletes cannot be clarified in detail based on these findings alone, but our data suggest that the endogenous pain inhibitory system may be less responsive in athletes. Further research should be conducted to investigate the underlying mechanisms in greater detail, including longitudinal studies that address this "chicken and egg" question.

Study 5 will combine clinical variables and psychophysiological measures because we showed that CBP patients exhibit differences in both types of variables. Moreover, the investigation of the association between clinical context/symptoms and psychophysiological measures is a strong candidate subject for a comprehensive approach.

3.5 Study 5: Research agenda on mechanism-based concepts in chronic non-specific musculoskeletal pain

Gerhardt, A., Hartmann, M., Tesarz, J., Janke, S., Leisner, S., Seidler, G., & Eich, W. (2012).

The establishment of a mechanism-based subgroup classification of pain and the development of associated specific treatments were suggested more than a decade ago (Woolf et al., 1998). Since then, the topic has been controversial (Jensen & Baron, 2003; Turk, 2005; Wand & O'Connell, 2008; Woolf & Mannion, 1999). The small effect sizes of chronic pain treatments were suspected to be due to non-specific treatment approaches that could not address many different pain generating and maintaining mechanisms (C. Maier et al., 2010; Woolf & Mannion, 1999). This is also supported by clinical experience, which shows that the subgroups of chronic pain patients are heterogeneous despite suffering from the same disease, i.e., non-specific CBP.

Study 1 and 2 showed that the group of CBP patients is heterogeneous and that patients differ in many sociodemographic and clinical variables (Gerhardt et al., in review; Gerhardt et al., 2011). Study 3 added that the group of CBP patients is also heterogeneous in terms of psychophysiological patterns (Blumenstiel et al., 2011). Study 4 showed that behavioral aspects are associated with psychophysiological changes in pain perception and pain processing, suggesting that the psychophysiological differences due to factors in addition to different pain characteristics (Gerhardt et al., 2012). In summary, our studies validate the hypothesis that that chronic musculoskeletal pain patients are heterogeneous due to the number of mechanisms involved in chronic pain.

These findings support the assumptions of mechanism-based approaches in CBP. The identification of patient subgroups is necessary to establish distinct pathophysiological mechanisms and targets for mechanism-based treatment options. However, only a few studies have aimed to identify different pain mechanisms (Blumenstiel et al., 2011; C. Maier et al., 2010), and those studies have predominantly focused on the general aspects of pain

processing, thus neglecting the heterogeneity of patients with musculoskeletal pain. Consequently, there is a need for studies that comprise a multitude of the mechanisms that are potentially involved in the chronicity and spread of pain.

We developed a theoretical framework (Figure 4) that accounts for many of the variables that are of interest in chronic pain. In the current study, we consider this comprehensive framework in addition to the mental co-morbidities and psychophysiological patterns that we have studied previously. Thus, we link sociodemographic and clinical variables with neurobiological observations to account for the heterogeneity of CBP patients. Consequently, specific mechanism-based subgroups of pain patients should be identified and eventually matched to specific mechanism-based treatment options (Gerhardt et al., 2012).
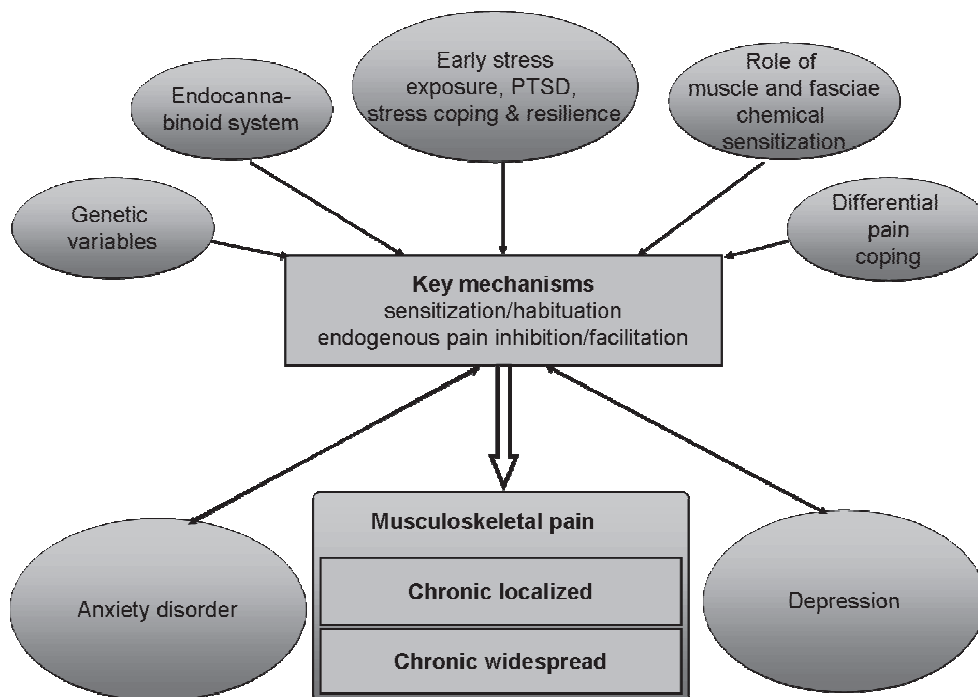
Figure 4. Theoretical framework.

Our research is novel in its comprehensive approach and its use of reliable and valid diagnostic tools. This approach comprises many variables that have been shown to be involved in changes in sensory processing. This comprehensive approach, which combines clinical manifestations and neurobiological variables, will foster research on CBP and the treatment of CBP patients.

4.0 Summary and conclusions

CBP is widespread and is associated with a high burden to the patient and immense costs. However, CBP treatments are typically unsuccessful. This might be due to the use of nonspecific treatment options that do not account for the heterogeneity among CBP patients. In addition, research on CBP is typically based on highly selected samples, often relies on data gathered from questionnaires rather than interviews or examinations, and usually neglects the heterogeneity of patients. This might lead to biases.

Therefore, we conducted several studies that combined the advantages of epidemiological and clinical research (e.g., the use of representative samples and more objective and valid data, respectively). These studies also accounted for patient heterogeneity, and, in a second step, tried to link the clinical manifestations and psychophysiological/pathophysiological mechanisms.

Our results show that CBP is highly prevalent in the general population (17.7%; study 1) and is often associated with mental co-morbidities (35.5%; study 2). Individuals with CBP were twice as likely as individuals from the general population to suffer from a mental co-morbidity, with anxiety disorders as the leading disorder. We also confirmed the assumption that the group of CBP patients is heterogeneous. This was true for many sociodemographic and clinical variables (study 1) as well as psychophysiological variables (study 3). We also showed that physical activity, as a behavioral, preventative and curative method for CBP, is associated with changes in pain perception and pain processing (study 4).

Our findings have implications for further research as well as treatment. The reported high prevalence of CBP will foster health services research to address the socioeconomic burden of CBP. Moreover, our results showed that pain drawings indicating the spatial extent of pain could be used to identify a highly burdened group of CBP patients with high health care utilization that require more detailed assessments of pain and associated variables. Our research also suggests that primary care physicians should assess patients with BP complaints for anxiety disorders to avoid exacerbating BP and to potentially prevent the spread and chronification of the pain. In addition, our results especially highlight the need for

more research on mechanism-based aspects of CBP to address the high heterogeneity of CBP patients and to link clinical manifestations with potential underlying pathophysiological mechanisms. This might foster the development of specific mechanism-based treatment options that might be more successful than the existing treatments. Our research shows that therapies should include physical activity, which is recommended in many CBP treatment guidelines.

However, there are also some limitations to our studies. We did not account for all the complexities of CBP patients, which would require more comprehensive approaches (e.g., using the methods of studies 1 to 3 within one study). Moreover, one important challenge will be to account for the interactions of different variables (e.g., CBP and depression, CBP and anxiety, CBP and anxiety and depression); research has shown that those results might differ in patients who only satisfy one criterion (e.g., anxiety) rather than multiple criteria (e.g., anxiety and depression). This will require large sample sizes of patients and a comprehensive assessment of pain and associated variables. This is addressed within a current research project in which the author of this dissertation thesis is participating (study 5). We also hope to encourage other researchers to confront this challenge, as well as to replicate our findings and address its limitations.

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Anhang

Pain Medicine

The prevalence rate and the role of the spatial extent of the pain in non-specific chronic back pain – A population-based study

1

The prevalence rate and the role of the spatial extent of the pain in non-specific chronic back pain – A population-based study

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Running Title: Prevalence rate of chronic back pain

2

ABSTRACT

Objective: To determine the prevalence rate of chronic back pain in the general population and to establish an evidence-based sub-classification system for chronic back pain.

Design: Representative population-based survey.

Setting: The city of Heidelberg (southwestern Germany) and 10 adjacent communities.

Subjects: Four-thousand representative inhabitants were contacted. Those suffering from chronic back pain (pain ≥45 days/last three months) were invited to a clinical examination. The corrected response rate was 61.8% (n=2,408), and 427 responders suffered from chronic back pain. Of these, 303 (71%) consented to participate in the clinical examination.

Outcome Measures: Prevalence rate of chronic back pain, pain drawing (the spatial extent of the pain), sociodemographic and clinical variables.

3

Results: Age- and sex-adjusted prevalence rate for chronic back pain was 17.7%.

Analysing pain extent, we found that only 19.6% suffered strictly from chronic local

back pain, while the majority indicated additional pain regions. Thus, we developed a

sub-classification system based on pain extent that consists of four more

homogeneous groups (19.6% strict chronic local pain, 42.1% chronic regional pain,

24.3% common chronic widespread pain, 13.9% extreme chronic widespread pain).

Interestingly, in this system, increasing pain extent was significantly associated with

higher distress, as reflected by sociodemographic and clinical variables.

Conclusions: Chronic back pain is highly prevalent and usually involves more than

just back pain. This challenges the concept of chronic back pain as a distinct entity.

To identify patients who are especially distressed by chronic back pain, a four-class

taxonomy based on pain drawings is both feasible and clinically useful.

Introduction

Chronic pain conditions of the musculoskeletal system are common and have high
socioeconomic relevance [1, 2]. This is especially true for pain conditions with widely
unknown pathogenesis, such as non-specific chronic back pain (CBP) and the
subgroup of chronic widespread pain (CWP). The prevalence rates for these
conditions vary widely depending on case definition, methodological factors,
geographical area, and the investigated population sample [3-5]. The average
prevalence rates range from 10-27% for CBP [6-8] and 7-13% for CWP [9, 10].

However, when CBP is discussed, two major problems arise. First, most of the
information on back pain is gained through clinical studies and thus represents a
highly selective population. Population-based studies, on the other hand, have found
that 20-50% of all back pain cases do not seek medical care [6, 11]. Therefore, to
rule out selection bias, there is an urgent need for population-based surveys of CBP.
Second, in most cases, CBP is only one aspect of a more complex syndrome
consisting of further pain and additional symptoms [12, 13]. Thus, it is also important
to consider the spatial extent of the pain, comorbidities, and other correlates of
chronic musculoskeletal pain. Third, most studies use questionnaire-based data to
diagnosis pain and comorbidities, which hampers validity in contrast to true clinical
examination.

Current pain assessment minimally includes the intensity, quality, duration, and
localisation/spatial extent of the pain [14]. There is little consensus on how to

measure or classify the spatial extent of the pain because this topic has been

neglected for a long time and has been omitted from previous assessment

recommendations [15]. The basis for the assessment of pain extent is always a pain

drawing filled in by the patient. However, there is no gold standard how to analyse a

pain drawing. The existing scoring systems differ widely in complexity and the time

required for analysis, but most measure the percentage or number of painful body

surfaces [16]. One of the most elementary classifications is to differentiate pain into

chronic local pain (CLP) and CWP according to the 1990 American College of

Rheumatology (ACR) criteria [17]. More complex, computer-based procedures count

the number of pixels and capture the indicated pain sensations [18]. However,

existing scoring systems neglect concomitant feasibility and clinical usefulness.

The aim of the present study was 1) to determine the prevalence rates for CBP, CLP,

and CWP in a representative population-based study, and 2) to assess and classify

pain extent in a valid way with regard to other variables that are thought to be

associated with CBP. The advantages of a population-based sample and a clinical

examination should be combined to produce valid and representative results.

6

Methods

Study design

This study is part of the population-based longitudinal multiregional postal survey on back pain managed by the German Back Pain Research Network (GBPRN) [19-22]. Of 55 cities and communities in the south-western "Rhein-Neckar" district of Germany, Heidelberg and ten adjacent communities were randomly selected for this study, including urban and rural areas. A representative sample of 4,000 persons aged 18 to 74 with their first residence in the chosen regions was randomly drawn from these communities in proportion to the number of inhabitants. For this purpose, the registration offices provided population registers of the respective areas. Because registration is mandatory in Germany, population registers provide almost complete coverage of the general population.

The study was performed in accordance with the Declaration of Helsinki. The ethics committee of the Medical Hospital of Heidelberg approved this study, and all participants gave their written informed consent. More details on the study design can be found elsewhere [21, 22].

Inclusion and exclusion criteria

Inclusion criteria consisted of being 18 to 74 years of age, having German language skills, non-specific origin of CBP, and chronicity of pain defined as pain on at least 45 days within the last three months. Exclusion criteria were specific causes of CBP.

Subjects

The 4,000 persons were contacted by mail and asked to complete and return a short screening questionnaire that was targeted at CBP (social and demographic variables, the occurrence, intensity, duration, and extent of pain, and psychometric tests). If necessary, up to two reminders were sent three and six weeks after the first mail. Of the 4,000 persons addressed by mail, 3,899 were reached, and 2,408 answered the questionnaire, yielding a corrected response rate of 61.8%. The response rates were approximately 30% after the first letter, approximately 20% after the first reminder, and approximately 10% after the second reminder.

The 427 persons who suffered from back pain on at least 45 days in the last three months (the definition of CBP in this study) were invited to a clinical examination at our university outpatient clinic. The clinical examination for all participants comprised a more detailed questionnaire, a pain drawing, and a physical examination. Finally, 303 subjects agreed to participate in the study (71%).

Twenty participants were found to suffer from specific CBP validated by physical

examination (see below) and were excluded from further analysis (5 suffered from

Bechterew's disease, 3 from rheumatoid arthritis affecting the spine, 1 from

polymyalgia rheumatica, 3 from tumour/metastases, 1 from fracture of the vertebral

body, 1 from spondylolysis, and 6 from disc hernia). Three additional persons did not

adequately complete the questionnaire and/or pain drawing and were also excluded.

Ultimately, 280 participants with non-specific CBP were included in the analysis. For

the participation flow, see Figure 1.

--- Figure 1 ---

Physical examination

The physical examination consisted of a detailed general, rheumatological,

neurological, and orthopaedic examination (including blood tests and past medical

history). The examination attached special importance to findings indicative of a

specific origin of the CBP. Therefore, the "red flags" (hints for the presence of serious

pathology [23] were considered, and former medical reports and discharge letters

were taken into account whenever available. If a person was likely to suffer from

specific causes of CBP, then he or she was excluded from the study. Moreover, he or

she was recommended to see a specialist or make an extra appointment in our

outpatient department.

9

During the physical examination we also used the Physical Impairment Scale (PIS).

The PIS is an objective measure of impairment due to CBP. It was developed as a

simple and standardised clinical observation to evaluate physical impairment in CBP.

The test battery combines objective physical findings that indicate current functional

limitations due to pain. It consists of seven tests that measure movement in the lower

back (total flexion, total extension, and average lateral flexion measured with the

inclinometer), straight leg raise, spinal tenderness, and strength (bilateral active

straight leg raise and sit-up). Measurements are translated into values of 0 or 1

according to cut-off values and summed (range 0 to 7). Higher scores indicate higher

impairment. As subjective disability in non-specific CBP is not explained by anatomic

or structural impairment, the PIS measures functional limitations as influenced by the

patient's pain behaviour. The PIS is able to discriminate between pain patients and

healthy controls and is related to self-reported disability in activities of daily living [24].

Pain drawing

Each participant seen in our outpatient department was asked to complete a pain

drawing (Figure 2(a)). To ensure that patients focused not only on back pain, the

instructions stated: "Mark all areas where you experience pain (That is, all affected

areas, not only the back!). Mark the total area where pain is experienced." After

completion of the pain drawing, it was discussed jointly by the participant and the

physician to rule out any misunderstandings. Using this information as a first step, all

participants were classified into the categories of chronic local pain (CLP) and

chronic widespread pain (CWP) based on the ACR criteria [17] and the more precise

definition by Harkness et al. [25]. According to this definition, CWP is present when

subjects report contra-lateral limb pain in addition to axial skeletal pain for at least

three months. Upper limb pain was present if pain in any of the following regions was

reported [25]: hand, wrist, forearm, elbow, upper arm, or shoulder. Lower limb pain

was defined as pain in the hip, thigh, knee, lower leg, ankle, or foot. Axial skeletal

pain included pain in the cervical, thoracic, and/or lumbar spine.

In a second step, when it became obvious that the ACR criteria were too rough to

depict or capture the true clinical variety of pain extent, we developed the Heidelberg

Pain Drawing Mask. The Heidelberg Pain Drawing Mask is a transparent template

that denotes the boundaries of different body regions (Figure 2(b)). To analyse the

pain drawings, it was placed over the pain drawing. The pain drawing was evaluated

by rating each spinal segment and each limb independently. An algorithm resulted in

the respective pain category (see the section on the "classification of pain extent"

below). Thus, the presence of pain in the respective limbs as well as the affected

segments of the spine was recorded. Pain drawings were assessed by two raters

independently with high inter-rater reliability (κ = 0.90). When ratings disagreed,

"true" scores were reached by consensus.

--- Figure 2 (a) and (b) ---

Classification of pain extent/Heidelberger Pain Drawing Mask

Because the CBP population is a highly non-homogeneous group, and persons

labelled CLP can range from pain in a single circumscribed area to pain affecting one

entire half of the body, we developed a more detailed pain classification system. This

system forms more homogeneous groups of pain extent, but remains feasible for

clinical application. Therefore, the CLP and CWP groups were subdivided,

respectively. As a result, we defined pain restricted to the back as "strict back pain,"

which is a more limited form compared to local pain. In contrast, extremely

widespread pain had to affect all body areas, representing "panalgesia". This resulted

in four groups of pain extent (Figure 3):

Strict chronic back pain (SBP): Pain in 1 to 3 spinal areas/back (cervical spine,

thoracic spine, or lumbar spine) and no further pain.

Chronic regional pain (CRP): Pain in the spinal area/back plus additional pain, but

the criteria for CWP is not fulfilled.

Common chronic widespread pain (CoCWP): Pain in the spinal area/back and at

least two contra-lateral limbs but less than four limbs (i.e., CWP, but not ExCWP).

Extreme chronic widespread pain (ExCWP): all three spinal areas and all four limbs

are affected ("panalgesia").

--- Figure 3 ---

Questionnaires

Sociodemographic factors included age, sex, living with a partner (yes or no), school

education (≤ 10 vs. > 10 years), occupational situation, and application for disability

pension (yes or no). To determine social class, we used the Winkler-index [26], which

includes school education, current occupation, and income. Each indicator is rated

on a scale from 1 to 7, with higher scores indicating higher education, income, and

occupational status, respectively. The Winkler-index classifies persons into three

categories: 'lower class' (3-8 points), 'middle class' (9-14 points), and 'upper class'

(15-21 points).

The questionnaire also covered pain variables. Participants were asked about the

number of days they were in pain within the last three months (0-90). The intensity of

the pain was rated on a numeric rating scale (NRS 0-10). We also documented the

number of consultations over the last three months and the use of medications within

that period (yes or no). Moreover, self-reported impairment on the job and in daily

activities was measured with a NRS (0-10). The questions are derived, in part, from

the graded chronic pain scale [27].

To measure disability in more detail, we used the Hannover Functional Ability

Questionnaire (FFbH) [28]. The FFbH measures pain-related functional disability

caused by backache. It consists of 12 self-administered items that especially focus

on daily activities that are restricted by musculoskeletal disorders (e.g., putting on

socks, sitting on a hard chair, and lifting). The response format is in 3 stages ("yes,"

"yes with trouble," and "no or with the help of another person"). The answers were

transformed into a functional ability score that ranges from 0-100% (80-100%=no

functional disability, roughly 70%=moderate disability, and <60%=relevant disability).

The results from different studies indicate that the FFbH meets relevant psychometric criteria and is sensitive to change [28, 29]. We also measured health-related quality of life with the general health perception subscale and the vitality subscale of the SF-36. Higher scores reflect better health-related quality of life [30, 31].

To screen for mental comorbidity, we used the German version of the "Patient Health Questionnaire" (PHQ-D) [32], which is based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria. The PHQ-D captures eight mental disorders (major depression, other depressive disorders, panic disorder, other anxiety disorders, somatoform disorders, alcohol dependence, bulimia nervosa, and binge eating disorder). In accordance with other pain publications [33], we omitted the items of the somatisation subscale because it is difficult to decide if a complaint is clearly organic or not fully explainable through medical conditions in a single diagnostic session. If any other disorder screened positive, the patient was classified as mentally comorbid.

Data analysis

All statistical calculations were performed using the SPSS for Windows 19.0 software. Continuous data are presented with means and standard deviations or 95% confidence intervals. Categorical data are presented with numbers and percentages.

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Non-responder analysis

Non-responder analysis was conducted using logistic regression. The first non-responder analysis addressed the persons who returned the questionnaire compared to the subjects who did not. As a result, older people and women were significantly more likely to participate. The second non-responder analysis was conducted for the subjects with CBP who took part in the clinical examination compared to the subjects who refused participation. The results showed no differences in terms of age or gender; differences were noted, however, both in terms of pain intensity over the last three months and social class. High pain intensity was associated with a decreased probability to participate, whereas subjects from a higher social class were more likely to participate. The following factors did not influence participation: marital status, education, occupational status, receiving disability pension, self-reported impairment, and the number of consultations over the last three months.

Main analyses

To determine the prevalence of CBP and CWP, the counts were adjusted for age and sex because previous research as well as our non-responder analysis showed response differences for these variables.

To determine whether CBP patients differed with regard to pain extent in sociodemographic and pain-related factors, an analysis of variances (ANOVA) was used in cases of normal data distribution. The Kruskal-Wallis-Test was used to assess significance in cases where data were not normally distributed. Pain extent was entered as an independent variable, and sociodemographic and pain-related factors were entered as dependent variables. We always present the results of the tests for normally distributed data, except for the results of tests where non-normally distributed data differ from those for normally distributed data. If dependent variables were categorical, we applied Fisher's exact test.

In secondary analyses, we assessed whether there were linear associations between pain extent and the specified additional variables. These analyses were not pre-specified, however, but rather appeared when we examined the results of the ANOVAs and found increasing values for different clinical variables. Therefore, we used Jonckheere's trend test to test for linear contingency. The significance level for all analyses was set to $p < 0.05$. Due to the exploratory/descriptive nature of the study, no adjustment for multiple testing was made.

Results

Prevalence rates of CBP and CWP

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Of the 280 subjects with non-specific CBP, 173 (61.8%) subjects were classified with

CLP and 107 (38.2%) fulfilled the criteria for CWP. With respect to the general

population in the Heidelberg region, the age- and sex-adjusted prevalence for all

CBP is 17.7%. The adjusted prevalence rate for CWP was estimated at 6.7%.

Sociodemographic and medical aspects of CBP subjects

Sociodemographic and medical variables of the 280 subjects are presented in Table

1. The mean age was 49.3 ± 12.8 years and 56.4% of the subjects were female.

--- Table 1 ---

Pain extent according to the Heidelberg Pain Drawing Mask

The refined analysis of the pain drawings led to a classification of the subjects into

four groups (see methods section). According to this classification, only 55 subjects

(19.6%) were rated as having strict local pain (SLP), 118 (42.1%) as having chronic

regional pain (CRP), 68 (24.3%) as having common chronic widespread pain

(CoCWP), and 39 (13.9%) as having extreme chronic widespread pain (ExCWP).

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Pain extent and group differences in sociodemographic and clinical variables

The variables stratified to the four subgroups of pain extent are presented in Table 1. The sociodemographic variables showed a significant group difference for education ($p < 0.05$). However, the pain extent groups did not differ due to age, the proportion of female subjects, or social class, although it seemed that older age, female sex, and a lower social class are associated with a higher pain extent (Table 1).

With regard to pain measures, we observed multiple group differences. The pain extent groups differed significantly in their days of back pain ($p < 0.05$) and in their pain intensity over the last three months ($p < 0.01$). There was also a significant group difference in the number of consultations ($p < 0.05$) and the use of pain medications ($p < 0.001$) over the last three months. There was no group difference due to the age at which back pain was first experienced or to the duration of back pain.

Group differences were also observed for the measures of disability. The groups differed significantly in their impairment on the job ($p < 0.001$), their impairment in daily activities ($p < 0.01$), and disability as measured with the FFbH ($p < 0.001$). The objective measure of disability and impairment, the PIS, also differed significantly between the groups ($p < 0.001$).

There were group differences with regard to general health perception ($p < 0.001$)

and the prevalence of psychiatric comorbidity ($p < 0.05$).

Linear association of pain extent and sociodemographic and clinical variables

Explorative tests for linear trends (Table 1) showed that many variables are

significantly associated with increasing pain extent. Increasing pain extent was

significantly associated with older age (SLP 46.5y vs. ExCWP 51.1y, $p < 0.05$), more

females (SLP 47.3% vs. ExCWP 71.5%, $p < 0.05$), less education ($p < 0.01$), more

unemployment ($p < 0.05$), and lower social class ($p < 0.01$). Moreover, higher pain

extent was significantly associated with higher pain intensity ($p = 0.001$), a higher

number of consultations ($p < 0.05$), more usage of pain medications ($p < 0.001$), and

higher impairment (*p-values* < 0.001). In addition, higher pain extent was associated

with a lower health-related quality of life ($p < 0.001$) and a higher percentage of

psychiatric comorbidity ($p < 0.001$).

Discussion

The aim of our study was to determine the prevalence rate of non-specific CBP in the

general population and to consider the pain extent in a systematic way. Therefore,

we combined a representative, population-based approach with a clinical

examination to increase the validity of our findings and overcome the limitations of

previous studies.

In our population-based sample with validated data on diagnosis and clinical status,

we found prevalence rates of 17.7% for CBP, 11% for CLP, and 6.7% for CWP.

Other studies report prevalence rates for CBP from 10% [6] to 27% [7, 8]. Thus, the

prevalence for CBP found in our study ranks in the middle of the range that previous

studies have reported. The prevalence rate for CWP ranks at the lower end

compared to previous studies [9, 10, 34]. This is an important finding because current

representative population-based data on CBP in Germany were not yet available.

Additionally, the finding that every sixth citizen suffers from CBP highlights the fact

that CBP is a widespread disease with socioeconomic relevance.

Of the CBP subjects, 38.2% fulfilled the criteria for CWP. This finding is very

interesting and has clinical implications. Usually, CBP is treated as a distinct disease.

However, according to our data this approach seems artificial because almost 40% of

the CBP subjects fulfilled the criteria for CWP. Moreover, our data show that the CBP

population is a rather heterogeneous group, and persons labelled as having CLP can

range from pain in a single circumscribed area to pain affecting one entire half of the

body. Therefore, the common categorisation of pain into the usually applied groups

of CLP and CWP is inadequate.

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Consequently, we developed a new pain classification system to form more homogeneous groups of pain extent. When applying our Heidelberg Pain Drawing Mask to four pain-extent groups, the situation became clearer. In our study population, only a minority (19.6%) indicated SLP, while an even smaller proportion (13.9%) indicated ExCWP. The vast majority turned out to have pain in the spinal area plus an additional pain site (regional pain; CWP not fulfilled) or generalised pain that did not fulfil the criteria for ExCWP. This result is similar to other studies showing that most patients report pain in more than one body location [12, 35, 7], but that the extreme distribution of pain is usually rare [35]. The finding that CBP patients frequently have further pain areas shows that results that refer to CBP must be interpreted with care when isolated from concomitant symptoms. In fact, biopsychosocial models that account for a multilevel perspective on CBP that involves broader pain regions, other somatic symptoms, psychological factors, and the social and occupational context appear to be more appropriate [36-38]. Therefore, in our study we considered these additional variables.

Overall, when testing the association of our four pain-extent groups with the clinical picture, we found that an increase in pain extent is concomitant with higher levels of distress. Distress is represented by higher pain intensity, higher disability, more medical consultations, more frequent use of pain medications, and a higher rate of application for disability pensions.

The increase in pain intensity and self-reported and objectively assessed impairment with increasing pain extent fits data gained from tertiary care studies where moderate

correlations between pain extent and both pain severity and impairment were found
[35, 39]. Moreover, the higher the extent of pain the more consultations were
reported and the more pain medication was used. In the SLP group, only 18.5% of
the patients used pain medications, whereas in the ExCWP group, 56.4% used pain
medications. With respect to occupational status, increasing pain extent was
associated with a higher rate of applications for disability pension. A closer look
reveals that in the SLP group, approximately 4% of the subjects address the topic of
disability pension, whereas in the ExCWP group, nearly one of four of those currently
employed either plans to apply or has already applied for pension due to CBP. This
example may illustrate the need for a classification system based on extreme patient
groups, as suggested in this study. Our findings are in accordance with a prospective
study that showed that a higher number of pain locations is associated with the
prevalence of disability pensions [40].

Overall, our findings might explain why a small number of patients claim a large
share of the total costs for CBP [2, 41]. Our data suggests that these might be the
patients with a higher pain extent (the CoCWP and ExCWP groups) because of the
associations mentioned above.

Limitations and strengths:

Currently, there is no uniform definition of CBP. When interpreting the data, one must
keep in mind that our CBP subjects had back pain on at least 45 days over the last

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three months. According to this tight definition, our study population may represent a

rather chronic and unwell segment of the total number of people who experience

back pain. On the other hand, this is not an exceptional definition, as most of the

definitions of "chronic" use temporal aspects [42, 3]. Nevertheless, differences in

reported prevalence rates between our study and other studies may in part be due to

heterogeneous definitions [3, 4, 42].

A further limitation of our study is that we could not reach all persons with CBP;

however, with an overall return rate of 60.1% we are comparable with other studies

[19, 43]. Non-responder analyses revealed only slight differences between

participants and non-participants. The return of the initial pain assessment

questionnaire was associated with older age and the female sex. The second

dropdown from the patients identified with CBP to the patients who participated in the

clinical examination revealed that subjects from a higher social class and subjects

with less pain intensity were more likely to participate. More females and older

patients might overestimate the extent of pain, whereas lower pain intensity and a

higher social class might lead to an underestimation of the pain extent. We thus

expect the effect on the pain extent measure to be marginal because differences

between the response and non-response groups were only slight. This is supported

by the fact that analysis showed that the effect of non-response on the prevalence

rates was negligible. The small to negligible effects of attrition in CBP studies are

also supported by others [20].

The methodological strength of our study is its population-based setting that was

combined with a clinical examination. This approach enabled us to include subjects

with CBP that did not seek medical care. Because 20-50% of back pain cases do not

seek medical care [11, 6], studies of selective clinical settings may bias the research.

Moreover, in contrast to questionnaire studies that rely solely on self-reported data,

the addition of a personal clinical examination in our study strengthens the validity of

our data. Subjects with specific causes of CBP that most likely biased other research

could be excluded. We were also able to objectify patient self-ratings and measure

pain comprehensively. For example, one study showed that roughly two-thirds of

patients add to their pain drawing if it is discussed with a physician even though they

had been asked to give a full report of their pain symptoms on a pain drawing within a

questionnaire [44]. Thus, our study combined the advantages of epidemiological and

clinical research.

In conclusion, our data show that CBP is highly prevalent and that in most people

with CBP, pain is not restricted to pain in the back. Due to the heterogeneity of the

CBP group, a more detailed classification system than the dichotomous grouping into

CWP and non-CWP/CLP is required. We propose a four-group classification that

forms more homogeneous groups relative to the pain extent. This classification

system revealed diagnostic and clinical relevance. Our data support that the

classification groups are associated with further relevant variables, including higher

pain intensity, higher disability, more medical consultations, more frequent use of

pain medications, and a higher rate of application for disability pensions. Thus, using

our classification system, which is feasible in clinical practice, the heterogeneous

group of CBP subjects is subdivided into four clinically distinguishable groups that are

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more homogeneous. Clinically, the developed classification system can be used to identify highly distressed/burdened subjects that claim a large share of the costs associated with CBP. These patients are generally those CBP patients with high pain extent (CWP). Physicians should pay attention to clinical variables other than pain extent, especially the thoroughness and extent of pain. Future studies will have to confirm the value of the classification system for prognostic purposes.

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Figure legends

Figure 1: Flow-chart of subject inclusion

Chronic back pain (CBP) was defined as pain in the back on at least 45 days within the last three months.

Figure 2: Heidelberg pain drawing mask. (a) Participants were given drawings of the body (front view and back view) and were asked to mark all of the painful areas of the body. (b) A transparent template indicates the boundaries of each region. It was placed over the pain drawings to assist in analysis.

The regions are as follows: a) Cervical spine, b) Thoracic spine, c) Lumbar spine, and d) Limb.

Figure 3: Classification of pain extent into four groups according to the suggested new classification system. (a) Strict back pain: pain in 1 to 3 spinal areas, no further pain. (b) Chronic regional pain: pain in the spinal area plus additional pain, but criteria for CWP is not fulfilled. (c) Common CWP: pain in the spinal area plus at least two contra-lateral limbs, but less than four limbs. (d) Extreme CWP: all spinal areas and all four limbs are affected.

Table 1: Classification of non-specific CBP subjects in the four pain extent groups and associated sociodemographic and clinical variables

	Total	Chronic strict local pain	Chronic regional pain	Common chronic widespread pain	Extreme chronic widespread pain	ANOVA/ Chisq^2 p-value	J-T test p-value
Number of subjects (N = 280)	280 (100%)	55 (19.6%)	118 (42.1%)	68 (24.3%)	39 (13.9%)		
Sociodemografics							
Age; Mean [95% CI]	49.3 [47.8;50.8]	46.5 [43.1;50.0]	48.8 [46.3;51.2]	51.3 [48.5;54.0]	51.1 [47.1;55.1]	0.160	0.026
Female Sex; N (%)	158 (56.4%)	26 (47.3%)	65 (55.1%)	39 (57.4%)	28 (71.8%)	0.124	0.031
Living with partner (yes); N (%)	186 (67.6%)	35 (64.8%)	83 (70.9%)	43 (66.2%)	25 (64.1%)	0.569	0.792
Education; N (%)							
> 10 years	77 (28.1%)	24 (44.4%)	32 (27.6%)	12 (18.5%)	9 (23.1%)	0.015	0.004
Occupation; N (%)							
Employed (full-time or part-time)	167 (59.6%)	39 (70.9%)	72 (61.0%)	36 (52.9%)	20 (51.3%)		
Unemployed	113 (40.4%)	16 (29.1%)	46 (39.0%)	32 (47.1%)	19 (48.7%)	0.144	0.023
Social class[*]; N (%)							

Upper class	74 (27.2%)	22 (42.3%)	30 (25.9%)	14 (21.5%)	8 (20.5%)		
Middle class	158 (58.1%)	26 (50.0%)	69 (59.5%)	39 (60.0%)	24 (61.5%)		
Lower class	40 (14.7%)	4 (7.7%)	17 (14.7%)	12 (18.5%)	7 (17.9%)		
	272 (100%)	52 (100%)	116 (100%)	65 (100%)	39 (100%)	0.181	0.007
Pain measures							
Age at first time back pain	32.7 [31.1;34.3]	31.8 [28.3;35.3]	32.3 [29.8;34.9]	34.8 [31.5;38.0]	31.5 [27.1;35.8]	0.530	0.360
Duration of back pain	16.4 [15.0;17.7]	14.3 [11.1;17.4]	16.2 [14.1;18.3]	16.9 [14.2;19.5]	18.7 [15.2;22.1]	0.308	0.035
Days of back pain over last 3 months; Mean [95% CI]	74.5 [72.4;76.6]	70.5 [66.0;75.1]	76.6 [73.4;79.8]	76.1 [72.0;80.2]	70.9 [65.0;76.8]	0.037[§]	0.602
Pain intensity over last 3 months on NRS (0-10); Mean [95% CI]	4.4 [4.1;4.6]	4.1 [3.5;4.6]	4.1 [3.8;4.5]	4.7 [4.2;5.2]	5.0 [4.5;5.5]	0.009[§]	0.001
Number of consultations over last 3 months; Mean [95% CI]	1.5 [1.2;1.9]	1.1 [0.5;1.6]	1.2 [0.8;1.5]	2.4 [1.3;3.5]	1.8 [0.9;2.7]	0.024	0.033
Pain medication in the last 3 months (yes); N (%)	111 (40.7%)	10 (18.5%)	44 (38.3%)	35 (53.8%)	22 (56.4%)	<0.001	<0.001
Disability measures							
Potentially employable; N (%)	203 (72.5%)	46 (83.6%)	88 (74.6%)	43 (63.2%)	26 (66.7%)	0.061	0.012
Disability pension (applied for or	20 (9.9%)	2 (4.3%)	7 (8.0%)	5 (11.6%)	6 (23.1%)	0.186	0.049

planned) †

Self-reported impairment (job) over last 3 months on NRS (0-10); Mean [95% CI]	3.3 [3.0;3.6]	2.3 [1.6;3.0]	3.0 [2.6;3.4]	3.9 [3.3;4.5]	4.5 [3.7;5.3]	<0.001	<0.001
Self-reported impairment (daily activities) last 3 months on NRS (0-10); Mean [95% CI]	3.2 [2.9;3.4]	2.4 [1.7;3.0]	3.0 [2.6;3.5]	3.3 [2.7;4.0]	4.3 [3.7;5.0]	0.002	<0.001
FFbH	74.4 [72.3;76.6]	82.7 [78.4;86.9]	76.2 [72.9;79.6]	70.8 [66.5;75.2]	64.0 [58.9;69.0]	<0.001	<0.001
Physical Impairment Scale; Mean [95% CI]	2.16 [2.0;2.3]	1.6 [1.2;2.0]	2.1 [1.8;2.3]	2.3 [1.9;2.6]	3.0 [2.4;3.6]	<0.001	<0.001
Psychological measures							
SF36-GHP (0-100); Mean [95% CI]	62.7 [60.3;65.1]	70.4 [65.7;75.2]	64.4 [60.9;67.8]	57.2 [52.2;62.1]	54.1 [46.3;62.0]	<0.001	<0.001
SF36 Vitality (0-100); Mean [95% CI]	53.3 [50.8;55.9]	55.4 [50.3;60.5]	56.2 [52.2;60.2]	50.3 [44.8;55.7]	46.5 [39.3;53.7]	0.054	0.012
Psychiatric comorbidity (PHQ-D) ‡	40 (14.3%)	2 (3.6%)	17 (14.4%)	12 (17.6%)	9 (23.1%)	0.026	0.006

Descriptive statistics are presented with means and 95% confidence intervals for continuous variables and numbers and percentages for categorical variables. Between group differences of continuous data was analyzed with analysis of variances (testing group differences). In case of not normally distributed variables we report results of Kruskal-Wallis-Tests if the level of significance differs from that in analysis of variances. Categorical data were analyzed with Fisher's exact test. J-T test = Jonkheere Trend test was used to test a linear trend across groups.

95% CI = 95% confidence interval; NRS = Numerical Rating Scale; GHP = General Health Perception; PHQ-D = Patient Health Questionnaire

(German Version).

* According to the Winkler-Index

† % refers to potentially employable persons

‡ excluding somatoform disorders

§ non-parametric Kruskal-Wallis-Test

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| Complete back pain survey: n = 4,000 | ⟹ | Could not be reached by mail: n = 101 (2.5%) |

| Could be reached by mail: n = 3,899 (97.5%) | ⟹ | Did not return the questionnaire: n = 1,491 (38.2%) |

| Returned the questionnaire: n = 2,408 (61.8%) | ⟹ | No chronic back pain reported: n = 1,981 (82.3%) |

| Chronic back pain reported: n = 427 (17.7%) | ⟹ | Refused clinical examination: n = 124 (29%) |

| Clinical examination: n = 303 (71.0%) | ⟹ | Excluded due to specific causes of CBP n = 20 |

| Patients with non-specific CBP n = 283 | ⟹ | Did not complete examination n = 3 |

| Patients with non-specific CBP included in analysis n = 280 |
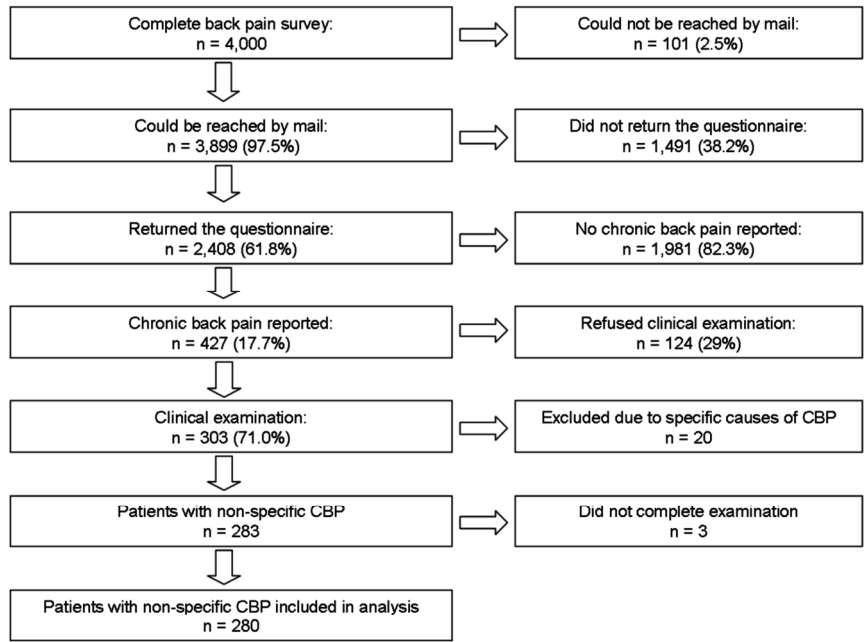
Figure 1: Flow-chart of subject inclusion
Chronic back pain (CBP) was defined as pain in the back on at least 45 days within the last three months.

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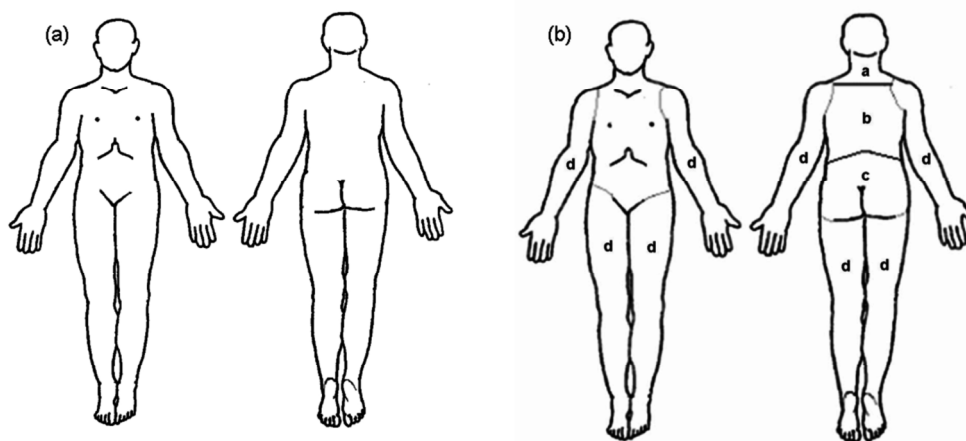
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Figure 2: Heidelberg pain drawing mask. (a) Participants were given drawings of the body (front view and back view) and were asked to mark all of the painful areas of the body. (b) A transparent template indicates the boundaries of each region. It was placed over the pain drawings to assist in analysis. The regions are as follows: a) Cervical spine, b) Thoracic spine, c) Lumbar spine, and d) Limb.

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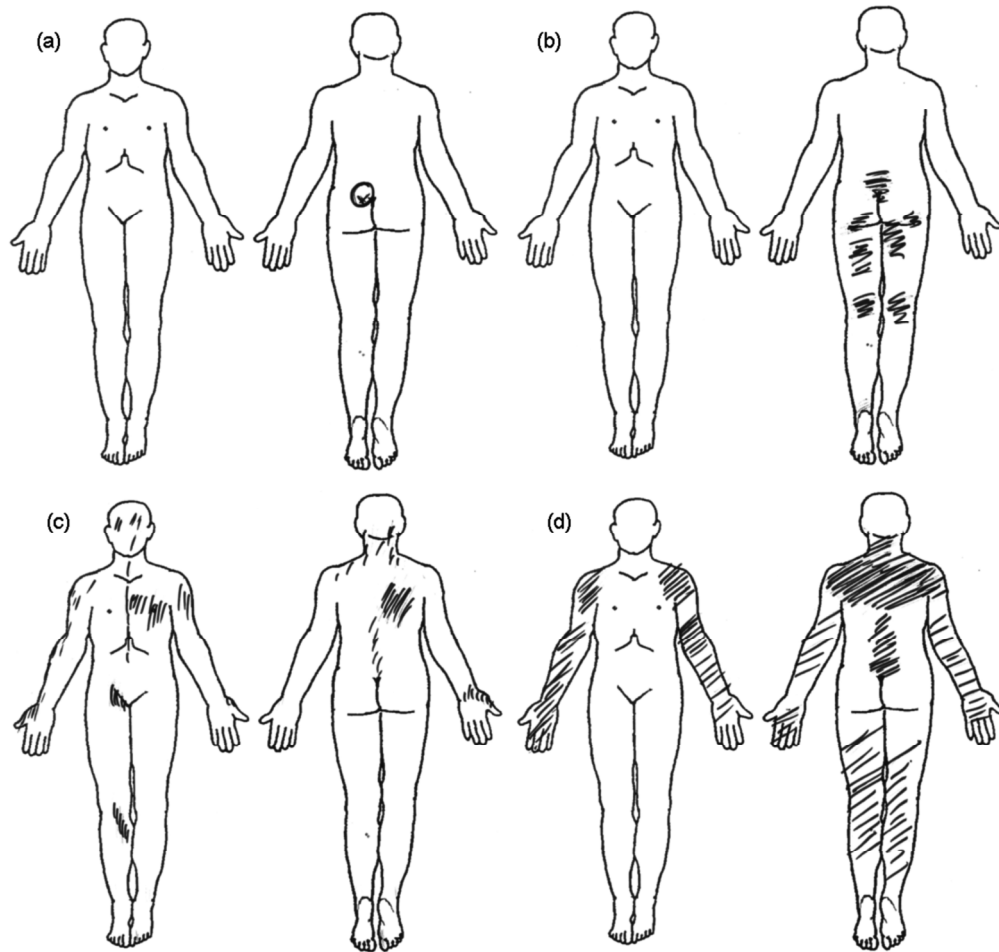
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Figure 3: Classification of pain extent into four groups according to the suggested new classification system. (a) Strict back pain: pain in 1 to 3 spinal areas, no further pain. (b) Chronic regional pain: pain in the spinal area plus additional pain, but criteria for CWP is not fulfilled. (c) Common CWP: pain in the spinal area plus at least two contra-lateral limbs, but less than four limbs. (d) Extreme CWP: all spinal areas and all four limbs are affected.
190x181mm (600 x 600 DPI)

PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION

Original Research Article

The Prevalence and Type of Axis-I and Axis-II Mental Disorders in Subjects with Non-Specific Chronic Back Pain: Results from a Population-Based Study

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There are no conflicts of interest related to the manuscript on the part of the authors.

Abstract

Objective. To investigate the prevalence and the type of mental comorbidity in a population-based sample of subjects with non-specific chronic back pain.

Design. Representative population-based survey.

Setting. The city of Heidelberg (in southwestern Germany) and 10 adjacent communities.

Patients. From a random sample of individuals (N = 2,000), 1,091 subjects completed a questionnaire including a pain assessment. Of those, 188 subjects (17%) fulfilled the criteria for chronic back pain ($\geq$45 days of back pain in the last 3 months) and were subsequently invited to undergo a detailed clinical examination; 131 subjects (70%) agreed to participate. The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV) (SCID-I + II) was used to assess current (defined as the previous 4 weeks) mental comorbidity and was completed in 110 subjects (84%) with non-specific chronic back pain.

Intervention. N/A.

Outcome Measures. DSM-IV mental comorbidity diagnoses.

Results. The overall prevalence of mental comorbidity of Axis-I and -II disorders were 35.5% and 15.5%, respectively. Of Axis-I disorders, anxiety disorders (20.9%) and affective disorders (12.7%) were the most frequent. Of Axis-II disorders, 9.1% of diagnoses was of the Cluster C category (anxious/inhibited). Compared with the general population, the total rate of Axis-I comorbidity was significantly higher, while the total rate for Axis-II personality disorders was only slightly different.

Conclusions. The consistent diagnoses of anxiety, fear, and avoidance in these subjects indicate that also primary care health professionals should consider anxiety disorders in patients with chronic pain, in addition to the affective disorders that are most frequently self-reported in pain patients.

Key Words. Non-Specific Chronic Back Pain (CBP); Mental Disorders; Prevalence; SCID; Epidemiologic Design; Mental Comorbidity

Introduction

Today, pain of the musculoskeletal system is the most common pain syndrome worldwide [1–3]. This type of pain is on the increase and is of immense cost to the public health system [4]. About one third of patients who were treated at the primary care level had a predominance of musculoskeletal pain [5]. Chronic back pain (CBP), a major subgroup of musculoskeletal diseases, is of high prevalence and patients often respond poorly to treatment [6–8]. Therefore, research identifying various factors associated with the development and maintenance of back pain is highly relevant.

Empiric studies of the etiology of CBP have identified somatic as well as psychological and social factors as risks for developing a chronic condition [9,10]. Of these variables, mental comorbidity is of interest. Several studies found an increased prevalence of mental disorders in CBP patients, ranging from 31% to 98% [11,12]. Reasons for the high variability in prevalence include differences in study design, instrumentation, or the quality of the collection of somatic and mental diseases [11].

A study by Polantin et al. found that 59% of CBP patients demonstrated current symptoms of at least one Axis-I diagnosis according to the DSM-IV and 51% met the criteria for any Axis-II personality disorder (PD) [12]. Similar high prevalence rates were found in other studies of chronic musculoskeletal pain [13,14]. Differences in patients with acute (23% Axis-I and 21% Axis-II disorders) or chronic (68% Axis-I and 60% Axis-II disorders) low back pain show that mental comorbidity may play an important role in CBP [15]. In contrast, only about 15% of the general population was identified as suffering from acute mental disorders in the National Institute of Mental Health Epidemiologic Catchment Area Survey [16].

In patients with CBP, affective disorders were the most frequently reported diagnoses (32.4–68.0%), followed by substance abuse (13.2–40.5%), and anxiety disorders (10.6–19.0%) [12,14,17]. These results differ from representative population-based samples, in which anxiety disorders are the most prevalent (9.0–14.5%) [18]. In more recent studies of chronic pain, there is some evidence that anxiety disorders might occur as frequently as mood disorders [19–21].

The studies mentioned above either were confined to patients receiving clinical treatment, or had methodological shortcomings. In fact, it is known that only half of the individuals suffering from musculoskeletal pain seek treatment through the medical system [22]. Therefore, the purpose of the present study was to investigate the prevalence and the type of mental comorbidity in a representative population-based sample of individuals with CBP. To reliable diagnose non-specific CBP subjects were physically examined. The use of a clinical, standardized assessment method (Structured Clinical Interview for DSM-IV [SCID]; Axis-I + Axis-II) was used to yield reliable information about the prevalence and the type of mental disorders in a representative population of subjects with CBP.

Methods

Design and Sample Selection

The study is part of a population-based longitudinal multiregional postal survey of back pain [23] by the German Back Pain Research Network (GBPRN). Heidelberg and 10 adjacent communities were randomly chosen out of 55 cities and communities in the southwestern district (Rhein-Neckar) of Germany. A random sample of 4,000 persons was drawn from these communities, proportional to the number of inhabitants.

To identify the sample, we asked the registration offices to provide lists of inhabitants suitable for our requirements (18–74 years old and residing in the chosen regions). This procedure ensured that a representative sample of the entire population was included. From a list of 4,000 individuals, 3,899 were reached by mail and were asked to fill out a screening questionnaire that included questions regarding the occurrence, intensity, duration, and radiation of back pain, social and demographic variables, and psychometric tests. Additionally, space was provided where they could register their contact information (telephone number and availability). If necessary, up to two reminders were sent at 3- and 6-week intervals after the first mailing. The questionnaires were returned by 2,408 individuals (61.8%). The response rates were approximately 30% after the first letter, approximately 20% after the first reminder, and approximately 10% after the second reminder.

All individuals suffering from back pain for ≥ 45 days during the last 3 months (N = 427) were contacted by telephone and invited to a clinical (physical and psychological) examination at the university outpatient department. If no telephone number was available, individuals were contacted by mail. If an individual was not reached with the first call, he or she was recontacted up to five times. If an appointment was missed, the individual was called up to two more times to schedule a new appointment. A total of 303 individuals accepted the invitation for a clinical examination.

To examine the prevalence and the type of mental comorbidity among non-specific CBP subjects, we administered the SCID (SCID-I and SCID-II), a comprehensive and highly valid instrument. Because of time and personnel constraints, we initially randomly allocated half of the population (2,000 out of 4,000 individuals) for the Structured Clinical Interview. Of the randomized subsample, 1,091 subjects returned the questionnaire; 198 of them fulfilled the criteria for CBP. These 198 subjects were invited to a physical examination in our outpatient department to verify self-diagnosis of CBP and to exclude patients with specific causes of CBP. Of those invited, 57 patients refused participation. The remaining 141 subjects were examined (general, rheumatological and neurological
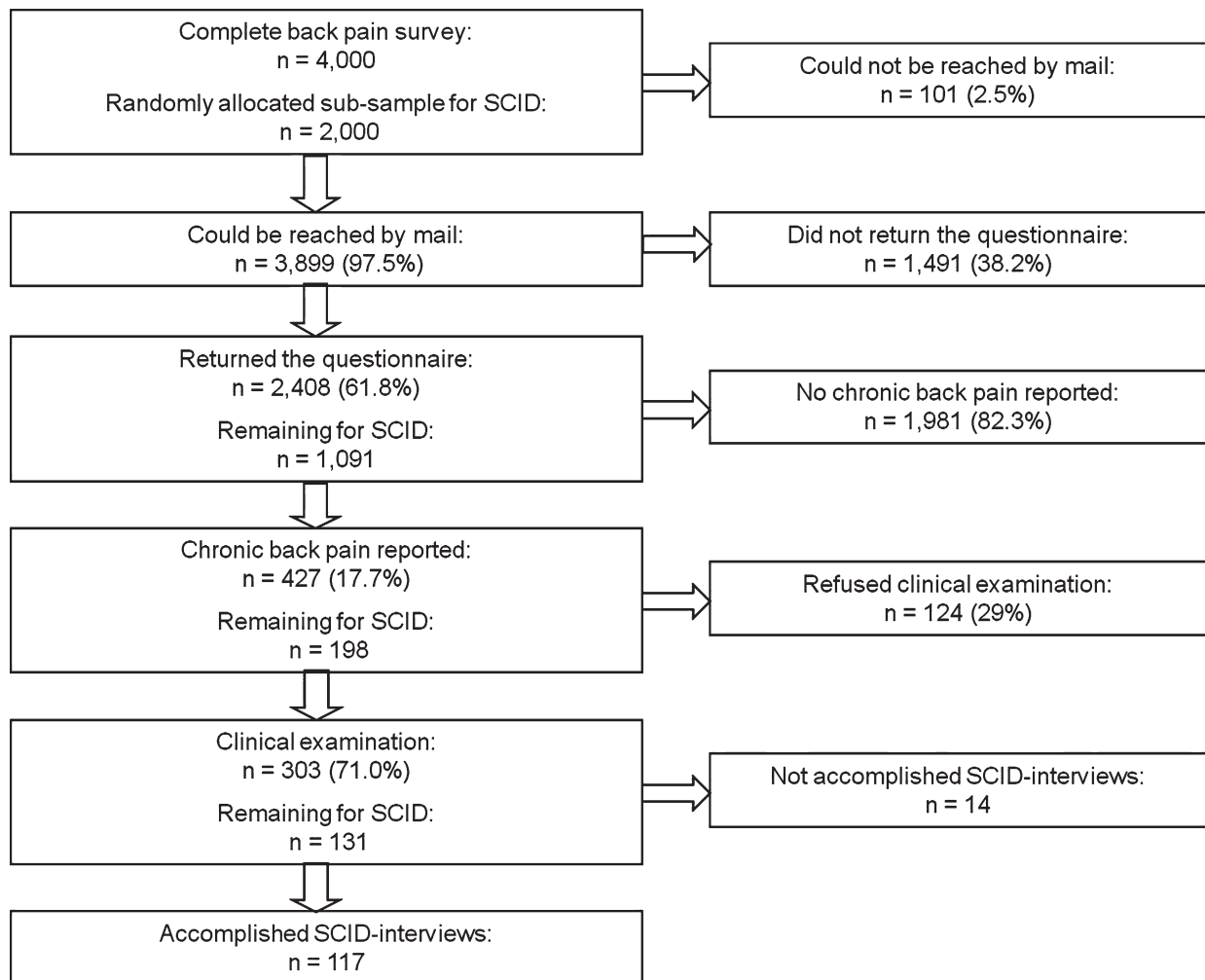
Figure 1 Participation flow, including SCID subsample. SCID = Structured Clinical Interview for DSM-IV.

examination, blood tests, past medical history, past severe injuries) for specific causes of CBP. After the physical examination, 10 patients were excluded due to specific causes of CBP (two suffered from Bechterew's disease, two suffered from rheumatoid arthritis affecting the spine, one suffered from polymyalgia rheumatica, one suffered from tumor/metastases, one suffered from spondelolysis, three suffered from disc hernia). The remaining 131 subjects with non-specific CBP were scheduled for the SCID procedure (psychological examination). Fourteen of the scheduled SCID interviews could not be completed for the following reasons: an incomplete physical examination (N = 4), exhaustion after the physical examination (N = 6), refusal to participate in the study (N = 2), and lack of language skills (N = 2). The detailed participation flow is shown in Figure 1.

Overall, 117 individuals participated in the SCID interview, but seven interviews were not included in the analysis because the interview was incomplete or interrupted. Thus, 110 interviews (84%) were evaluated.

The study was carried out in accordance with the Declaration of Helsinki of 1975. The ethics committee of the Medical Hospital of Heidelberg approved this study, and all participants gave their written informed consent. Participants received an allowance of EUR 10 ($14) for attending the entire examination.

Assessment

To assess mental comorbidity, the German version of the SCID, which consists of two parts, was used [24]. The SCID-I is a semi-structured interview for the evaluation of major DSM-IV Axis-I diagnoses. In this study, we used the non-patient version. By using the SCID-I, it is possible to derive both a current and a previous history of psychiatric illness. The category of somatoform pain disorder is highly controversial with respect to back pain. Therefore, in accordance with other authors, we excluded the diagnosis of somatoform pain disorder [14].

The SCID-II procedure for assessing PDs is a two-stage process. First, subjects complete a 120-item questionnaire with questions based on the criteria from the DSM-IV. In the second stage, a semi-structured interview is administered. Positive answers must be re-evaluated by the interviewer in order to diagnose Axis-II PD. According to the SCID-II protocol, we interviewed only those subjects who achieved the cut-off (a specified number of positive answers in a specific PD section) on the questionnaire.

All SCID interviews were conducted by two psychologists with graduate training in clinical psychology. To ensure diagnostic reliability, 20 interviews (10 from each interviewer) were videotaped and SCID rated by both psychologists. A kappa coefficient was calculated to assess inter-rater reliability. For Axis-I disorders, the kappa coefficient was 0.89, indicating a good agreement between the raters [25]. For Axis-II disorders, there was agreement in 80% of the ratings, but it was not possible to calculate the kappa coefficient due to the small number of subjects diagnosed with an Axis-II disorder. In case of missing inter-rater agreement, an experienced psychiatrist was consulted to moderate.

Statistical Analysis

Variables are presented as means (M) and standard deviations (SD) for continuous variables, and numbers (N) and proportions (%) for categorical variables. We compared our prevalence data for current (the previous 4 weeks) Axis-I and Axis-II disorders with those reported in other general population-based studies (control groups), using Fisher's exact test [18,26]. The prevalence in the general population was adjusted by age and sex compared with the population of the Rhein-Neckar district. All statistical measures were calculated using SPSS (Version 17.0; Chicago, IL, USA).

Non-Responder Analysis

Non-responder analysis was conducted by logistic regression. A first non-responder analysis compared the subjects who returned the questionnaire to the subjects who did not respond. We found that older people and women were more likely to participate. The second non-responder analysis compared the subjects with CBP who took part in the clinical examination to the subjects who refused to participate. There were no differences in terms of age or gender. However, differences were noted in pain intensity over the previous 3 months and in social class. High intensity pain was associated with a decreased probability of participation, whereas subjects from a higher social class were more likely to participate. The following factors did not influence participation: marital status, education, occupational status, receiving disability pension, self-reported impairment, and the number of consultations over the last 3 months.

Table 1 Socio-demographic variables of non-specific chronic back pain patients

CBP Patients: N = 110	M (SD)
Age	48 ± (13.3)
	N (%)
Gender	
Female	63 (57)
Marital status	
Single/divorced/widowed	32 (29)
Married	78 (71)
Education	
<10 years	50 (45)
≥10 years	54 (49)
Occupational status	
Employed	67 (61)
Unemployed	12 (11)
School/apprenticeship	2 (2)
Occupational disability pension	4 (4)
Retirement pay	19 (17)

If subpoints (e.g. "employed," "unemployed") of a heading (e.g., "occupational situation") do not sum up to 100%, this is due to missing data.
CBP = chronic back pain.

Results

The socio-demographic characteristics of subjects who took part in the SCID study are shown in Table 1. The mean age was 48 ± 13.3 years, and 57% of the subjects were female. A pain figure was used to categorize subjects as to localized or widespread pain [27]. Approximately, 45.5% of the subjects administered the SCID interview had chronic local pain (CLP) and 54.5% had chronic widespread pain (CWP). The group of CWP included one patient with diagnosis of fibromyalgia syndrome diagnosed according to American College of Rheumatology (ACR) criteria [28]. Sixty percent of women and 47% of men were diagnosed to have CWP (NS).

Table 2 shows the current prevalence and type of Axis-I disorders in subjects with non-specific CBP, excluding somatoform pain disorder. Of the subjects with non-specific CBP, 39 subjects (35.5%) received at least one Axis-I diagnosis. We observed no sex difference (men = 36%, women = 35%, NS) and no differences comparing CLP with CWP (17% and 18%, respectively) regarding prevalence of mental disorders. Anxiety disorders (20.9%) and affective disorders (12.7%) were the most frequently diagnosed, followed by substance-related disorders (7.3%) and eating disorders (5.5%).

The prevalence and the type of Axis-II disorders in the non-specific CBP subjects are presented in Table 3. Seventeen (15.5%) of the participants met the criteria for at least one Axis-II PD. The most frequent diagnoses

Table 2 Current prevalence of Axis-I disorders (DSM-IV) for non-specific CBP patients (N = 110)

	DSM-IV Code	N	Prevalence (%)
At least one Axis-I disorder		39	35.5*
Affective disorders		14	12.7[†]
Major depression, single episode, mild	296.21	1	0.9
Major depression, single episode, moderate	296.22	1	0.9
Major depression, recurrent, mild	296.31	2	1.8
Major depression, recurrent, moderate	296.32	4	3.6
Dysthymia	300.4	3	2.7
Depressive disorder, not otherwise specified	311	2	1.8
Affective disorder due to a general medical condition	293.83	1	0.9
Anxiety disorder		23	20.9[†]
Panic disorder without agoraphobia	300.01	5	4.5
Panic disorder with agoraphobia	300.21	2	1.8
Agoraphobia without history of panic disorder	300.22	4	3.6
Social phobia	300.23	5	4.5
Specific phobia	300.29	7	6.4
Substance-related disorder		8	7.3[†]
Alcohol dependence	303.90	3	2.7
Multiple substance dependence	304.80	1	0.9
Alcohol abuse	305.00	4	3.6
Eating disorder		6	5.5[†]
Anorexia nervosa	307.1	2	1.8
Eating disorders, not otherwise specified	307.5	2	1.8
Bulimia nervosa	307.51	2	1.8
Acute stress disorder	308.3	1	0.9
Adjustment disorders		3	2.7
— With depressive mood	309.20	2	1.8
— With mixed anxiety and depressed mood	309.28	1	0.9

* Due to multiple diagnoses in some CBP patients, the sum for the prevalence of the different disorder-groups (e.g. "Affective Disorders", "Anxiety Disorders", "Eating Disorders") is higher than the prevalence for co-morbid Axis-I disorder ("At least one Axis-I disorder"). [†] Deviations between the sum of the single diagnoses (e.g., "Anorexia Nervosa," "Bulimia Nervosa") and the proportion of the disorder group ("Eating Disorders") are a result of rounding.
CBP = chronic back pain; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, IV*.

were obsessive-compulsive and avoidant PD (4.5% each), followed by borderline PD (3.6%), paranoid PD (2.7%), and narcissistic PD (0.9%). Thus, diagnoses in Cluster C (anxious/inhibited) were the most prominent and accounted for 9.1% of diagnoses.

In addition, we compared the prevalence of both Axis-I and Axis-II disorders with their prevalence in other population-based studies. Comparison of current (the previous 4 weeks) Axis-I disorders between the study participants and data from another population-based study revealed a significant difference between the non-specific CBP subjects in this study and individuals in the general population [18]. Our CBP subjects showed a significantly higher prevalence in each of the accumulated categories (any Axis-I disorder: odds ratio [OR] 2.23, $P < 0.001$; any anxiety disorder: OR 2.67, $P < 0.001$; any mood disorder: OR 2.16, $P < 0.05$; any substance related disorder: OR 2.64, $P < 0.05$; any eating disorder: OR 29.04, $P < 0.001$). The comparison of Axis-II PDs in our subjects and the data from the general population showed no significant differences, other than in avoidant PD in Cluster C (OR 4.24, $P < 0.05$) [26].

Discussion

To our knowledge, this is the first study of the prevalence and the type of mental comorbidity in subjects suffering from non-specific CBP who were recruited by a randomized representative population-based survey and administered the SCID. The main advantage of our approach was the large number of individuals with non-specific CBP that were drawn from the general population, rather than from a specific clinical setting. The second strength of this study was the simultaneous assessment of Axis-I and Axis-II disorders. To the best of our knowledge, there is no representative population-based study of patients with CBP that assesses the prevalence and type of Axis-II PDs using a validated instrument for DSM-IV. In addition, the criterion for inclusion in the chronic pain group was determined by a physical examination and was not based solely on patients' self-report, as is typical of other studies.

In our sample, approximately one third (35.5%) of the subjects had at least one current Axis-I disorder, excluding somatoform pain disorders. This result is at the lower end

Table 3 Prevalence of Axis-II disorders (DSM-IV) for non-specific CBP patients (N = 110)

	DSM-IV Code	N	Prevalence (%)
At least one Axis-II disorder		17	15.5*
Cluster A (odd/eccentric)		3	2.7
Paranoid PD	301.00	3	2.7
Cluster B (dramatic/erratic)		5	4.5
Borderline PD	301.83	4	3.6
Narcissistic PD	301.81	1	0.9
Cluster C (anxious/inhibited)		10	9.1[†]
Obsessive-compulsive PD	301.4	5	4.5
Avoidant PD	301.82	5	4.5
Negativistic (passive-aggressive) PD[‡]		1	0.9

* Due to multiple diagnoses in some CBP patients, the sum of the prevalence of the different Clusters is higher than the prevalence for comorbid Axis-II disorder ("At least one Axis-II disorder").
[†] Deviations between the sum of the single diagnoses (e.g., "obsessive-compulsive PD," "avoidant PD") and the proportion of the Clusters (e.g., "Cluster C") are a result of rounding.
[‡] This is not yet an official category of Axis-II disorders in the DSM-IV but it is listed in DSM-IV Appendix B as a suggestion for a new category.
CBP = chronic back pain; PD = Personality Disorder; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, IV.*

of the previously reported range of mental comorbidity in subjects with back pain [12–14,17]. However, this prevalence is still significantly elevated compared with the general population. The prevalence of Axis-II PDs in this study was 15.5%. Compared with clinical samples of patients with back pain, this prevalence is rather low and similar to the total prevalence of mental disorders in the general population.

Other studies are in agreement with our findings of a significantly higher, although moderate, prevalence of mental comorbidity in patients with CBP (31%–38%) [11,21,29,30]. A population-based case-control study found that only 16.9% of individuals with CWP were estimated to have a psychiatric diagnosis [31]. However, this study used a non-representative population and inadequate screening methods. To summarize, the studies in the literature recruited patients from a clinical setting, did not apply an international standardized assessment instrument for the evaluation of mental disorders or used another defined pain condition.

In our population, anxiety disorders were the most common category of Axis-I mental disorders (20.9%), followed by affective disorders (12.7%), substance-related disorders (7.3%), and eating disorders (5.5%). Of Axis-II disorders, PDs of Cluster C (anxious-avoidant) were the most frequent (9.1%). When the psychopathological aspects of both Axes are considered together, a consistent

tendency toward vulnerability to anxiety, fear and avoidance were observed among our subjects, as reported elsewhere [32]. Sensitivity toward anxiety can be viewed as a precursor to pain-related fear or depression; avoidance behavior or disability is thought to be a response to experiencing pain [33–38]. Furthermore, avoidance may contribute to the maintenance or exacerbation of chronic pain and produce a number of additional negative physical and psychological symptoms. Fearful people are more conscious of possible threatening signals and are therefore less able to shift their attention away from pain-related information [37]. Additional longitudinal studies are needed to better understand the role of anxiety in chronic pain.

In our subjects, the prevalence of affective disorders (12.7%) was greater than that of the general population. The observation that affective disorders are the most frequent mental comorbidity in patients suffering from pain has been reported by others [12,15]. In our sample, however, anxiety disorders were the most prevalent, which is in agreement with data from the general population [18]. This might be due to our population-based setting, as confirmed by other recent population-based studies [19–21]. It can be hypothesized that in the medical system, depressed patients tend to be identified more easily than patients with anxiety disorders, perhaps because patients with depression are more likely to seek help than patients with anxiety disorders. Between one third and one half of patients with depression seek help, whereas a lower number of patients with anxiety disorders seek help [39–42]. Therefore, clinicians should consider screening for affective and anxiety disorders in patients with CBP. The rehabilitation of patients with chronic pain may be compromised if concurrent psychiatric disorders are not recognized and adequately treated [43,44].

In our subjects, the prevalence of substance-related disorders was low (7.3%). This result differs from Anglo-American studies of patients with CBP, where reported ranges of prevalence vary from 19% to 23% [12,45]. One explanation for this difference may be cultural differences in perceiving and/or reporting substance-related disorders. This conclusion is supported by comparably small rates in the comparison group [18].

The observed prevalence of eating disorders in our subjects (5.5%) is high compared with other studies of CBP patients as well as to the general population. This is surprising, considering that psychophysiological studies show an elevated pain threshold and a decreased sensitivity to painful stimuli in patients diagnosed with either bulimia or anorexia nervosa [46–48]. On the other hand, it is known that obesity, which is often found in atypical eating disorders, is a risk factor for developing CBP [49]. In addition, osteoporosis (which is common in anorexia) is associated with an increased risk of symptoms of pain [50,51]. However, our findings should be interpreted carefully due to the small sample size.

The prevalence of PDs in our study are remarkably low in comparison to a previous study [12]. It could be con-

cluded that the relatively moderate prevalence of PD observed in our study may be attributed to our non-selective population-based sample that was not confounded by a high rate of help-seeking behavior. It would be interesting to compare further samples of pain subjects with respect to PD.

Our study has several limitations. The overall rate of return of our postal survey was 60.1% after two reminders. However, this is comparable with other studies [23,52–54]. Non-responder analyses revealed only slight differences between participants and non-participants. Return of initial pain assessment questionnaire was associated with older age and female sex. In general, women are more likely to suffer from mental disorders than men [18]. Thus, there might be an overestimation of mental comorbidity in our study. However, in our study, women were not more likely to have mental comorbidity than man. In regard to age, most disorders develop early in life [18]; thus, influence of a higher proportion of older aged participants might be attenuated.

The second dropdown from the identified 188 patients with non-specific CBP to the 110 patients that completed SCID procedure was addressed by second non-responder analyses. Analyses revealed that subjects from a higher social class and subjects with less pain intensity were more likely to participate in the physical examination and SCID procedure. Lower socioeconomic status is usually associated with greater risk for mental disorders [18]. The higher response rate of patients with higher socioeconomic status might also explain the low rate of Axis-II disorders because especially PDs are concentrated in lower socioeconomic groups [55]. Moreover, it might be that especially the group with high pain intensity has greatest psychiatric comorbidity, thus underestimating prevalence of mental comorbidity in our CBP sample. These findings offer the possibility of underestimating prevalence.

We were also surprised not to capture generalized anxiety disorder (GAD) with the SCID. Perhaps it might be that patients with GAD have belonged to the non-responders and were less likely to participate in a voluntarily study on CBP that might not target at their GAD symptomatology.

The observed influence of age, sex, and socioeconomic class on participation in research is well known [52,56,57]. Moreover, studies have shown that persons who respond to surveys on CBP or mental disorders might be slightly more likely to suffer from the complain in focus [52,58,59]. Thus, a low response rate offers potential to slightly over-estimate prevalence. Strictly speaking, results can only be generalized for groups containing more women and older aged people with higher socioeconomic status. Therefore, we advocate studies targeting especially at lower socio-economic groups. Moreover, inclusion of a higher number of subjects would be desirable.

However, other studies have shown that non-responders do not, or only slightly, affect prevalence data for pain or mental variables [52,58–60]. A recent study shows that this is also the case in the event of attrition [61]. Furthermore, the response rate to the SCID interview was high. Therefore, we assume that the moderately higher prevalence of Axis-I disorders that we observed is not a matter of sampling bias.

It should also be mentioned that the differences in prevalence between our sample and other populations might have been affected by unequal methods of diagnostic assessment. We therefore based our comparisons on groups of disorders rather than on a single diagnosis, to overcome differences in assessment method. We decided to use the SCID method because it is the most valid and widely used assessment standard today. For optimal comparison and to improve explanatory power, future studies should implement a case control design with equal assessment methods.

Conclusion

The high prevalence of mental comorbidity in subjects with non-specific CBP emphasizes the need for an increased awareness of the possibility of mental disorders in patients with CBP. In particular, the observed consistency of anxiety, fear, and avoidance points to the importance of being aware of anxiety disorders, in addition to the affective disorders that are the most frequently self-reported disorder, in patients with CBP. The recognition of anxiety, fear, and avoidance may be well established in research and in specialized pain centers. However, our population-based setting captures also patients with low pain intensity and probably low help-seeking behavior. These patients suffer from mental comorbidity, too. Not treating that condition might burden patients and possibly maintain or exacerbate CBP. Therefore, we recommend that a standardized screening for and assessment of mental disorders should be implemented in conjunction with the initial pain assessment at regular intervals. This should also be done in primary care and not only in research or specialized pain centers. This procedure might help to eliminate a high number of untreated patients who may be reluctant to seek help in overcoming pain due to their anxiety disorder.

Acknowledgments

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Quantitative Sensory Testing Profiles in Chronic Back Pain Are Distinct From Those in Fibromyalgia

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Objectives: Alterations in the central nervous system leading to higher pain sensitivity have been shown in both chronic back pain (CBP) and fibromyalgia syndrome (FMS). The aim of this study was to disclose commonalities and differences in the pathophysiology of FMS and CBP.

Methods: We used the quantitative sensory testing protocol of the German Research Network on Neuropathic Pain to obtain comprehensive profiles of somatosensory functions. The protocol comprised thermal and mechanical detection and pain thresholds, vibration thresholds, and pain sensitivity to sharp and blunt mechanical stimuli. We studied 21 FMS patients (mean pain duration: 13.4 y), 23 CBP subjects (mean pain duration: 15.9 y), and 20 healthy controls (HCs). Each participant received the test battery on the back and on the dorsal hand (pain-free control site).

Results: On the back, FMS patients showed increased thermal and mechanical pain sensitivity compared with HCs and CBP participants. On the hand dorsum, FMS patients showed higher mechanical pain sensitivity compared with CBP participants and HCs and higher cold pain sensitivity compared with HCs. CBP participants showed increased pressure pain sensitivity and lower vibration sensitivity on the back, but no significant differences on the hand dorsum compared with HCs.

Discussion: FMS patients showed increased sensitivity for different pain modalities at all measured body areas, suggesting central disinhibition as a potential mechanism. CBP participants in contrast, showed localized alterations within the affected segment possibly due to peripheral sensitization.

Key Words: fibromyalgia syndrome (FMS), chronic back pain (CBP), quantitative sensory testing (QST)

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Fibromyalgia syndrome (FMS) and chronic back pain (CBP) are common, an increasing cause of consultations in primary care, and of enormous socioeconomic relevance.[1,2] Therapeutic interventions are often unspecific and of minor success,[3,4] probably because of the fact that their etiologies and pathogeneses are still widely unknown.

Despite much research, the pathogenesis of FMS is still a matter of debate. One of the most promising approaches addresses the role of the (central) nervous system (CNS). A series of techniques have been applied to detect abnormalities in the CNS, such as functional neuroimaging, electrophysiological techniques, laser-evoked potentials, investigation of spinal fluid, and, in particular, quantitative sensory testing (QST).[5] QST is a method that is used to assess the somatosensory function. A comprehensive QST protocol allows to determine pain and detection thresholds and to distinguish local versus generalized and peripheral versus central nervous mechanisms. To date, QST studies in FMS have shown decreased mechanical/pressure and thermal pain thresholds,[6–9] temporal summation of pain ("wind-up") reflecting an increased excitability of spinal cord neurons,[10] and signs of central hypersensitivity.[11] Other studies suggest a reduced habituation to pain[12] and central sensitization[13,14] as mechanisms involved.

QST aberrations including signs for abnormal central nervous pathways have also been found in nonspecific CBP, the most common type of all CBPs.[15] Studies reported low pain thresholds and pain tolerance values.[16] A study by Giesecke et al[17] revealed hyperalgesia in FMS and CBP patients in comparison with healthy controls (HCs) when experimental pain was applied to a neutral site (thumbnail). Moreover, patients with FMS and CBP showed similar activation in pain-related cortical areas in functional magnetic resonance imaging, which was different from that in HCs. Baraniuk et al[18] studied opioid neurotransmitters in the cerebrospinal fluid and found that Met-enkephalin-Arg6-Phe7 was greater in both FMS and CBP patients than in HCs. In addition, FMS patients often report that their disease started with simple back pain[19,20] and thus CBP may be a pre-stage to FMS.[21]

It is the main hypothesis of a mechanism-based diagnosis in chronic pain syndromes that defined symptoms and signs reflect possible underlying neurobiological pain mechanisms.[22,23] Although in the case of a central disinhibition all types of thermal and mechanical pain thresholds may be generally decreased with an increased response to suprathreshold stimuli, thermal and mechanical detection and pain thresholds are increased in the presence of deafferentiation due to axonal damage. Moreover, localized pin-prick hyperalgesia and/or dynamic mechanical

allodynia may point to a central sensitization of the nociceptive system, whereas localized heat and pressure hyperalgesia are cardinal signs of a peripheral sensitization. Hence, we addressed the following questions in the present study:

(1) Are there distinct sensory profiles in FMS and CBP?
(2) If so, do clinical signs conclusively reflect possible underlying neurobiology?
(3) Do FMS and CBP share the same neurobiological mechanisms as indirectly reflected by QST?

MATERIALS AND METHODS

Participants

In the present study, 21 patients with a diagnosis of FMS, 23 participants with CBP, and 20 HCs were included. Inclusion criteria were female sex and being free of diseases affecting sensory processes (for sociodemographic data, see Table 1). Study participants were screened (physical examination, blood tests, past medical history, and, if indicated, further technical investigations such as x-ray or magnetic resonance imaging) to rule out diseases affecting sensory processes. Patients were also excluded if they reported pain at the hand dorsum, as this area was destined to be the control site.

FMS patients who fulfilled the diagnostic American College of Rheumatology criteria[24] were recruited from an outpatient clinic of the Medical University Hospital of Heidelberg. The CBP sample was drawn from participants who had a sample in an epidemiological study on CBP (Generalization of Pain: A Prospective Population-based Survey with Clinical Examination as part of the German Back Pain Research Network, supported by the Federal Ministry of Education and Research). A representative sample of 4000 inhabitants in the south-west of Germany was approached by mail and they were asked whether they had CBP. CBP was defined as the presence of back pain for at least 45 days within the last 3 months. A total of 2408 individuals responded to the mail survey. Of them, 427 fulfilled the criteria of CBP and were invited to a clinical investigation. Finally, 303 individuals participated in the study. Participants were questioned about the existence of comorbidity (explicitly neuropathy, diabetes, relevant alcohol consumption, infections, inflammatory diseases, disc hernia, past severe injuries) and they received a physical examination (general, rheumatological, neurological). In case of signs for serious pathological findings (eg, ischialgia or severe injuries such as whiplash), participants were excluded, and a further investigation was advised. Of the 303 participating individuals, 20 reported specific back pain (5 had Bechterew disease, 3 rheumatoid arthritis affecting the spine, 1 polymyalgia rheumatica, 3 tumor/metastases, 1 fracture of the vertebral body, 1 spondylolysis, and 6 disc hernia). The remaining 283 participants represented a nonhomogeneous group of nonspecific CBP according to the distribution in the general population. Of them, 23 female participants with nonspecific back pain were included in the present QST investigation consecutively. Participants were advised not to take pain medication 24 hours before investigation. HCs were recruited per advertisement. All participants were white.

The present study has been approved by the Ethics Research Committee of the Faculty of Medicine, University of Heidelberg. Participants gave written informed consent. They received an allowance of 10 Euros (about 12 dollars). The study was carried out in compliance with the Declaration of Helsinki.

Disability

Disability levels were measured using the FFbH (Hannover Functional Ability Questionnaire for measuring pain-related disability). It consists of 12 self-administered items that especially focus on daily activities restricted by musculoskeletal disorders (eg, "Can you wash your hair in a washbasin"). The response format is in 3 stages ("yes," "yes with trouble," "no or with the help of another person"). The answers were transformed to a functional ability score ranging from 0% to 100% (80% to 100% = no functional disability, about 70% = moderate disability, < 60 = relevant disability). Data from different studies indicate that the FFbH meets relevant psychometric criteria and is sensitive to change.[25]

QST Protocol

The somatosensory function was assessed using the comprehensive QST protocol that was developed as part of the German Research Network on Neuropathic Pain (DFNS).[26] It covers all relevant aspects of the somatosensory system, including large and small fiber function, and signs of central sensitization (dynamic tactile allodynia, punctate mechanical hyperalgesia). In this manner, detailed profiles of somatosensory function for the tested body areas are obtained.

Test sites were over paraspinal muscles and on the dorsum of the hand. Patients with FMS and CBP were tested on the most painful area in the back and on the hand dorsum of the same side of the body as a pain-free control site. The most painful area was determined on the basis of the patient's report during the office visit about present ongoing pain. Nine FMS patients were tested on the left, whereas 12 were tested on the right side of the body. Among CBP patients, 9 were tested on the left and 14 on the right side of the body, which was not significantly different from the FMS group ($\chi^2 > 0.05$). In CBP, all paraspinal test sites were in lumbar segments. For FMS, 16 test sites were in cervical and 5 were in lumbar segments. We had previously found that pressure pain thresholds (PPTs) are quite uniform across different muscles.[27] Pain-free controls were tested on the hand dorsum and in cervical segments (over the trapezius muscle) of both sides of the body. All tests were first conducted over an area that was not tested later during the QST session.

Thermal Detection and Thermal Pain Thresholds

The tests for thermal detection, thermal pain thresholds, and paradoxical heat sensations (PHS) were conducted using a TSA 2001-II (MEDOC, Israel) thermal sensory testing device.[28] All thresholds were obtained with ramped stimuli (1°C/s, 32°C baseline, 0°C and 50°C cutoffs, 8 cm² thermode), which were terminated when participants pressed a button. The mean of 3 consecutive measurements was calculated. Thermal sensory limen, a test with alternating warming and cooling ramps, was used only as a provocative test to induce PHS.

Mechanical Detection Threshold

Mechanical detection threshold (MDT) was measured with a standardized set of modified von Frey filaments

TABLE 1. Sociodemographic Variables

	Fibromyalgia	**Chronic Back Pain**	**Pain-free Healthy Controls**
N	21	23	20
Age, mean (SD)	50.6 (9.5)	43.4 (8.6)	38.3 (7.6)
Marital status, N (%)			
Unmarried	9 (45)	3 (13)	12 (58)
Married	9 (45)	14 (61)	5 (24)
Divorced/separated	2 (15)	6 (26)	1 (5)
Widowed	0	0	2 (9)
Not specified	0	0	2 (9)
Education, N (%)			
< 10 y of education	13 (64)	9 (39)	1 (5)
≥ 10 y of education	6 (29)	14 (61)	19 (95)
Not specified	2 (9)	0	0
Occupational situation, N (%)			
Full-time working	5 (24)	8 (35)	10 (50)
Part-time working	5 (24)	6 (26)	8 (40)
Not working/homemaker	1 (5)	8 (35)	2 (10)
Retired	6 (26)	0	0
Unemployed	2 (9)	0	0
Not specified	2 (9)	1 (5)	0
Pain intensity before QST, mean (SD)	5.8 (1.8)	3.0 (2.2)	0
Pain duration in years, mean (SD)	13.4 (10.4)	15.9 (11.5)	0
Painful tender points	15.2 (2.3)	4.7 (3.8)	0
FFbH (disability), % (SD)	60 (18)	70 (16)	

Pain intensity before QST was assessed on a numeric rating scale 0 to 10. "0" indicating "no pain," "10" indicating "worst pain imaginable." Painful tender points were identified by tenderness examination using ACR criteria. FFbH (Hannover Functional Ability Questionnaire): measures pain-related disability (80% to 100% = no functional disability; about 70% = moderate disability; < 60% = relevant disability).

(Optihair$_2$-Set, Marstock Nervetest, Germany) that exert forces between 0.25 and 256 mN.[29] The contact area was of uniform size and shape (round, 0.5 mm diameter). The threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical Pain Threshold

Mechanical pain threshold (MPT) was measured using a set of weighted pinprick stimulators with a flat contact area of 0.25 mm diameter that exert forces between 8 and 512 mN.[30] Again using the method of limits, the threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical Pain Sensitivity Including Dynamic Mechanical Allodynia

Mechanical pain sensitivity (MPS) was tested using the same weighted pinprick stimuli as that for MPT. To obtain stimulus response function, these 7 pin pricks were applied in balanced order, 5 times each. The participant was asked to rate each stimulus for pain on a 0 to 100 numerical rating scale (0 indicating "no pain," and 100 indicating "most intense pain imaginable"). The geometric mean of the 35 pain ratings was the final value for MPS. Stimulus response functions for dynamic mechanical allodynia (DMA) were determined using a set of 3 light tactile stimulators.[30,31] They were intermingled with the pin-prick stimuli in balanced order and participants were asked to give a rating on the same numeric rating scale.

Wind-up Ratio

The ratings of single pin-prick stimulation were compared with those of a series of 10 repeated pin-prick stimuli of the same force (256 mN) over the same area. Wind-up ratio (WUR) was calculated by dividing the mean ratings of series by the mean pain ratings of single stimuli.

Vibration Detection Threshold

Vibration detection threshold (VDT) was determined with a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale), which was placed 3 times over a bony prominence of the tested body area. Participants indicated the disappearance of vibratory sensations.

PPT

The PPT was measured using an Algometer (Somedic, Sweden) with a probe diameter of 1.1 cm that exerts pressure up to 2000 kPa. The PPT is determined by 3 ramped stimuli, each applied with a slope of 50 kPa/s.

Statistical Analysis

Most QST parameters cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen, PPT, MPT, MPS, DMA, WUR, and MDT) are log-normally distributed and were therefore log-transformed.[26] The QST values of each tested body area of the control group were averaged across both sides of the body. To compare QST measures at both sides (most painful area in the back and hand dorsum) between the 3 groups, analyses of covariance (ANCOVA) were calculated for each modality, followed by Fisher least significant difference tests (Tables 2 and 3). QST values were entered as dependent variables and pain group (FMS, CBP, and HC) was entered as the independent variable. As the 3 groups significantly differed in age ($P < 0.001$), age was included as a covariate, because QST parameters are age dependent.[32]

To compare the 2 test sites within each patient group (localized vs. generalized QST aberrations), all QST measures were standardized by z-transformation referring to the group of pain-free controls (QST profiles in Figs. 1, 2). This is carried out through z-transformation of all QST measures of the FMS and CBP groups, referring to the

TABLE 2. Analysis of Covariance, Mean Values, and Confidence Intervals for Quantitative Sensory Testing of the Most Painful Area in the Back

		ANCOVA		Fibromyalgia		Chronic Back Pain		Pain-free Controls	
		F	P	Mean	95% CI	Mean	95% CI	Mean	95% CI
CDT	Δ°C	0.650	0.526	1.55	1.13-2.10	1.72	1.31-2.25	1.37	1.02-1.85
WDT	Δ°C	1.36	0.264	2.72	2.18-3.38	3.22	2.66-3.90	2.61	2.12-3.21
CPT	°C	5.70	< 0.01	22.96[†,‖]	18.46-27.47	13.97	10.05-17.90	12.89	8.59-17.20
HPT	°C	3.88	< 0.05	41.60[*,§]	39.82-43.39	44.73	43.17-46.29	44.65	42.94-46.36
PPT	kPa	7.15	< 0.01	199[‡] = 0.001	161-244	239.3[†]	200-287	352	286-432
MPT	mN	7.26	< 0.01	21.38[‡] = 0.001[‖]	14.52-31.48	45.71	32.89-63.68	61.94	42.36-90.57
MPS	NRS$_{100}$	9.73	< 0.001	1.82[‡,¶]	0.99-3.37	0.35	0.21-0.60	0.31	0.17-0.57
WUR		2.03	0.141	2.36	1.67-3.32	2.36	1.74-3.21	3.61	2.56-5.11
MDT	mN	1.05	0.355	6.10	3.45-10.79	6.05	3.75-9.77	3.67	2.09-6.43
VDT	/8	3.41	< 0.05	7.10	6.72-7.47	6.69[*]	6.36-7.02	7.31	6.93-7.69

Values of CDT, WDT, PPT, MPT, MPS, WUR, and MDT were calculated by back transformation from the log-means.
*$P < 0.05$ vs. controls.
†$P < 0.01$ vs. controls.
‡$P < 0.001$ vs. controls.
Significant test results for fibromyalgia vs. chronic back pain are denoted.
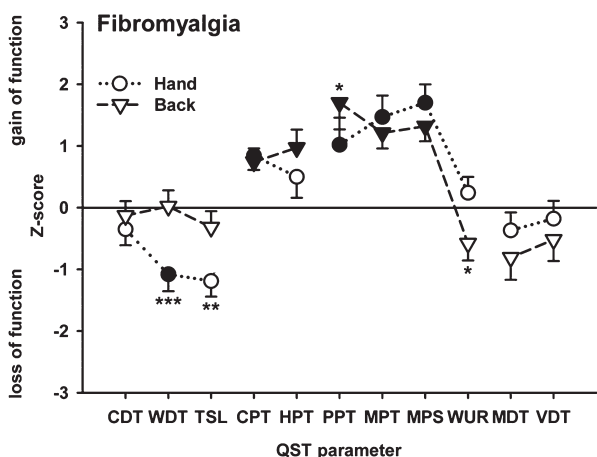§$P < 0.05$.
‖$P < 0.01$.
¶$P < 0.001$, respectively.
CDT indicates cold detection threshold; CI, confidence interval; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WDT, warmth detection threshold; WUR, wind-up ratio.

mean and standard deviation of the pain-free control group. Whenever log-transformed scores were calculated, the log scores were used for z-standardization. The representation of QST profiles as z-transformed data allows the direct comparison between sensory tests that are measured in different units (eg, °C and mN) and the comparison of test sites that have different ranges of normal values. To compare standardized QST measures of the most painful area in the back with standardized QST measures of the hand dorsum, paired t tests were calculated for both disease groups. Moreover, to compare QST parameters of the hand and back in FMS and CBP patients with that of HCs (Figs. 1 and 2), t tests were applied. Sensory findings on the hand were also compared with the published DFNS reference data,[32] both by group comparison and by counting the number of patients who were outside the 95% confidence interval (CI); DFNS reference data for the back are not yet available.

RESULTS

In FMS patients, the mean duration of pain was 13.4 ± 10.4 years (mean ± SD). The average duration of

FIGURE 1. QST profiles in fibromyalgia syndrome. Circles: hand, triangles: back. Filled symbols: significant versus healthy controls (open symbols: n.s.; *t* test). *$P<0.05$, **$P<0.01$, ***$P<0.001$, paired *t* test hand versus back. Parallel profiles between hand and back indicate generalized sensory changes. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio; Values are mean±SEM.

FIGURE 2. QST profiles in chronic back pain. Circles: hand, triangles: back. Filled symbols: significant versus healthy controls (open symbols: n.s.; *t* tests). *$P<0.05$, ***$P<0.001$, paired *t* test hand versus back. Significant differences indicate that sensory changes are localized to the back. For abbreviations, see legend to Figure 1. Values are mean±SEM.

CBP was 15.9 ± 11.5 years (mean $\pm$ SD). FMS patients rated pain intensity (directly before QST investigation) higher on a numeric rating scale (0 to 10) compared with CBP participants (mean $\pm$ SD 5.8 ± 1.8 vs. 3.0 ± 2.2, $P < .001$). Moreover, measuring disability showed that FMS patients were more severely burdened in daily activities than were CBP patients (relevant vs. moderated, respectively, *n.s.*). FMS patients showed 15.2 ± 2.3 painful tender points, whereas the CBP group revealed 4.7 ± 3.8 painful tender points (mean $\pm$ SD).

Comparison of QST Values on the Most Painful Area in the Back

As shown in Table 2, ANCOVA revealed significant group differences for all pain thresholds [cold pain threshold (CPT), heat pain threshold (HPT), PPT, and MPT], as well as for suprathreshold pin-prick pain (MPS) and vibration detection (VDT). Compared with pain-free HCs, FMS patients showed higher sensitivity toward cold and heat pain (CPT $P < 0.01$, HPT, $P < 0.05$) and toward mechanical pain induced by pin-prick stimulation (MPT $P = 0.001$, MPS $P < 0.001$) and by blunt pressure (PPT $P = 0.001$). In addition, CPT ($P < 0.01$), HPT ($P < 0.05$), and MPT ($P < 0.01$) were lower and MPS ($P < 0.001$) ratings were higher than those in CBP participants. Compared with pain-free HCs, CBP participants showed higher sensitivity with regard to PPT levels ($P < 0.01$) and lower sensitivity toward VDT ($P < 0.05$).

Comparison of QST Values on Hand Dorsum

As shown in Table 3, ANCOVA revealed significant group differences for all mechanical pain parameters (MPT, MPS, and PPT) and for cold pain sensitivity (CPT). Compared with pain-free HCs, FMS patients showed an elevated pain sensitivity for pin-prick stimulation (MPT $P < 0.01$, MPS $P < 0.01$), pressure pain (PPT $P < 0.05$), and cold pain (CPT $P < 0.01$). Compared with CBP participants, FMS patients were more sensitive toward pin-prick pain (MPS $P < 0.001$, MPT $P < 0.01$) and

pressure pain (PPT $P = 0.001$). CBP participants did not differ from controls with regard to QST values on the hand dorsum.

Comparison of QST Values With DFNS Reference Data

A group comparison between FMS patients and pain-free HCs with regard to DFNS reference data[32] revealed a significantly lower sensitivity to nonpainful warming ($P = 0.02$) and 5 of 21 FMS individuals ranged outside the 95% CI of the published reference data. Increased sensitivity to cold pain (CPT $P < 0.001$), pin-prick pain (MPT $P < 0.001$, MPS $P < 0.001$), and pressure pain (PPT $P < 0.001$) was also significantly different from the DFNS reference data. Several individual values were outside the 95% CI of the published reference data: 4/21 for CPT, 7/21 for MPT, 8/21 for MPS, and 9/21 for PPT.

DMA and PHS

Allodynia on the back occurred in 6 FMS patients, in none of the back pain participants, and in none of the HCs ($P < 0.01$, Fisher exact test). On the hand dorsum, allodynia occurred in 2 FMS patients, in none of the CBP participants, and in 1 HC (not significant). Because of this lack of variance, the allodynia score could not be included in the ANCOVA. Similarly, only 3 FMS patients reported PHS, 1 on hand dorsum, 1 on the back, and 1 on both sites. None of the CBP participants and HCs reported PHS.

Localized Versus Generalized Sensory Changes

To distinguish between localized and generalized QST aberrations, we compared the sensitivity of the hand dorsum with that of the most painful area in the back. As there are regional differences between these 2 test sites in normal participants, the QST values of FMS and CBP participants were standardized in relation to the QST values of the pain-free control group using z-transformation. As allodynia and PHS did not occur in the control group, the respective values could not be standardized.

TABLE 3. Analysis of Covariance, Mean Values, and Confidence Intervals for Quantitative Sensory Testing of the Dorsum of the Hand

		ANCOVA		Fibromyalgia		Chronic Back Pain		Pain-free Controls	
		F	P	Mean	95% CI	Mean	95% CI	Mean	95% CI
CDT	Δ°C	0.187	0.830	1.05	0.84-1.32	1.09	0.90-1.33	1.16	0.93-1.45
WDT	Δ°C	1.44	0.245	2.51	1.86-3.38	1.85	1.42-2.4	1.79	1.33-2.4
CPT	$^\circ$C	4.73	< 0.05	21.03†	17.21-24.85	16.80	13.46-20.14	12.22	8.45-15.98
HPT	$^\circ$C	0.990	0.378	43.43	41.55-45.32	45.02	43.37-46.68	45.19	43.33-47.06
PPT	kPa	6.53	< 0.01	238*,∥ = 0.001	204-278	345	301-394	318	273-370
MPT	mN	6.18	< 0.01	26.73†,§	17.86-39.90	64.27	45.50-90.57	65.01	43.75-96.61
MPS	NRS$_{100}$	10.57	< 0.001	2.13‡,∥	1.24-3.67	0.45	0.28-0.71	0.46	0.27-0.78
WUR		0.764	0.470	3.08	2.27-4.17	3.57	2.74-4.67	2.81	2.07-3.82
MDT	mN	0.699	0.502	2.22	1.37-3.60	2.78	1.85-4.18	1.96	1.22-3.16
VDT	/8	0.691	0.505	7.90	7.78-8.02	7.97	7.87-8.07	7.89	7.77-8.00

Values of CDT, WDT, PPT, MPT, MPS, WUR, and MDT were calculated by back transformation from the log-means.
*$P < 0.05$ vs. controls.
†$P < 0.01$ vs. controls.
‡$P < 0.001$ vs. controls.
Significant test results for fibromyalgia vs. chronic back pain are denoted.
§$P < 0.01$.
∥$P < 0.001$, respectively.
CDT indicates cold detection threshold; CI, confidence interval; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WDT, warmth detection threshold; WUR, wind-up ratio.

All other QST parameters were standardized for all individuals and mean z-scores for both disease groups were calculated separately (Figs. 1, 2).

FMS patients showed similar QST profiles for both areas, indicating that their hyperalgesia was generalized and not local (Fig. 1). WDT was only significantly elevated in the hand, whereas PPT was decreased significantly more in the back than in the hand. In addition, there was a significant difference in WURs, although both areas did not differ significantly from those of control participants (Tables 2 and 3). WUR varied around 3.0, but this variation was in the opposite direction in control participants. In CBP participants, the lowered vibratory sensitivity and the enhanced pressure pain sensitivity of the back were significant compared with the hand, indicating a localized sensory alteration (Fig. 2). As for FMS, WUR varied opposite to that of control subjects.

Punctate Mechanical Hyperalgesia

Fibromyalgia patients exhibited an increased pain sensitivity to pin-prick stimulation (MPT) and enhanced ratings to pinprick stimuli on a numeric rating scale (MPS), both on the back and on the hand dorsum. We calculated a repeated-measure ANCOVA comparing the 3 groups with regard to MPS, including the single stimulus intensity as a covariate. We detected overall differences between FMS

patients and both HC and CBP participants (back: $F = 18.63$ $P < 0.001$; hand dorsum: $F = 23.93$ $P < 0.001$).

These data are analyzed in more detail by plotting stimulus-response functions for the 7 stimulus intensities used (Fig. 3). These functions were shifted upward by a factor of 5. All participants were able to discriminate the stimulus intensities. There was also a stimulus effect, indicating higher pain ratings for more intense pin-prick stimuli. There was no interaction effect between the groups and the stimulus intensity, indicating that the profiles of the 3 groups are almost parallel (Fig. 3).

DISCUSSION

The present study used a comprehensive QST protocol to assess the somatosensory profiles of FMS patients, CBP participants, and HCs. FMS patients showed hyperalgesia generalized in space and including both superficial and deep pain modalities, whereas CBP participants revealed a profile of a localized pain condition with a decreased threshold only for deep pain and only at the affected area. Thus, we can conclude that there are distinct sensory profiles in FMS and CBP participants.

Somatosensory Profiles in FMS

FMS patients showed increased mechanical and thermal pain sensitivity (with the exception of HPT over hand dorsum) compared with CBP and HC participants,
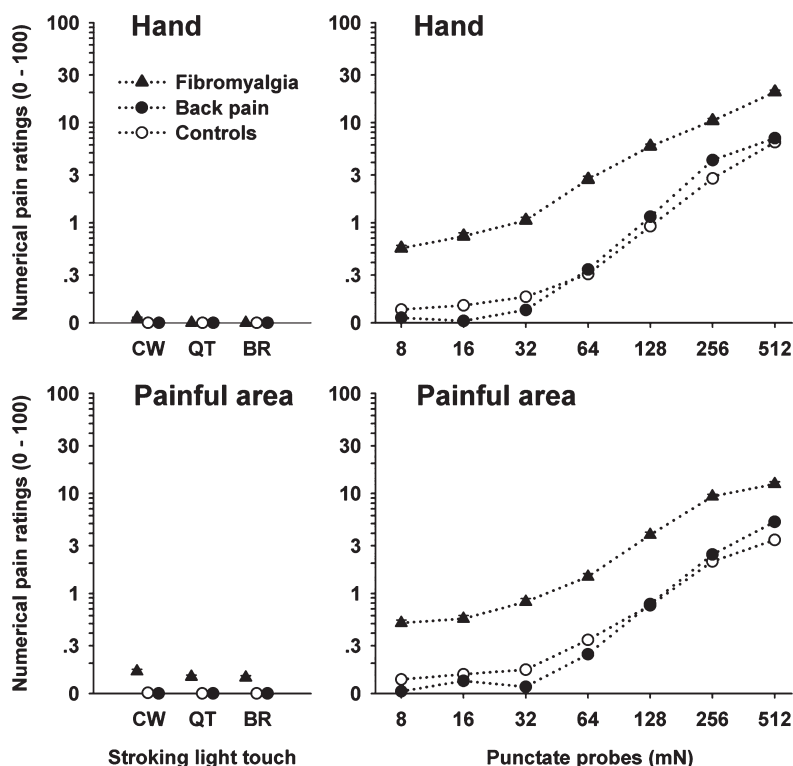
FIGURE 3. Stimulus-response functions of pin-prick pain and dynamic mechanical allodynia in the hand and back of patients with fibromyalgia (closed triangles), chronic back pain (closed circles), and control participants (open circles). Patients with fibromyalgia exhibit static hyperalgesia to pinprick, both over the pain-free hand and the most painful area of the back. Pain evoked by the same set of graded punctate probes (numbers indicate force in mN) was about 5-fold stronger in fibromyalgia patients than in chronic back pain or control participants. Stroking with gentle tactile stimuli (BR, brush; CW, cotton whisp; QT, cotton wool tip) elicited a slight amount of pain (dynamic mechanical allodynia) in fibromyalgia patients only. Patients with chronic back pain and healthy control participants showed similar SR functions.

whereas detection sensitivity was not increased. Our sensory profile suggests that hyperalgesia in FMS may involve all nociceptive submodalities. Pin-prick sensitivity and DMA have not been addressed before. Moreover, pain sensitivity is increased over back and hand dorsum (parallel profiles for back and hand in Fig. 1). Thus, increased sensitivity in FMS is generalized in space (superficial and deep pain, back and hand) and across nociceptive submodalities, but not to other somatosensory functions. The best possible explanation for such a generalized hyperalgesia is a deficient pain inhibitory system.[33] Mechanisms of descending control of pain also include descending facilitation.[34,35] The term "central sensitization" often used in the context of FMS[6,14] does not describe the clinical picture sufficiently. It implies an increased excitability of central neurons, but its effects are restricted in space to the receptive fields and often limited to mechanical test stimuli.[36,37] Disinhibition, in contrast, strikes the entire body and may explain a generalized pain syndrome such as FMS adequately. Thus, disinhibition should be addressed in future studies.[38,39] Possibly, multiple neuronal mechanisms such as disinhibition, central sensitization, and lack of habituation[12] work together.

The presence of DMA, usually interpreted as an indicator for a central sensitization of the nociceptive system, in a relevant number of FMS patients suggests that a deficit in pain inhibitory systems may facilitate the occurrence of central sensitization. Yet, this sensory sign was significantly present only over the back. Sensory findings on the hand in FMS were characterized by a pronounced pin-prick hyperalgesia in the absence of DMA. This type of finding has also been observed in patients with restless legs syndrome. In restless legs syndrome, pinprick hyperalgesia is slowly reversed by dopaminergic treatment.[40] Notably, a recent positron emission tomography study demonstrated a dopaminergic hyporesponsivity in FMS patients,[41] pointing to a possible pathophysiological commonality between these 2 disorders.

The decreased sensitivity to nonpainful warmth (WDT) in FMS, which has not been described so far, is difficult to interpret. In fact, Hurtig et al[7] found no differences in CDT and WDT compared with HCs. Considering this, the mismatch in age distribution between FMS patients and HCs has to be taken into account. On the one hand it is a likely explanation, as the comparison with age-matched and sex-matched control participants in the DFNS reference database[32] yielded the same result. On the other hand, however, the difference in WDT was no longer significant in an ANCOVA with age as a covariate. A thermal hypoesthesia is usually interpreted as a sign of disturbed small fiber function, but recently a correlation between ongoing pain intensity and suppressed sensitivity to nonpainful thermal stimuli has been reported in chronic non-neuropathic pain.[42] Ongoing pain in FMS patients may thus contribute to the decreased sensitivity in nonpainful warmth (WDT) in FMS. Anyway, our data clearly show that the sensitivity toward nonpainful warmth is not increased, supporting the view that the elevated sensitivity in FMS is specific to painful stimuli and not generalized for all somatosensory stimuli.

The wind-up of pain and wind-up after sensations are often described in FMS patients[10,43] and are thought to denote altered CNS processing. This feature, however, is missing in our results, and the WUR for the back was even lower than that for the hand. Magerl et al[44] revealed that, in a capsaicin model, the difference between the first and last stimuli of trains of pin-pricks was increased, but the ratio was unchanged. Our findings are consistent with these results. FMS patients already rate the first (single) stimulus significantly higher than do controls or CBP participants, and thus the relative increase in pain rating after the series of 10 stimuli is not as high. Hence, wind-up was present in our FMS patients, but its magnitude was unchanged as the denominator and numerator of the WUR change by a similar amount.

Somatosensory Profiles in CBP

In this population-based sample of CBP participants, we found features of a localized pain condition with no evidence of spatial generalization, although pain duration was as long as in FMS patients. Significant differences in pain thresholds compared with HCs were only seen for pressure pain, which primarily reflects muscle nociception and peripheral sensitization.[45,46] Moreover, the alterations were limited to the painful area at the back, meaning that there were no signs for a pain generalization. CBP participants differed from FMS patients in all modalities in the same way as HCs, except for PPT at the back, where CBP and FMS both showed decreased PPT. These results suggest localized alterations in muscles and joints. There was no evidence of central sensitization or disinhibition in this sample of CBP participants, indicating that chronic pain per se is not a sufficient condition for these abnormalities. This finding appears intriguing as other studies, for example,[17] suggested central sensitization in both FMS and CBP. As our CBP sample was drawn from the general population, widespread pain sensitivity observed in pain clinic samples may not be representative for all patients with CBP. Therefore, parameters other than chronic ongoing nociceptive pain are likely to be the predisposing factors for widespread pain and FMS. Such factors may be pain intensity, the subtype of CBP, and psychosocial factors. In our CBP sample, the average pain intensity before QST was nearly 50% lower than in the FMS group. The broad range of pain intensity is probably due to the heterogeneity of the CBP sample comprising 1 episode of CBP, intermittent, and continuous CBP according to the distribution in the general population. This is consistent with epidemiological data[47] showing that only a subgroup of a population with localized pain developed FMS later on.

An interesting result was a lower sensitivity toward vibration at the back of CBP participants. In fact, VDT was, on average, 6.7/8 in CBP participants, 7.1/8 in FMS patients, and 7.4/8 in HCs. This result is in line with secondary tactile hypoesthesia in other painful conditions.[48,49] It describes the phenomenon that, in a painful body area, nonpainful stimuli are suppressed. A recent QST study showed decreased VDT in patients with pseudo-radicular back pain as well.[50]

Technical Considerations

There are several limitations of the study that should be mentioned. One limitation is the small group size, with about 20 participants in each group. Further, the groups significantly differed in age. In future research, it would be desirable to match patient groups according to age. However, our results are controlled for age by ANCOVA. Besides, QST may be described as a "semi-objective"

procedure, as it still includes the subjective rating of the participants.[51] This raises the question whether QST would rather measure health behavior than pain thresholds. On the other hand, we used 2 methods to assess pain thresholds (method of limits, and direct scaling using randomized stimuli). Patients with FMS perform consistently at different body sites in both paradigms and specifically in the randomized paradigm (Fig. 3). Similarly, brain imaging techniques with FMS patients show fitting activated areas/patterns in the brain when compared with QST.[17,52]

A critical problem consists of the testing sites at the back. CBP participants suffered from pain especially at the lower back, whereas FMS patients indicated the most painful area predominantly at the upper back. The test site in HCs (trapezius muscle) matches the FMS group better than the CBP group. Nevertheless, the FMS group had more sensory aberrations, suggesting that inhomogeneity in test sites had no major effect on our data. This pitfall becomes even less important, given that both FMS and CBP participants revealed abnormal QST profiles at the painful areas; however, only FMS patients showed abnormal QST profiles at the pain-free control site as well, indicating the phenomenon of generalization.

CONCLUSIONS

There is ongoing debate about the classification of FMS [See discussion in Baillieres Best Practice and Research: Clinical Rheumatology Vol. 13 (1999)]. Some authors emphasize the entity of FMS as a distinct and circumscribed disease[53]; others argue that FMS is 1 end of a continuous spectrum of pain diseases.[54,55] The other end of the spectrum may constitute localized pain syndromes such as CBP. Within this spectrum, a switch between pain syndromes is possible[20,47] and common pathogenetic pathways may be assumed. Our data suggest that FMS pathogenesis may be explained at least partly by disinhibition, which can explain the spatial generalization of pain and the involvement of multiple pain modalities. In contrast, CBP offered features of a local pain condition with peripheral sensitization. Given that pain duration did not differ in CBP participants and FMS patients, our population-based data suggest that CBP may persist as a localized pain condition for many years without turning into widespread pain or FMS. Thus, if CBP is a pre-stage to FMS and findings show involvement of central nervous pathways in some patients, as observed in pain clinics, factors other than ongoing peripheral nociceptive pain itself are likely to account for this generalization in place of the ongoing pain.

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Alterations in endogenous pain modulation in endurance athletes: An experimental study using quantitative sensory testing and the cold-pressor task

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ABSTRACT

There is evidence for long-term alterations in pain tolerance among athletes compared with normally active controls. However, scientific data on pain thresholds in this population are inconsistent, and the underlying mechanisms for the differences remain unclear. Therefore, we assessed differences and similarities in pain perception and conditioned pain modulation (CPM) at rest in endurance athletes and normally active controls.

The standardised quantitative sensory testing protocol (QST) of the 'German-Research-Network-on-Neuropathic-Pain' was used to obtain comprehensive profiles on somatosensory functions. The protocol consisted of thermal and mechanical detection as well as pain thresholds, vibration thresholds, and pain sensitivity to sharp and blunt mechanical stimuli. CPM (the diffuse-noxious-inhibitory-control-like effect) was measured using 2 tonic heat pain test stimuli (at the temperature exceeding a subjective pain rating of 50/100) separated by a 2-min cold-pressor task (CPM-TASK; conditioning stimulus). Pain ratings were measured with a numerical rating scale. Endurance capacity was validated by assessment of maximum oxygen uptake (VO_2max). Participants included 25 pain-free male endurance athletes (VO_2max > 60 mL/min * kg) and 26 pain-free normally active controls (VO_2max < 45 mL/min * kg) matched based on age and body mass index.

Athletes were significantly less sensitive to mechanical pain but showed higher sensitivity to vibration ($P < 0.05$). In athletes, CPM was significantly less activated by the conditioning stimuli ($P < 0.05$) when compared with normally active controls.

Our data show that somatosensory processing in athletes differs in comparison with controls, and suggest that the endogenous pain inhibitory system may be less responsive. This finding may explain the paradoxical propensity of athletes to develop chronic widespread pain.

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1. Introduction

Pain is a common phenomenon in athletes [3,22,26,51,60,67]. This is paradoxical, as physical activity is part of most multimodal pain treatment programmes. Thus, on the one hand, physical activity might be the origin of a variety of pain syndromes in athletes who engage in rigorous physical activity [3,22,26,51,60,67], whereas on the other hand, physical activity also represents an important therapeutic concept in pain syndromes [20,21,43,55]. Therefore, increased knowledge concerning the role of physical activity on pain perception and processing may impact the medical care of pain patients in general, and athletes in particular.

There has been consistent evidence that after an episode of intense exercise, pain perception is reduced for a limited period of time, i.e., 'acute exercise-induced analgesia' [29,31]. It has been theorised that physical activity activates some generalised endogenous pain-modulatory mechanisms, e.g., conditioned pain modulation (CPM; formerly termed 'diffuse noxious inhibitory control') [5,29], baroreflex-mediated analgesia [7,30], stress-induced hypoalgesia [29], or attentional factors [29,31]. Although different mechanisms have been proposed [29,30], CPM is of special interest, as alterations in this system have been reported for a variety of chronic pain conditions [19,27,28,36,40,41,44,63,71]. Moreover, a deficit in this system is associated with chronic widespread pain (CWP) [44], which is frequently reported in athletes (prevalence 31% [23]).

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To date, research has focused on pain perception during physical activity rather than the potential long-term consequences of regular exposure to physical activity on pain processing at rest. In particular, the endogenous pain inhibitory system is a little-researched issue in athletes and, to date, no data have been published about CPM.

Researchers have postulated that long lasting physical activity may alter pain perception at rest and have often concluded that athletes possess higher pain thresholds and a higher pain tolerance in general [50,53]. A recent meta-analysis confirmed significantly higher pain tolerance in athletes at rest and specific alterations in pain thresholds [57]. But, although some studies have reported elevated pain tolerance or pain thresholds [16,18,56], there are also data demonstrating normal [49] or even lower [45] pain thresholds in athletes. This ambiguity may be because different pain induction methods with non-standardised and non-validated testing paradigms have been used [10,11,16,18,45,49,50,66]. The situation is aggravated because the definition of an athlete in most pain studies has been characterised arbitrarily, and to date, there are almost no pain studies in which physical fitness has been assessed objectively [57].

To overcome some of these shortcomings, this study assessed for the first time pain perception and endogenous pain modulation in athletes using a comprehensive standardised quantitative sensory testing protocol (QST [47]) and an objective evaluation of 'physical fitness.' The aim of this study was (1) to examine whether there are differences in pain perception at rest between athletes and normally active controls, and if so, (2) to determine if endogenous pain-modulating mechanisms are involved. It was predicted that athletes are characterised by specific sensory profiles and that the endogenous pain modulation of athletes is significantly different compared with normally active controls.

2. Methods

2.1. Study population

In the present study, 25 endurance athletes and 26 normally active controls were included. Athletes were recruited from regional sport clubs. Healthy normally active controls were recruited via flyers posted in the local community. Inclusion criteria were as follows: male sex, age 18-35, and without pain. The study sample was restricted with respect to sex and age, as QST and CPM are sex-[9,46] and age-dependent [8,48]. Athletes trained for at least 3 h/wk for more than 3 years and were characterised by a maximal oxygen consumption (VO$_2$max) >60 mL/min * kg. Controls were age- and BMI-matched, did not engage in regular physical activity, and had a VO$_2$max < 45 mL/min * kg.

Study participants were screened using a questionnaire, physical examination, and electrocardiogram to rule out acute or chronic pain; in addition, data concerning regular medication use, diseases affecting sensory processing (e.g., diabetes, polyneuropathy) or contraindications to treadmill testing were used to screen patients. Subjects were excluded if they reported any history of injury of the hand dorsum or arm, as this was the area tested in our paradigm. Participants were advised not to take any medication 24 h prior to the investigation and to refrain from intensive or prolonged training on the day prior to each test.

2.2. Instruments

2.2.1. Assessment of athletic performance

Maximal oxygen consumption (VO$_2$max, mL/min * kg) was measured in a ramp protocol on a motor-driven treadmill (Quasar med, H/P/Cosmos, Traunstein, Germany). After warming-up for 2 min at 4 km/h at an incline of 1.5%, the test began at a speed of 7.2 km/h, and the speed was increased by 0.6 km/h over 30 s until volitional exhaustion. Oxygen consumption was measured using a metabolic card (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany). VO$_2$ max related to body weight was considered to be the highest VO$_2$ over a period of 30 s during the test. Prior to each test, both sensors were calibrated according to the manufacturer's instructions. During the treadmill test, a continuous 12-lead ECG was recorded.

Specifications of physical activity were also captured using a questionnaire that included a detailed self-report of the type, frequency, intensity, and duration of physical activities.

2.2.2. Assessment of pain perception

Somatosensory function was assessed using the comprehensive QST protocol, which was developed as part of the German Research Network on Neuropathic Pain (DFNS) [47]. It covers all relevant aspects of the somatosensory system, including large and small fibre functions, and signs of central sensitisation (dynamic tactile allodynia, punctate mechanical hyperalgesia, and paradoxical heat sensations). In this manner, detailed profiles of somatosensory function for the tested body areas were obtained. The dorsum of the dominant hand was tested.

To familiarise participants with the test procedure, all tests were first conducted over an area that was not tested later during the QST session.

The tests for thermal detection thresholds (warm detection threshold, WDT, and cold detection threshold, CDT), thermal pain thresholds (heat pain threshold, HPT, and cold pain threshold, CPT), and paradoxical heat sensations (PHS) were conducted using a TSA 2001-II (MEDOC, Israel) thermal sensory testing device [72]. All thresholds were obtained using ramped stimuli (1°C/s, 32°C baseline, 0°C and 50°C cut-offs, 8 cm^2 thermode), which were terminated when participants pressed a button. The mean of 3 consecutive measurements was calculated. Thermal sensory limen (TSL), a test with alternating warming and cooling ramps, was used as a provocative test to induce PHS.

The mechanical detection threshold (MDT) was measured with a standardised set of modified von Frey filaments (Optihair$_2$-Set, Marstock Nervetest, Germany), which exert forces between 0.25 and 256 mN [13]. The contact area was of uniform size and shape (round, 0.5 mm diameter). The threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

The mechanical pain threshold (MPT) was measured using a set of weighted pinprick stimulators with a flat contact area of 0.25 mm diameter, which exert forces between 8 and 512 mN [4]. Again, using the method of limits, the threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical pain sensitivity (MPS) was tested using the same weighted pinprick stimuli as that for MPT. To obtain stimulus response function, these 7 pinpricks were applied in balanced order 5 times each. The participant was asked to rate each stimulus for pain on a 0 to 100 numerical rating scale (0 indicating 'no pain,' and 100 indicating 'most intense pain imaginable'). The geometric mean of the 35 pain ratings was the final value for MPS. Stimulus response functions for dynamic mechanical allodynia (DMA) were determined using a set of 3 light tactile stimulators [4,34]. They were intermingled with the pinprick stimuli in a balanced order, and participants were asked to give a rating on the same numeric rating scale.

The vibration detection threshold (VDT) was determined with a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale), which was placed over the bony prominence of the processus styloideus radii of the dominant hand 3 times. Subjects indicated the time at which they no longer experienced vibratory sensations.

2.2.3. Assessment of conditioned pain modulation

To test CPM (the term CPM rather than diffuse noxious inhibitory control/DNIC is chosen based on the recent recommendations of Yarnitsky et al. [70]), we used the protocol of Tousignant-Laflamme et al. [59] and consulted the guidelines for the cold-pressor task (CPM-TASK) as an experimental pain stimulus [65]. The CPM-TASK activates the diffuse noxious inhibitory control-like effect (CPM), as it is a strong nociceptive stimuli that takes place over a lengthy span of time [69] and is applied over a large body surface area [39]. Thus, the CPM-TASK allows us to modify the endogenous pain-modulating system. To quantify CPM, we evaluated the pain intensity of two tonic heat pain (THP) test stimuli separated by a CPM-TASK. Even if the THP may lead to both habituation and sensitisation according to the dual process theory, the THP is a reliable stimulus to induce CPM [59].

CPM-TASK: The cold-pressor task was used as a conditioning stimulus to elicit a strong and prolonged pain sensation to trigger CPM. The CPM-TASK consisted of immersing the non-dominant hand and wrist and approximately 5 cm of the forearm in circulating cold water (22 L + circulating with 15 L/min) for 2 min (informed ceiling task). To maintain the water temperature at $12 \pm 0.2°C$, we used an immersion cooler and a thermostat to control for temperature variations in both directions (Immersion cooler FT 200 and clip thermostat model ED, Julabo, Seelbach, Germany). The temperature of the water was set at 12°C to ensure that the CPM-TASK was sufficiently painful to elicit CPM while tolerable enough to be endured for 2 min. To control depth of immersion, the hand was placed on a grid (rubber isolated metal grid) that permitted the circulation of water on all sides of the immersed hand. Participants were instructed to lay their hand loosely on the grid and were asked to not move the hand or explore their grid. An armrest of silicone made testing more comfortable and prevented participants from changing the depth of immersion. During the test, subjects verbally rated their pain intensity every 5 s using the numerical rating scale ($NRS_{0/100}$). The rating scale ranged from 0, i.e., 'no pain,' to 100, i.e., 'most intense pain imaginable.' The experimental setup was approved by our local medical engineering department.

THP: To determine the temperature for the 2-min THP, an initial pre-test was completed. To familiarise participants with the testing procedure, participants were asked to continuously rate their pain intensity using the $NRS_{0/100}$, while the temperature of the thermode was gradually increased from 32°C to 50°C (0.3°C/s). The procedure was conducted twice. After participants were acclimated to the procedure and after a short break, we determined the temperature at which participants rated the THP with a score of 50/100 (0 'no pain' to 100 'most intense pain imaginable'). This procedure was performed until the temperature in 2 consecutive runs did not differ by more than ±1°C. The mean temperature eliciting pain ratings of 50/100 on the $NRS_{0/100}$ ($Temp_{50}$) was used for the THP. After a short break, the first THP (Pain baseline, THP_0) was applied to the palm of the dominant forearm (Peltier Thermode, TSA II, Medoc, Advanced medical systems, Israel). Participants were instructed that the temperature could increase, decrease, or remain constant. Then, the temperature of the thermode was increased from 32°C at a rate of 0.3°C/s to the individually determined temperature. Thereafter, the pain stimulus remained constant for 2 min. Pain intensity was measured every 5 s using the $NRS_{0/100}$. Following the first THP (THP_0), the CPM-TASK was used to trigger CPM. One minute after the CPM-TASK, we applied the second THP (THP_1). We quantified the amount of CPM by subtracting the mean pain rating of the first THP before the CPM-TASK (THP_0) from the second THP after the CPM-TASK (THP_1).

2.2.4. Assessment of pain experience

To evaluate different aspects of the pain experience, the Pain Experience Scale ('Schmerzempfindungsskala,' SES), a well-validated instrument used in pain research, was administered. The SES consists of 24 items and distinguishes between the affective and sensory dimensions of pain [14]. The response format was 4-staged, from 1 'not applicable,' to 4 'absolutely applicable.' To calculate values for the affective (items 1–14, e.g., "exhausting," 'cruel') and sensory (items 15–24, e.g., 'hot,' 'stabbing') subscales, items for each subscale were summed. We asked participants to rate the SES after assessment of CPM. Participants were instructed to rate 'pain sensations during testing.' The SES is sensitive to change and has proven validity and reliability for the affective and sensory subscales ($\alpha = 0.81$ and 0.92 respectively) [14].

2.3. Study design

All tests were performed at the same time in the afternoon. Before starting the tests, the subjects rested for half an hour in their respective environments. The test procedure began with the QST protocol and was followed by an assessment of conditioned pain modulation. Directly after the assessment of CPM, pain experience was evaluated with the SES. Maximal oxygen consumption was determined 30 min after the pain assessment procedure. The present study was approved by the Ethics Research Committee of the Faculty of Medicine, University of Heidelberg and was carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent and received an allowance of 30 Euros (approximately 40 dollars) for their participation.

2.4. Statistical analysis

All analyses were conducted using SPSS for Windows (Version 19.0). Descriptive statistics are presented as the means and standard deviations for continuous variables, and absolute numbers and percentages for categorical variables. All analyses were explorative and not of confirmatory nature.

CPM was determined by subtracting the mean pain intensity of the THP prior to the CPM-TASK from the mean pain intensity of the THP after the CPM-TASK. Therefore, negative values indicate inhibitory conditioned pain modulation. Between group differences with respect to the CPM were tested using t tests, and paired t tests were used to determine within group differences. Variables that exhibited a non-normal distribution were analysed using non-parametric Mann–Whitney U tests. Most QST parameters (CDT, WDT, TSL, MPT, MPS, DMA, WUR, PPT, and MDT) are log-normally distributed and were therefore log-transformed [47]. Group differences between athletes and normally active controls were tested using t tests. We also standardised all QST measures of athletes using a z-transformation referring to the mean and standard deviation of the control group. This procedure allowed for direct comparison between sensory tests that are measured in different units (e.g., °C and mN) as well as judgement of a gain or loss of function in profiles between athletes and normally active controls. Hyperfunction is indicated by z-values above '0,' i.e., patients are more sensitive to the tested parameter compared with controls (lower thresholds, gain of function), whereas z-scores below '0' indicate hypofunction and therefore a loss of or lower sensitivity of the patient compared with controls (higher thresholds). Whenever log-transformed scores were calculated, the log-scores were used for z-standardisation and t tests.

Because of the explorative nature of the study, we abstained from adjustment for multiple testing and interpreted P-values cautiously as descriptive measures of effect. Statistical significance was accepted if $P < 0.05$.

3. Results

3.1. Subjects

A total of 25 male endurance athletes (14 triathletes, 10 runners, and 1 cyclist) and 26 age- and BMI-matched normally active subjects were included in the analysis. Descriptive statistics for demographic and clinical variables are summarised in Table 1. Athletes were characterised by a mean training time of 9.6 ± 3.5 h/wk and a mean frequency of 5.4 ± 1.6 training d/wk. All athletes had participated regularly in competitions during the previous 3 years. Maximal oxygen uptake (VO_2max) was significantly higher (62%) in athletes compared with normally active controls (65.9 ± 4.6 mL/min ∗ kg and 40.6 ± 6.2 mL/min ∗ kg, respectively, $P < 0.001$). Values indicate a highly trained population of athletes, whereas normally active controls were characterised by an appropriate level of inactivity. There were no significant differences in age, BMI, or skin temperature between athletes and normally active controls. In control subjects, 21 of the 286 QST parameters were outside the published reference range for age- and gender-matched subjects [37], which is close to the expected value of 5%. That about 5% are outside the published reference data range indicates that our controls are representative for the published reference data of healthy controls, and thus underpins the representativeness and quality of our data [37].

3.2. Comparison of QST values

As shown in Table 2 and Fig. 1, *t* tests revealed significant group differences for the mechanical pain threshold (MPT) and for the vibration detection threshold (VDT). Compared with normally active controls, athletes showed an elevated pain threshold with respect to pinprick stimulation (MPT: $P < 0.05$), but increased sensitivity to vibration stimuli (VDT: $P < 0.05$). Athletes did not differ significantly from controls for cold and heat stimuli (CDT, WDT, CPT, HPT, and TSL), non-painful mechanical stimuli (MDT), mechanical pain sensitivity (MPS), and mechanical pain induced by blunt pressure (PPT).

To validate the results for MPT, post hoc analysis for mechanical pain sensitivity stratified for stimulus-force revealed that athletes were less sensitive to low stimulus intensities but did not differ for higher stimulus intensities. Therefore, as differences were restricted only to the lower forces and not to higher stimulus intensities, group differences in MPS did not reach the level of significance. Analysis for outliers showed that 1 subject in the control group had an MPT outside the 95% confidence interval (CI). This highlights the validity of a loss of function among the athlete group, indicating that the results were not based on pathological outliers. With respect to VDT, 1 control subject and 1 athlete reported a loss of function that was outside the 95% CI. This also highlights the validity of the gain of function in athletes, as it is not explainable by outliers within the respective groups. Correla-

Table 2
Somatosensory profiles obtained by quantitative sensory testing of athletes and normally active healthy controls.

		Athletes		Controls		ES	P-value
		Mean	SD	Mean	SD		
CDT	Δ°	−0.03	0.26	−0.02	0.17	−0.05	0.931
WDT	Δ°	0.19	0.25	0.17	0.22	−0.09	0.771
TSL	°C	0.35	0.23	0.32	0.24	−0.13	0.725
CPT	°C	11.35	10.66	15.79	10.43	−0.42	0.148
HPT	°C	44.06	3.87	43.44	4.08	−0.16	0.581
PPT	kPa	2.58	0.14	2.55	0.12	−0.23	0.332
MPT	mN	1.92	0.53	1.58	0.49	−0.67	0.027
MPS	NRS$_{0/100}$	−0.18	0.38	-0.02	0.44	−0.4	0.187
WUR		0.34	0.23	0.41	0.3	−0.26	0.356
MDT	mN	0.15	0.5	0.11	0.38	−0.09	0.72
VDT	/8	7.81	0.29	7.58	0.46	0.61	0.047

CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; NRS$_{0/100}$, numeric rating scale; mN, millinewton; kPa, kilopascal.
Data are given as log-transformed values (mean ± SD) except PHS, HPT, CPT, and VDT, which are listed as absolute values according to [43].
Two-tailed Student *t* test was used to determine level of significance.
Effect sizes (ES) were calculated as Hedge's g.
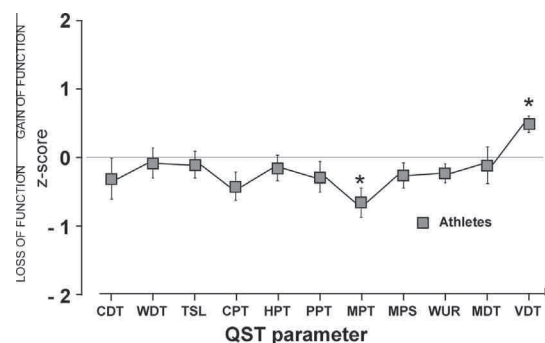
Fig. 1. Quantitative sensory testing (QST) profiles in athletes. Somatosensory profiles at hand dorsum in athletes. Values are mean ± SEM. To obtain *z*-values, athletes' values were standardised according to mean and standard deviation of normally active controls. *$P < 0.05$, *t* test vs normally active controls. CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold.

tion analyses of VO_2max with sensory parameters revealed a significant correlation only for VDT ($r = 0.419$, $P = 0.008$).

No signs of central sensitisation (dynamic tactile allodynia, punctate mechanical hyperalgesia or paradoxical heat sensations) were found for athletes or the control group. In addition, there was no difference in the temporal summation of pain (WUR) between the 2 groups.

Table 1
Demographic and clinical variables of athletes and controls.

		Athletes (n = 25)	Controls (n = 26)	P-value
Age	(years)	27.8 ± 4.1	28.0 ± 4.5	0.920
BMI	(kg/m^2)	22.1 ± 1.5	22.7 ± 2.2	0.229
VO$_2$max	(mL/min ∗ kg)	65.9 ± 4.6	40.6 ± 6.2	<0.001
VCO$_2$max	(mL/min ∗ kg)	5.4 ± 0.5	3.8 ± 0.6	<0.001
VE	(L/min)	158 ± 17	115 ± 24	<0.001
Training hours	(h/wk)	9.6 ± 3.5	<0.5	<0.001
Number of training	(d/wk)	5.4 ± 1.6	–	–
Training since when	(mo)	119.6 ± 82.9	–	–

BMI, body mass index; VO$_2$max, maximal oxygen uptake; VCO$_2$ max, maximal carbon dioxide production; VE, maximal air ventilation.
Data are indicated as the mean ± standard deviation.
A two-tailed Student *t* test was used to determine level of significance.

Table 3
Conditioned pain modulation in athletes and normally active controls.

		Athletes (n = 25)	Controls (n = 26)	P-value
Pain baseline T_0 (THP_0)	($NRS_{0/100}$)	34.2 ± 21.9	38.8 ± 15.7	0.411
Conditioned pain modulation (CPM)	($T_1 - T_0$)	−3.1 ± 8.7	−9.6 ± 12.2	0.020[a]
Pain CPM-TASK	($NRS_{0/100}$)	58.6 ± 24.0	68.9 ± 15.6	0.088

Data are indicated as the mean ± standard deviation.
THP: the tonic heat pain stimulus was applied as test stimulus at individual determined temperature (temperature at which participants rated the THP with 50 of 100 on the $NRS_{0/100}$) for 2 min by a thermode on the palm of the dominant forearm.
Conditioned pain modulation (CPM): CPM was quantified by subtracting the mean pain rating of the first THP (THP_0) before the CPM-TASK from the second THP (THP_1) after the CPM-TASK. Therefore, negative values indicate inhibitory CPM.
CPM-TASK: pain ratings during the cold-pressor task; the CPM-TASK as conditioning stimulus consisted in the immersion of the non-dominant hand for 2 min in circulating 12°C cold water.
Variables that were normally distributed were analysed using independent samples *t* test, whereas variables that exhibited non-normal distribution were analysed using non-parametric Mann–Whitney *U* tests ([a]). Difference in CPM remained significant ($P < 0.05$) even after controlling for cold-pressor test pain intensity.

However, although the majority of differences did not reach the conventional level of significance, there were trends for significance for all of these variables towards a loss of function (hypoesthesia, hypoalgesia) in athletes.

3.3. Comparison of conditioned pain modulation (CPM)

Table 3 shows that there was a significant difference in CPM between athletes and normally active controls ($P < 0.05$). There was a strong activation of CPM by the CPM-TASK in controls ($P < 0.001$), whereas CPM was only slightly induced by CPM-TASK in athletes ($P = 0.091$, Fig. 2). The effect size of the CPM on the differences in mean THP ratings before and after the CPM-TASK was small in athletes (Cohen's d = 0.14), whereas the inhibitory effects of this paradigm in controls were characterised by a moderate effect size (Cohen's d = 0.55).

There were no significant differences in the temperature of the $Temp_{50}$ stimulus ($P = 0.212$), the mean THP pain ratings prior to the CPM-TASK ($P = 0.411$) or in the mean pain rating for the CPM-TASK (conditioning stimulus, $P = 0.088$). However, because of the marginal difference in CPM-TASK ratings between athletes and normally active controls, we repeated the analysis for CPM and entered the CPM-TASK pain intensity as a covariate in the analysis of covariance. Differences in CPM, with less activity activated in athletes, remained significant ($P < 0.05$) even after controlling for CPM-TASK pain intensity. The intensity of the CPM-TASK was not significantly associated with CPM. Correlation analysis of CPM with

CPM-TASK pain intensity ($r = 0.032$, $P = 0.833$) or with VO_2max ($r = 0.161$, $P = 0.348$) showed no association. Athletes and controls did not differ in THP_0. None of the participants attained complete pain relief after conditioning stimulus. Exploratory analysis showed that in the control group there was a gain in 3 subjects and a loss in 20 subjects, whereas in athletes there was a gain in 7 subjects and a loss in 16 subjects. Outlier analysis revealed that in each group, 1 subject experienced a gain and 1 loss of function outside the 95% CI. This confirms the validity of the results.

3.4. Pain experience

Concerning differences in pain experience, assessed by the SES, there were no differences in affective (athletes: 20.1 ± 5.8, controls: 20.7 ± 6.3, $P = 0.762$, possible range 10–40) or sensory (athletes: 18.2 ± 4.3, controls: 18.5 ± 4.9, $P = 0.792$, possible range 14–56) pain experience for modified pain at T1 (THP_1) between athletes and normally active controls after the induction of CPM.

4. Discussion

This study has shown decreased sensitivity for MPT, increased sensitivity to vibration and a reduction in CPM in endurance athletes with validated athletic status.

No significant differences were found for heat, cold or pressure pain thresholds, or for temperature and mechanical detection thresholds. These findings are consistent with previous work, which also found no differences for heat [52,54] or pressure pain thresholds between athletes and normally active controls [38,49].

4.1. Sensory profiles in endurance athletes

The isolated loss of function for pinprick stimuli described in this study is an interesting finding, as MPT by pinprick has not been tested in athletes to date. An increase in MPT can result from both dysfunctions of the peripheral nociceptors and inhibition within the central nervous system [62,73]. The peripheral sensors for pinprick stimuli are a highly specific class of high threshold Aδ-mechanoreceptors with high relevance for protective guarding and withdrawal behaviour [61,73]. Alterations in peripheral nociceptors seem to be consistent with previous research, which has found abnormal nerve-conduction-tests in runners, suggesting asymptomatic neuropathy similar to that noted in subclinical entrapment neuropathy [6]. However, these data were restricted to the lower extremities of runners, whereas our data focused on the upper extremity. Moreover, researchers have not studied the peripheral nervous system in athletes systematically, and future studies on peripheral nociceptor function in athletes are recommended.
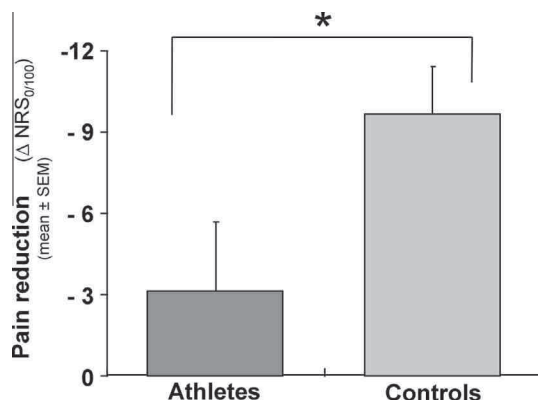
Fig. 2. Conditioned pain modulation (CPM). Reduction in pain intensity (conditioned pain modulation) between thermal pain measures (test stimulus) obtained before and after the cold-pressor task (CPM-TASK, conditioning stimulus). Controls (n = 26) had a 25% reduction (Cohen's d = 0.55) in thermal pain following the CPM-TASK, whereas there was only a small change (9%, Cohen's d = 0.14) for athletes (n = 25). *$P < 0.05$.

It is notable that most QST parameters showed a general trend towards a reduced sensitivity, indicating a 'loss of function', although the level of statistical significance was reached only for MPT.

It has been suggested that perception aberrations in athletes may be based on their lack of motivation ('stoicism') to report pain [24,25]. In this regard, 'stoic athletes' should feel as much pain as others but express their experience less. Therefore, if athletes offer fewer reports of pain, they would also experience a (pseudo-)reduction in their sensory response to noxious stimuli. In our study, pain reports relied on subjective pain ratings and may therefore have given the appearance of increased pain thresholds. Although there was a trend towards a 'loss of function,' the QST profiles observed in our study did not generally support the idea of stoicism to pain in athletes for several reasons. First, detection thresholds were shifted toward a loss of function in our study; however, detection thresholds do not exceed pain and therefore should not be affected by stoicism [24,25]. In addition, there was no difference in the affective dimension of pain experience between athletes and normally active controls as one might expect in the case of stoicism. Moreover, there was a significant decrease in VDT, suggesting that athletes were more sensitive to the detection of vibration than normally active controls.

The increased sensitivity to vibration is an interesting finding, as the vibration detection threshold was the only measure that was altered toward a gain of function (more sensitive perception). Vibration results in a small variation in muscle length, thereby activating low-threshold muscle spindle proprioceptors [12,64]. Decreased vibration-detection thresholds indicate an increased excitability of those non-pain-encoding proprioceptors or of the respective central projection pathways. There is evidence that vibration perception is associated with postural control [32,33]. Postural control is an important feature of the athlete's competence, and therefore specifically trained in athletes. In this regard, enhanced vibration sensitivity may be the result of a well-trained locomotive system. As a defective locomotive system is a key factor in the pathophysiology of restless leg syndrome, it is interesting to note that an increased sensitivity to vibration has also been demonstrated for patients suffering from restless leg syndrome [2]. However, this assertion is speculative, and further research is needed to better understand the underlying mechanisms.

4.2. Reduced CPM in athletes

Athletes were characterised by a significantly lower activation of the CPM induced by the CPM-TASK than normally active controls. Although, there is consistent evidence that intense physical activity results in the direct activation of endogenous pain inhibition for a limited period of time [29–31], the long-term consequences of the chronic activation of this system by regular high performance exercise have not been investigated thus far.

One possible explanation may be that tonically increased activation levels of the endogenous pain inhibitory system in athletes result in a ceiling effect: because of the continuous and heightened activation level of endogenous pain inhibition, additional activation as induced by the CPM-TASK may be truncated, and athletes failed to respond adequately when directly challenged using the CPM-paradigm. The 'elevated activation level hypothesis' of inhibitory pain control in athletes is consistent with our observation that all QST parameters, with the exception of VDT, showed a general trend towards reduced sensitivity. The constant activation of the descending pain inhibitory system in athletes might be the compensatory response to repeated noxious input induced by regular exhaustive training in these subjects. Without such continuous counter-regulatory pain inhibitory activity, athletes might not be able to endure daily physical activity.

Alternatively, there may be a shift in the activation threshold of the endogenous pain inhibitory system in athletes. The 'threshold hypothesis' postulates that the pain inhibitory system in athletes require higher stimuli to get activated or, using fixed stimulus intensity, the same stimulus will result in a lower activation of the pain inhibitory system in these subjects.

One may argue that it is easy to test this hypothesis directly by using more painful stimuli as conditioning stimuli. However, increased noxiousness of the conditioning stimuli results in an increased drop-out rate of subjects who are sensitive to pain, thus leading to a strong selection bias for the overall results. Nevertheless, the hypothesis is supported indirectly by the finding that the correlation between cold-pressor associated pain intensity and induced CPM was higher in the athlete group than for the entire sample ($r = 0.222$ vs $r = 0.032$). Accordingly, this might indicate that in some athletes the threshold to activate the CPM was not reached.

As chronic widespread pain, which is not rare in athletes [23], is often explained by exhaustion of CPM [44], the hypothesis of an elevated activation level may contain an interesting approach for future research on pain in athletes.

Notably, at present there are no accepted standards for the performance of CPM. There are different studies using either tonic [17,28,44,58,68] or phasic stimuli [1,15,35]. As the paradigm used in this study was based on a tonic heat stimulus as test stimulus, our findings cannot be extrapolated offhandedly to other kinds of stimuli. Further research is needed using other paradigms (e.g., phasic test stimuli) to induce such modulation, which might show different aspects of these systems, and, possibly, different clinical correlates.

4.3. Limitations

Limitations include lack of statistical power as a result of small sample sizes as well as risk of false positive results. Based on our explorative-descriptive approach, P-values should be interpreted more as a descriptive measure of effect than as a confirmatory judgement.

In addition, with the use of sensory measures at or near threshold to characterise pain sensitivity, the findings might not be transferable to pain tolerance. Moreover, the generalisability of our results to athletes in general is limited, as our study was restricted to male endurance athletes, accordingly, our results may not be representative for female athletes nor for other kind of sports (e.g., game or strength sports). Furthermore, although our athletes were characterised by both outstanding physical fitness and regular participation in official competitions, it should also be borne in mind, that 'athleticism' was not assessed explicitly in our study.

At last, determining the direction of causality of our findings is not possible given our study design. Whether athletes acquire altered pain perception because they engage in physical activity or whether they are able to engage in physical activity as a result of altered pain perception requires further longitudinal research.

4.4. Conclusions

The proposed alterations in endogenous pain modulation noted in our study may have consequences for future research. For example, various pain alleviating medications reduce pain through activation of pain-inhibitory circuits [42] and may therefore act differentially in athletes. Moreover, a chronic overstressing of the endogenous pain inhibitory pathways by heightened activation levels may eventually result in exhaustion over time. Such exhaustion may result in disinhibition of pain processing and in transition from acute to chronic pain conditions as well as spatial pain spreading, which are both common problems in athletes [33,22,26,51,60,67]. In contrast, a shift in the activation threshold

may protect the endogenous pain inhibitory pathways from chronic overstressing over the course of time and may thus contribute to an increase in the efficiency of pain inhibition on a continuing basis.

Together, the results of this research support the idea that athletes generally differ from non-athletes with respect to pain perception as well as pain processing and suggest a compensatory response of the endogenous antinociceptive system to the repeated noxious input induced by the regular exhaustive training in endurance athletes.

Conflict of interest statement

There are no conflicts of interest. No benefits in any form have been or will be received from a commercial party directly or indirectly related to the subject of this manuscript.

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Subgroups of musculoskeletal pain patients and their psychobiological patterns – The LOGIN study protocol

Andreas Gerhardt[*], Mechthild Hartmann, Jonas Tesarz, Susanne Janke, Sabine Leisner, Günter Seidler
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Abstract

Background: Pain conditions of the musculoskeletal system are very common and have tremendous socioeconomic impact. Despite its high prevalence, musculoskeletal pain remains poorly understood and predominantly non-specifically and insufficiently treated.

The group of chronic musculoskeletal pain patients is supposed to be heterogeneous, due to a multitude of mechanisms involved in chronic pain. Psychological variables, psychophysiological processes, and neuroendocrine alterations are expected to be involved. Thus far, studies on musculoskeletal pain have predominantly focused on the general aspects of pain processing, thus neglecting the heterogeneity of patients with musculoskeletal pain. Consequently, there is a need for studies that comprise a multitude of mechanisms that are potentially involved in the chronicity and spread of pain. This need might foster research and facilitate a better pathophysiological understanding of the condition, thereby promoting the development of specific mechanism-based treatments for chronic pain. Therefore, the objectives of this study are as follows: 1) identify and describe subgroups of patients with musculoskeletal pain with regard to clinical manifestations (including mental co-morbidity) and 2) investigate whether distinct sensory profiles or 3) distinct plasma levels of pain-related parameters due to different underlying mechanisms can be distinguished in various subgroups of pain patients.

Methods/Design: We will examine a population-based chronic pain sample (n = 100), a clinical tertiary care sample (n = 100) and pain-free patients with depression or post-traumatic stress disorder and pain-free healthy controls (each n = 30, respectively). The samples will be pain localisation matched by sex and age to the population-based sample. Patients will undergo physical examination and thorough assessments of mental co-morbidity (including psychological trauma), perceptual and central sensitisation (quantitative sensory testing), descending inhibition (conditioned pain modulation, the diffuse noxious inhibitory control-like effect), as well as measurement of the plasma levels of nerve growth factor and endocannabinoids.

Discussion: The identification of the underlying pathophysiologic mechanisms in different subgroups of chronic musculoskeletal pain patients will contribute to a mechanism-based subgroup classification. This will foster the development of mechanism-based treatments and holds promise to treat patients more sufficient.

Keywords: Chronic non-specific musculoskeletal pain, Endocannabinoids, Mental comorbidity, Pain drawing, Pain extent, Quantitative sensory testing, Mechanism-based, Subgroup classification, Nerve growth factor, Trauma

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Background

Chronic pain conditions of the musculoskeletal system are common and of high socioeconomic relevance [1-4]. This is especially true for pain conditions with widely unknown pathogeneses, such as non-specific chronic back pain (CBP), chronic widespread pain (CWP), and fibromyalgia syndrome (FMS). In addition, the prevalence of these conditions and the demand for consultation and treatment have increased over recent years [5,6], which results in high direct and indirect costs [1,3,7,8].

However, therapeutic approaches in chronic musculoskeletal pain patients are often of minor success [9-16]. This is likely because the aetiology and pathogenesis of chronic musculoskeletal pain are still widely unknown. As a result, treatment for this condition involves predominantly unspecific interventions, although the group of chronic musculoskeletal pain patients is believed to be heterogeneous [17,18]. Differences in response to the same treatment in patients with the same disease could be explained by different underlying mechanisms contributing to the generation and maintenance of pain [19,20]. The situation is complicated by the finding that the same disease can derive from various pathophysiological mechanisms. Conversely, the same pathophysiological mechanism may be of interest in distinct diseases [20].

The heterogeneity is supported by strong hints that subgroups exist that differ in terms of aetiopathology, clinical symptomatology, and psychophysiological patterns. A recent study revealed distinct somatosensory profiles in CBP and FMS: FMS patients showed increased sensitivity for different pain modalities in all measured body areas, which suggests central disinhibition (or a deficient pain inhibitory system) as a potential mechanism. CBP subjects, in contrast, exhibited localised alterations within the affected segment. Such alterations may be due to peripheral sensitisation [21]. This finding is in accordance with the main hypothesis of a mechanism-based diagnosis in chronic pain syndromes, which proposes that defined symptoms and signs reflect possible underlying neurobiological pain mechanisms [19,22]. Consequently, these subgroups should be treated with specific mechanism-based approaches, but to date, they have been treated with the same non-specific multimodal treatment programs. Therefore, the assessment of chronic pain and research identifying various factors associated with the development, maintenance, and spread of chronic pain, including their neurobiological correlates, is highly relevant.

Chronic pain has been found to be associated with a higher prevalence of mental co-morbidity. Patients with CBP [23,24], CWP [25], and FMS [26] suffer from mental disorders significantly more often than pain-free controls. This finding is especially true for anxiety disorders and mood disorders, which were found to have prevalence rates of 20.9% and 12.7%, respectively, in a population-based sample of patients with chronic back pain [23]. Of further interest is the role of psychological trauma, which has been neglected in previous research. Traumatic events have higher prevalence rates in patients with pain compared to pain-free controls or patients with other diseases [27-29]. Concerning traumatic experiences, it was suggested that multiple traumas have a cumulative effect on physical health, including back pain and that the impact of the trauma on health may be independent of post-traumatic stress disorder (PTSD) symptomatology [30,31].

The assessment of chronic pain and mental comorbidity on a psychobiological basis may detect common underlying pathophysiological changes. With regard to pain processing there are studies that suggest a role for central disinhibition mechanisms in depression and, to a lower extent, in patients with FMS compared to healthy controls [32]. Alterations in pain processing among patients with depression or FMS were reported previously, but this study found that hyperalgesia was more pronounced in patients with FMS than in those with depression [33]. In patients with FMS with comorbid depression or anxiety, pain processing was not altered in comparison to patients with FMS alone [34]. Thus there seems to be an association of chronic pain or depression with altered pain processing, although chronic pain and comorbid depression did not interact with pain processing.

In regard to anxiety disorders and the neglected role of trauma, a study by Defrin et al. described a unique sensory profile of hyposensitivity to non-noxious stimuli, accompanied by hypoalgesia to at-pain-threshold noxious stimuli and hyper-reactivity to suprathreshold noxious stimuli in patients with PTSD and chronic pain compared with healthy controls [35].

This pattern clearly differs from other patient groups with chronic pain, such as those with fibromyalgia, who tend to exhibit pain hypersensitivity [21,36], and from alterations in PTSD, in which context a decreased sensitivity to painful stimuli has been reported [37,38]. The results reported by Defrin et al. appear to be a hybrid of what has been found in pain-free PTSD patients and PTSD-free pain patients: decreased sensitivity to non-painful stimuli and increased hyperreactivity to painful stimuli. Sensory processing in anxiety disorders other than PTSD is believed not to differ from processing in healthy controls [35]. Another aspect of the psychobiology of pain is pain inhibition. It was found that pain inhibition is deficient in FMS patients but normal in those with depressive disorder [33]. Another study reports evidence that pain inhibition in FMS is more pronounced in

patients with comorbid depressive symptoms compared to those with FMS alone [39]. However, due to heterogenic sample selection and different testing methods, the results in regard to pain processing and pain inhibition in chronic pain and mental disorders are inconsistent and partially contradictory [40]. Therefore, a comprehensive measurement of the clinical manifestation and psychobiological aspects of chronic pain is necessary.

To challenge the topic of a mechanism-based subgroup classification of chronic pain patients and to establish specific mechanism-based treatments [41], further variables of interest must be considered to guarantee a more holistic approach, compared to that pursued in prior research. Therefore, we developed a theoretical framework (Figure 1), which investigates the role of chemical sensitisation (nerve growth factor; NGF) [42-46], the endocannabinoid system [47,48], and other psychological variables (e.g. early stress exposure, stress and pain coping, resilience) [49-51] as well as genetic variables [52-54] in addition to mental comorbidity and psychophysiological patterns. NGF is an important key mediator of some forms of persistent pain and plays an important role in the switch from acute to chronic pain as well as the spatial spread of pain [42-46]. The endocannabinoid system refers to a group of neuromodulatory lipids that is relevant for pain memory and pain extinction [47,48]. Accordingly, these variables have proven to be of interest in chronic pain and to be promising in its treatment. In line with that, the current study addresses the association between the clinical manifestation of chronic musculoskeletal pain (including mental comorbidity) and neurobiological changes.

Therefore, the purpose of the present study is to 1) identify and describe subgroups of patients with musculoskeletal pain with regard to clinical manifestation (including mental comorbidity), 2) investigate whether distinct sensory profiles due to different underlying mechanisms can be distinguished in different subgroups
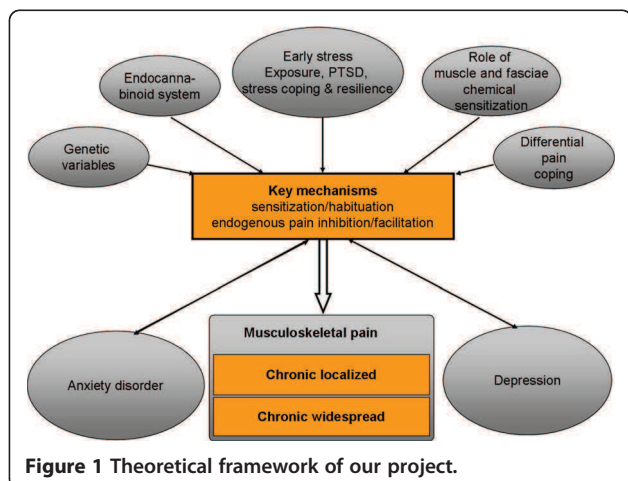
of pain patients 3) and to measure plasma nerve growth factor levels and to analyse distinct endocannabinoid profiles in different subgroups of pain patients.

Methods
This study is part of the consortium 'Localized and Generalized Musculoskeletal Pain: Psychobiological Mechanisms and Implications for Treatment (LOGIN)' funded by the German Federal Ministry of Research and Education (01EC1010A-F). More details concerning LOGIN can be found elsewhere [55,56]. This report focuses on subproject number six (SP6) 'Subgroups Characterised by Psychological Trauma, Mental Co-morbidity, and Psychobiological Patterns and Their Specialised Treatment'. All participants must provide written informed consent before inclusion in the study. The study has been approved by the Ethics Research Committee of the Faculty of Medicine, University of Heidelberg (S-261/2010) and will be carried out in compliance with the Helsinki Declaration.

Design
The study uses a descriptive and exploratory design. We will include 200 patients with chronic musculoskeletal pain from different settings (a population-based setting and a tertiary care setting) and 90 controls (pain-free patients with PTSD, depression, and healthy controls without mental disorders). All participants will undergo a physical examination. The relevant sociodemographics and measures of clinical manifestations of chronic pain are reported in Table 1: measurements of potential pathophysiological mechanisms are reported in Table 2.

Samples and patient recruitment
We will recruit patients with *non-specific chronic musculoskeletal pain* as well as control subjects that are not in pain: 1) Population-based sample: In a previous *population-based* study ("Generalization of Pain: A prospective population-based survey with clinical examination" as part of the German Back Pain Research Network, supported by the Federal Ministry of Education and Research; [21,23,57,58]), we established a representative sample of patients with chronic local and chronic widespread back-pain. For the present study, 100 patients from this representative study sample will be randomly recruited. 2) Tertiary care setting: We will recruit 100 consecutive musculoskeletal pain patients from the *tertiary care Musculoskeletal Pain Centre* at the University Hospital Heidelberg. 3) Control subjects: To determine whether the results are specific for pain, we will further investigate three groups of *pain-free patients*: a) *PTSD* patients (n = 30), b) patients with *depression* (n = 30), and c) *healthy controls* (n = 30). Patients with PTSD and depression will

Figure 1 Theoretical framework of our project.

Table 1 Variables and methods used to assess clinical manifestations of chronic non-specific musculoskeletal pain

Questionnaires	Variables
Chronic Pain Grade Questionnaire (CPG)* [65,66]	Severity of chronic pain problems (disability, pain intensity)
Pain Experience Scale (SES) [64]	Sensory and affective descriptors of pain
12-Item Short-Form Health Survey (SF-12)* [74,75]	Health-related quality of life
Resilience Scale (RS11)* [97,98]	Resilience (personal competence, acceptance of self and life)
Hospital Anxiety and Depression Scale (HADS-D)* [99,100]	Anxiety and depression
Childhood Trauma Questionnaire (CTQ)* [72,73,101]	Childhood and adolescence maltreatment (physical and emotional abuse, sexual abuse, physical and emotional neglect)
Pain drawing (pain location) [62] [63] [6]	Perceived location(s) of pain will be assessed using digitised pain drawings. Classification into categories of chronic local and chronic widespread pain.
Sociodemographics (self-report questions)	Age, sex, marital status, education, employment status
Interviews	
Structured Clinical Interview for DSM-IV Axis I Disorders + Axis II (SCID I + II)* [69]	DSM-IV Axis-I and Axis-II mental disorders
Physical examination	
ACR Criteria for Fibromyalgia (ACR Classification) [62] [102]	Tenderpoint count and documentation of specific symptoms
Physical Impairment Scale (PIS) [67]	Physical impairment (total flexion, total extension, average lateral flexion, straight leg raising, spinal tenderness, bilateral active straight leg raising, and sit-up)
Back Performance Scale (BPS) [68]	Disability. Tests of daily activities (Sock Test, Pick-up Test, Roll-up Test, Fingertip-to-Floor Test, and Lift Test)

* German Version.

be recruited in our Psychosomatic Outpatient Centre at the University Hospital of Heidelberg. Healthy controls will be recruited by flyers posted around the local community. All groups will be matched with respect to age, sex, and (if appropriate) pain location to our population-based sample. Thus, we will include at least 200 patients with non-specific chronic pain and 90 pain-free subjects.

Inclusion and exclusion criteria

The *inclusion criteri*a for pain samples are non-specific chronic musculoskeletal pain lasting for ≥ 45 days during the past three months, at least 18 years of age, and fluent German language skills. All control participants

(participants with PTSD, depression, and healthy controls) should be pain-free. Because the point prevalence of back pain in the German population was more than one third and the 1-year prevalence was higher than 75% [57], the recruitment of patients that were absolutely pain free within the last three months, will not be feasible and will not reflect reality. Therefore, we aim to recruit only absolutely pain-free participants. If this is not possible, we will define pain-free as follows: 1) less than one day (< 24 hours) spent in pain per week within the last three months. 2) Pain intensity < 3 on an 11-point numeric rating scale on the days when the patient is in pain. 3) Pain does not interfere with normal activities or work. These criteria are adapted from standardised definitions

Table 2 Methods used to assess the potential mechanisms involved in chronic non-specific musculoskeletal pain

Measures	Variables
Quantitative Sensory Testing (QST) [76,103]	Comprehensive profiles of somatosensory functions (thermal and mechanical detection and pain thresholds, vibration thresholds, and pain sensitivity to sharp and blunt mechanical stimuli). Discrimination between local vs. generalised and peripheral vs. central nervous mechanisms.
Conditioned Pain Modulation (CPM, the diffuse noxious inhibitory control-like effect) [77,78]	A descending pain inhibitory mechanism that inhibits nociceptive activity arising from the afferent primary fibres at multiple levels of the dorsal horn, resulting in diffuse pain inhibition. These descending pain pathways originate from the brainstem and have significant inhibitory actions on nociceptive activity, thereby affecting pain perception.
Blood Tests	
Nerve Growth Factor (NGF)	Plasma NGF levels (proximity ligand ELISA techniques)
Endocannabinoids + related lipids (ECs)	EC (anandamide (AEA), 2-arachidonoyl glycerol (2-AG), 1-arachidonoly glycerol (1-AG), palmitoyl ethanol amine (PEA), oleoyl ethanol amine (OEA), arachidonic acid) in human plasma (large- scale lipidomic profiling using the LC-MS/MS QTrap ABI5500)
Genetics	2* 9 ml EDTA tubes, stored for the second funding period

of back pain [59] and its recurrence [60]. Participants must also be pain free on the day of participation in the study. Patients who have a previous history of chronic pain will be excluded. Participants with PTSD and depression must fulfill DSM-IV diagnoses of the respective mental disorder. Patients with PTSD must be free of affective disorders, and patients with depression must be free of anxiety disorders. Healthy controls are not allowed to meet any DSM-IV diagnosis. The *exclusion criteria* are specific pathologies of CBP (e.g., spinal canal stenosis, disc hernia, spondylolisthesis, infection, malignancy, rheumatic and systematic inflammatory disorders, and fracture), sciatica pain ≥ than back pain, diseases affecting sensory processing (diabetes, alcohol or substance abuse, neuropathy, inflammatory diseases), pain or surgery at the dorsum of the hand or back surgery in the past three years (because the hand und back are to be subjected to investigation), and cognitive impairment.

Procedure
Chronicity of pain
The number of painful days in the last three months will be determined by a questionnaire and discussed with a physician to rule out misunderstandings. To be classified as suffering from chronic pain, the subject must report experiencing back pain on ≥ 45 days in the last three months.

Clinical examination
To verify the inclusion and exclusion criteria, all participants will be questioned about their past medical history and about co-morbidities (neuropathy, diabetes, relevant alcohol consumption, infections, inflammatory diseases, disc hernia, previous severe injuries). Patients will also receive a physical examination (general, rheumatological, orthopaedic, and neurological), including blood tests (and if indicated further technical investigations such as x-ray or MRI) with special attention paid to findings that indicate a specific origin of back pain. Therefore, the "red flags" (hints of the presence of serious pathology according to the Agency for Health Care Policy and Research Low Back Guidelines) and yellow flags will be considered [61], and former medical reports and discharge letters will be taken into account whenever available. In the case of signs of serious pathological findings, participants will be excluded, and a further investigation will be advised. Painful tender points will be identified by tenderness examination using ACR criteria [62].

Measures of clinical manifestation
The clinical manifestations of pain will be considered using the pain dimensions (pain intensity, pain location/ extent, pain quality, and pain affect), disability/ impairment (subjective as well as objective measures), and

psychological measures (mental comorbidity, early life stress, health-related quality of life, and resilience). Patients will be clustered in homogeneous groups according to their clinical manifestation. In subsequent analyses, we will test whether the clinical manifestation corresponds with specific mechanisms (see below).

Pain dimensions
There are at least four dimensions of pain experience that can be distinguished. These are intensity, location, quality, and affect. *Pain intensity*: Pain intensity is defined as how much a person hurts. It will be measured using a numerical rating scale, ranging from 0 'no pain' to 10 'worst pain imaginable'. *Pain location*: Pain location can be defined as the perceived location (s) of pain sensations that patients have on or in their body. Spatial distribution patterns (local vs. referred pain) will be assessed using a digitised pain drawings [63]. Moreover, categorisation as CLP, CWP, and FMS will be based on the ACR criteria [62] and a more precise definition elaborated by Harkness et al. [6]. Therefore, each participant will be asked to complete a body pain diagram, marking all areas where pain is experienced. Afterwards, the pain diagram will be discussed jointly by the participant and the physician to rule out any misunderstandings. *Pain quality and pain affect*: Pain quality refers to the specific physical sensations associated with pain. Pain affect is the degree of emotional arousal caused by the sensory experience of pain. The affective and sensory dimensions of pain will be measured using the Pain Experience Scale (SES). The SES is the standard instrument of the German chapter of the International Association for the Study of Pain. The SES consists of 10 items on a sensory subscale (e.g., 'throbbing', 'wrenching' or 'stinging') and 14 items on an affective subscale (e.g., 'exhausting', 'fearful', or 'unbearable'). The response format is a four-stage format (0 'not appropriate'; 1 'somewhat appropriate'; 2 'generally appropriate'; 3 'fully appropriate'). The sensory score of the SES is the mean of all sensory items; the affective score of the SES is the mean of all affective items. The retest-reliability of the SES lies between .89 and .96, and Cronbach's Alpha lies between .72 and .92 [64].

Disability/ impairment

Chronic pain grade (CPG) The CPG assesses the severity of chronic pain problems. It measures pain intensity and disability in regard to work and daily activities via patients' self-reports. The CPG comprises 6 items that can be answered on an 11-point numerical rating scale ranging from '0' to '10'. The number of days during which the patient experienced a disability during the

past three months is assessed. Pain severity can be graded in four hierarchical classes (Grade I, low disability – low intensity; Grade II, low disability – high intensity; Grade III, high disability – moderately limiting; Grade IV, high disability – severely limiting). The CPG has proven reliability (α = .82) and validity [65,66]. To objectify impairment and disability, we will use the Physical Impairment Scale and the Back Performance Scale.

Physical impairment scale (PIS) The PIS was developed as a simple and standardised clinical observation to evaluate physical impairment in patients with chronic low back pain. The test battery combines objective physical findings indicating current functional limitations due to pain. It consists of seven tests measuring lower back movement (total flexion, total extension and average lateral flexion as measured with the inclinometer), straight leg raises, spinal tenderness and strength (bilateral active straight leg raises, sit-ups). The measurements are translated into values of 0 or 1 according to cut-off values and summed. As subjective disability in non-specific low back pain is not explained by anatomic or structural impairment, the PIS measures functional limitation as influenced by the patient's pain behaviour. The PIS is able to discriminate between pain patients and healthy controls and is related to self-reported disability in the activities of daily living [67].

Back performance scale (BPS) The BPS is an objective clinical assessment tool that can be used to observe self-reported activity limitations in daily functioning caused by lower back pain. The BPS consists of five tests of daily activities (Sock Test, Pick-up Test, Roll-up Test, Fingertip-to-Floor Test, and Lift Test) frequently reported to be limited in back pain patients. Each performance is evaluated by the observer according to operational score definitions and then summed. The five tests are combined to obtain a performance measure of mobility-related activities requiring sagittal-plane mobility. The BPS is able to discriminate between pain patients with different return-to-work statuses and is sensitive to change. Cronbach's α was .73 [68].

Psychological measures

Structured clinical interview for DSM-IV (SCID) To examine the prevalence and the type of mental co-morbidity, the SCID interview, which consists of two parts, will be applied [69]. The SCID is a comprehensive and highly reliable and valid instrument [70]. The SCID-I is a semi-structured interview for the evaluation of major DSM-IV Axis-I diagnoses. With the SCID-I, it is possible to derive both a current and a previous history of psychiatric illness. The SCID-II procedure for assessing

personality disorders (PD) is a two-stage process. First, subjects complete a 120-item questionnaire with questions based on the criteria from the DSM-IV. In the second stage, a semi-structured interview is administered. Positive answers must be re-evaluated by the interviewer to diagnose Axis-II PD. According to the SCID-II protocol, we will interview only those subjects who achieve the cut-off (a specified number of positive answers in a specific PD section) on the questionnaire [69]. All SKID interviews will be conducted by two psychologists with graduate training in clinical psychology. To ensure diagnostic reliability, all interviews will be audiotaped. One-fifth of the interviews will be randomly selected and rated by both psychologists. A kappa coefficient will be calculated to assess inter-rater reliability. Both psychologists will conduct 10 SKID interviews in a pilot phase. In cases of low inter-rater agreement further, training will be conducted by an experienced psychiatrist.

The *Hospital Anxiety and Depression Scale (HADS-D)* will be used to determine the severity of anxiety and depression. The HADS-D was especially developed for patients with somatic diseases and thus excludes physical symptoms. Each scale consists of seven items that measure anxiety and depression via the patient's self-report with a four-stage response format. The HADS-D has good reliability (subscale depression: α = .81; subscale anxiety: α = .80) and validity [71].

Childhood Trauma Questionnaire (CTQ The German Version of the CTQ will be used to measure early stress exposure. The CTQ measures maltreatment during childhood and adolescence and will be applied because it captures factors that are relevant to chronic pain [50] that are neglected by the SKID. The CTQ consists of five subscales ('emotional abuse', 'physical abuse', 'sexual abuse', 'emotional neglect', and 'physical neglect'). Cronbach's α ranges from .89 to .96, except for the subscale 'physical neglect' which yields an α of .62 [72,73].

12-Item short form health survey (SF-12) The health-related quality of life (HRQoL) will be measured with the SF-12. The SF-12 consists of 12 items on eight scales ('physical functioning', 'role limitations due to physical problems', 'bodily pain', 'general health', 'vitality', 'social functioning', 'role limitations due to emotional problems', and 'perceived mental health'). Response categories vary from 2 to 6 and can be transformed to scale scores ranging from 0 ('the worst') to 100 ('the best') [74,75].

Resilience scale (RS-11) Resilience is a personality characteristic that moderates the negative effects of stress and promotes adaption. Thus it avoids any potentially negative effects of stress. Resilience will be

measured with the RS-11. The RS-11 comprises two factors – 'acceptance of self and life' and 'personal competence' – with a seven-point response format ranging from 1 'disagree' to 7 'agree'. Thus, scores can range from seven to 77, with higher scores reflecting higher resilience. The RS-11 has very good reliability ($\alpha = .91$).

Sociodemographic variables

Sex, age, education, employment status, marital status and further sociodemographic variables will by captured by a questionnaire.

Measures of chronic pain mechanisms

We will determine whether the patient's clinical manifestations of pain correspond with various specific potential pain mechanisms. In our study, potential mechanisms are captured through quantitative sensory testing (QST), the evaluation of conditioned pain modulation (CPM, the diffuse noxious inhibitory control-like effect), and analyses of nerve growth factor (NGF) plasma levels and endocannabinoid (ECs) profiles. Such potential mechanisms include peripheral sensitisation, central sensitisation, disinhibition, allodynia, and endogenous descending pain modulation.

Psychophysiological mechanisms

Quantitative Sensory Testing (QST) Somatosensory function will be assessed using the comprehensive *QST* protocol developed as part of the German Research Network on Neuropathic Pain (DFNS). Seven tests measuring 13 parameters (warm detection threshold, cold detection threshold, thermal sensory limen, paradoxical heat sensation, cold pain threshold, heat pain threshold, mechanical detection threshold, mechanical pain threshold, mechanical pain sensitivity, dynamic mechanical allodynia, wind-up ratio, vibration detection threshold, and pressure pain threshold) [76] will be conducted. QST testing covers all relevant aspects of the somatosensory system including large and small fibre function as well as signs of central sensitisation (dynamic tactile allodynia, punctate mechanical hyperalgesia). This way, detailed profiles of somatosensory function will be obtained for the tested body areas. The test sites will be distributed throughout the paraspinal muscles (5 cm ± 0.5 cm next to the midline on the autochthon back muscles [L1 to S1]) and on the dorsum of the ipsilateral hand.

Conditioned pain modulation (CPM) Inhibitory pain-modulating mechanisms will be assessed using the CPM, a diffuse noxious inhibitory control-like effect [77-79]. The difference in pressure pain threshold (PPT) before and after the induction of DNIC by phasic heat pain (PHP) will be measured. The appropriate temperature for PHP will be determined by measurement of the heat

pain threshold (HPT). The PHP will oscillate ± 1°C around the PHP-temperature. The ratings of PHP pain intensity will be assessed using a computerised Visual Analogue Scale (VAS). The HPT will be obtained using ramped stimuli (1°C/s, 32°C baseline, 0°C and 50°C cut-offs, 8 cm^2 thermode), which will be terminated when participants press a button. The mean of three consecutive measurements will be calculated. The PPT will be calculated as the mean of three consecutive measurements over the paraspinal muscles (5 cm ± 0.5 cm next to the midline on the autochthon back muscles [L1 to S1]; site contralateral to the QST).

Neurobiological measures

Nerve growth factor (NGF) NGF levels in human blood samples will be determined using proximity ligand Elisa techniques. *Endocannabinoids (ECs)*: EC (anandamide (AEA), 2-arachidonoyl glycerol (2-AG), 1-arachidonoly glycerol (1-AG), palmitoyl ethanol amine (PEA), oleoyl ethanol amine (OEA), arachidonic acid) analyses of human blood samples will be performed by large-scale lipidomic profiling using the LC-MS/MS QTrap ABI5500. All analyses of NGF and ECs will be performed in collaboration with our consortium partners.

Sample size estimation

A sample of more than 200 musculoskeletal pain patients (population-based sample and tertiary care sample) will be acceptable in order to recruit a sufficient number of "cases" with different clinical manifestations (e.g., local vs. generalised pain, different levels of pain affect, anxiety disorders, mood disorders, no mental comorbidity). To estimate the number of patients in different subgroups, we will refer to data from our population-based study. Approximately 61.8% of the patients in our population-based study had chronic local pain (CLP), and 38.2% had chronic widespread pain (CWP). We also found a prevalence of 12.7% for depression and 20.9% for anxiety disorders (using the SCID-I). The prevalence of depression and anxiety may be higher in a tertiary care pain setting, as reported by others [80,81]. Therefore, we expect group sizes that will be sufficient to gather abundant information regarding clinical manifestations. We also consulted recent QST studies and a review regarding DNIC to estimate the required group sizes. For DNIC testing, a systematic review [82] evaluated studies with an average group size of 20. A group size of 20 to 30 is also commonly used in recent QST studies [21,63,83]. We therefore expect our group sizes to be appropriate for the investigation of distinct sensory profiles. Studies investigating endocannabinoids used sample sizes between n = 10 and n = 20 patients per

group and reported mean effect sizes between .60 and .80 (e.g. [84,85]). Studies with NGF have reported effect sizes between 2.02 and 4.31 [44,86]. With regard to pain mechanisms, small sample sizes are sufficient to compare subgroups. This will also apply for the groups of pain-free patients with PTSD, depression, and healthy controls (each n = 30, respectively).

Quality assurance

To ensure that the measurements are reliable and high in quality, the project will have a pilot phase. In this pilot phase the study staff will be trained in the study procedures (if necessary) and conduct paired measurements to ensure reliability and validity. The pilot phase will be finished when the reliability and validity of the measurements has been verified. The study protocols will be tested and adapted if necessary.

Statistical analyses

Descriptive statistics will be presented with means and standard deviations for continuous variables and absolute numbers and percentages for categorical variables. Questionnaires will be dealt with according to questionnaire manuals. The prevalence of chronic local pain, chronic widespread pain, fibromyalgia, and mental comorbidities will be determined for the population-based sample and tertiary care setting. Explorative cluster analysis will be conducted to establish subgroups based on the clinical manifestations observed. Therefore, the dimensions of pain (see above) and mental comorbidity will be used as cluster variables. Then, we will explore whether different neurobiological profiles (QST profiles, CPM, NGF levels, EC profiles) correspond with these subgroups. Pain drawings will be scanned, superimposed, and transformed into two-dimensional color-coded images. Body areas with high occurrence of pain will be illustrated in dark red; body areas without pain will appear in white. To classify patients who suffer chronic local pain (CLP) or chronic widespread pain (CWP), pain drawings will be analysed according to the ACR criteria [62] and a more precise definition [6]. Quantitative sensory testing (QST) data pre-processing and statistical analysis will be performed according to the protocol established by Rolke et al. [76]. To quantify conditioned pain modulation (CPM), the PPT before PHP will be subtracted from the PPT after PHP. Negative values indicate an analgesic effect due to CPM. Differences between patient groups will be analysed using analyses of co-variance (ANCOVA), followed by Fisher's least significant difference test. Potential confounders will be included as covariates, if indicated. QST modalities or CPM will be entered as dependent variables, the patient groups as an independent variable. For more detailed information analysing QST data, we will refer to

the protocol proposed by Rolke et al. [76]. The same procedure will be applied with regard to nerve growth factor (NGF) and endocannabinoids (ECs).

Discussion

Establishment of a mechanism-based subgroup classification of pain and the development of specific treatments were suggested almost a decade ago [41]. Since then, the topic has been discussed amid controversy [19,22,87,88]. Small effect sizes of chronic pain treatments were suspected to be due to unspecific treatment approaches, but different pain generating and maintaining mechanisms [19,20]. This possibly is also supported by clinical experience, which shows that the subgroups of chronic pain patients are heterogeneous, even if suffering the same disease like non-specific chronic back pain. However, only a few studies have aimed to identify different pain mechanisms [20,21]. The identification of patient subgroups is needed if we wish to establish distinct pathophysiological mechanisms and targets that are necessary for the development of new analgesic drugs and non-pharmacological mechanism-based treatment options. There is a corresponding lack of evidence for subgroup-specific treatments.

In addition to the identification of specific pathophysiological mechanisms, we will implement a feasibility study that is designed as a randomised controlled trial. We will adapt the proven Eye-Movement-Desensitization-Reprocessing (EMDR) short-time therapy to the subgroup of patients with chronic pain who have experienced psychological trauma. This approach might be promising because EMDR is an effective treatment for patients with PTSD [89,90] or chronic pain [91-94] but has not yet been adapted to patients with chronic musculoskeletal pain who have experienced psychological trauma. However, there are initial signs that this might be a promising approach [95,96]. To identify potential underlying mechanisms, we will use all measurements of our study obtained before and after treatment (plus functional magnetic resonance imaging). Thus, our study will foster the development of new, more specific interventions for chronic pain patients.

The remaining challenge is to match a sign or symptom to a mechanism, but a sign or symptom could potentially be produced by several distinct mechanisms [19,20]. The novel aspect of our research is therefore its comprehensive approach that uses reliable and valid diagnostic tools. This approach comprises many variables that have been shown to be involved in alterations in sensory processing (e.g., mental comorbidity, descending pain modulating systems, nerve growth factor, endocannabinoids). A holistic approach is also needed because research shows that these variables influence each other [35]. The observed alterations might be

hybrids of alterations caused by single variables [21,37]. The inclusion of a population-based sample is also reasonable because prior research is usually based on highly selective clinical samples of pain patients, and this might bias research. Notably, the study is part of the LOGIN consortium. LOGIN comprises seven subprojects and includes basic and applied research in animals and humans as well as preclinical and clinical projects. All projects will use a core set of variables that investigates similar pathogenetic mechanisms. This approach enables LOGIN to study aspects in animals that cannot be investigated in humans (e.g., pathophysiological processes in the spinal cord or brain) and to transfer results to the human subprojects and vice versa. This approach will be fostered by the translational aspects of LOGIN. Thus, using the synergy of the different subprojects, the contemporary translation, implementation and dissemination of the results will be guaranteed.

Competing interest
The authors declare that they have no competing interests.

Author's contributions
AG has made substantial contributions to conception and design and has drafted the manuscript. He also participates in data collection, analyses of the data, and coordinates the project. JT has made substantial contributions to conception and design and revised the manuscript critically for important intellectual content. He also participates in data collection. MH and WE have made substantial contributions to conception and design and revised the manuscript critically for important intellectual content. SJ and SL participate in data collection and analyses of the data. GS revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript to be published.

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