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Chronicity and sensory-clinical phenotyping of musculoskeletal pain syndromes

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ABBREVIATIONS

ACR	American College of Rheumatology
CPG	Chronic Pain Grade
CP	control point in manual probe
CWP	chronic widespread pain
cUBP	chronic unspecific back pain
DSF	Deutscher Schmerzfragebogen [German Pain Questionnaire]
FMS	Fibromyalgia Syndrome
FS	Fibromyalgia Symptom Scale
IASP	International Association for the Study of Pain
LCA	latent class analysis
MPI-D	Multidimensional Pain Inventory (German version of the Westhaven-Yale Multiphasic Pain Inventory)
MPSS	Mainz Pain Staging System
MSP	musculoskeletal pain
PCA	principal component analysis
SSS	Symptom Severity Score
TP	ACR tender point in manual probe
WPI	Widespread Pain Index

1 INTRODUCTION

The biopsychosocial model of musculoskeletal pain (MSP) states that the process of MSP becoming chronic is initiated or maintained by multiple, interacting biological, psychological and social factors (e.g., Waddell, 2004). These factors reach from altered sensory processing to fear-motivated operant learning, social reinforcement of pain behavior and coping resources. This complexity of factors and the fact that pain is a multidimensional phenomenon in itself complicate diagnostic evaluation of clinical and work-related pain syndromes in occupational health settings. The goal of this thesis was to phenotype this complexity in chronic MSP syndromes.

Basically, two aspects were considered: The chronicity construct was reanalyzed in terms of differential characteristics underlying the assumed one-dimensional composition. Subsequently, necessary and sufficient primary sensory and clinical pain markers for chronic MSP were identified. The diagnostic and classification problems of chronic MSP presented in the following section were the driving factors to start this PhD project.

1.1 Phenomenology and chronicity mechanisms of musculoskeletal pain

The phenomenology of MSP changes over time due to the interacting biological, psychological and social factors. Eliciting mechanisms closely related to the potential tissue damage have to be separated from sustaining mechanisms that become relevant as the pain symptomatology persists. Following pain terms were considered relevant to characterize chronic MSP.

1.1.1 Pain terms: Acute vs. chronic pain; pain vs. nociception

Basically, acute pain has to be distinguished from chronic pain. Acute pain is provoked by a local injury and has an alarming function to prevent further potential nociceptive input thereby helping to accelerate the healing process (Loeser & Melzack, 1999). Chronic pain is regarded as a disease disproportional or different to the possible initial tissue damage and defined by pain lasting longer than the natural time of healing (Bonica, 1990; Loeser & Melzack, 1999).

Another important differentiation relates to the pain perception itself: Pain as phenomenon has to be differentiated from nociception: Whereas pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential

tissue damage, or described in terms of such damage" (p. 210, Merskey & Bogduk, 1994; terms and definitions originally introduced in Merskey et al., 1979), nociception is described with "the neural processes of encoding and processing noxious stimuli" (p. 473, Loeser & Treede, 2008). Consequently, nociception does not necessarily correspond to pain and vice versa, e.g., under local anesthesia peripheral nociception occurs without pain.

1.1.2 Eliciting vs. sustaining mechanisms of chronic musculoskeletal pain

Depending on the proximity to nociception different mechanisms are associated with the process of acute pain becoming chronic. Eliciting mechanisms in MSP are primarily related to the pain physiology (proximal level) and are largely neurobiological in nature, whereas sustaining mechanisms act mostly independent of the former (at the intermediate and distal level) and prevent the alleviation of the pain symptomatology (cf. Figure 1: process model of core eliciting and sustaining mechanisms in MSP becoming chronic). Selective mechanisms on the three levels contribute to the clinical endpoint criteria of chronic MSP syndromes, such as Fibromyalgia Syndrome (FMS) or chronic unspecific back pain (cUBP) with varying extent of functional disability (cf. Figure 1, right marked in red).

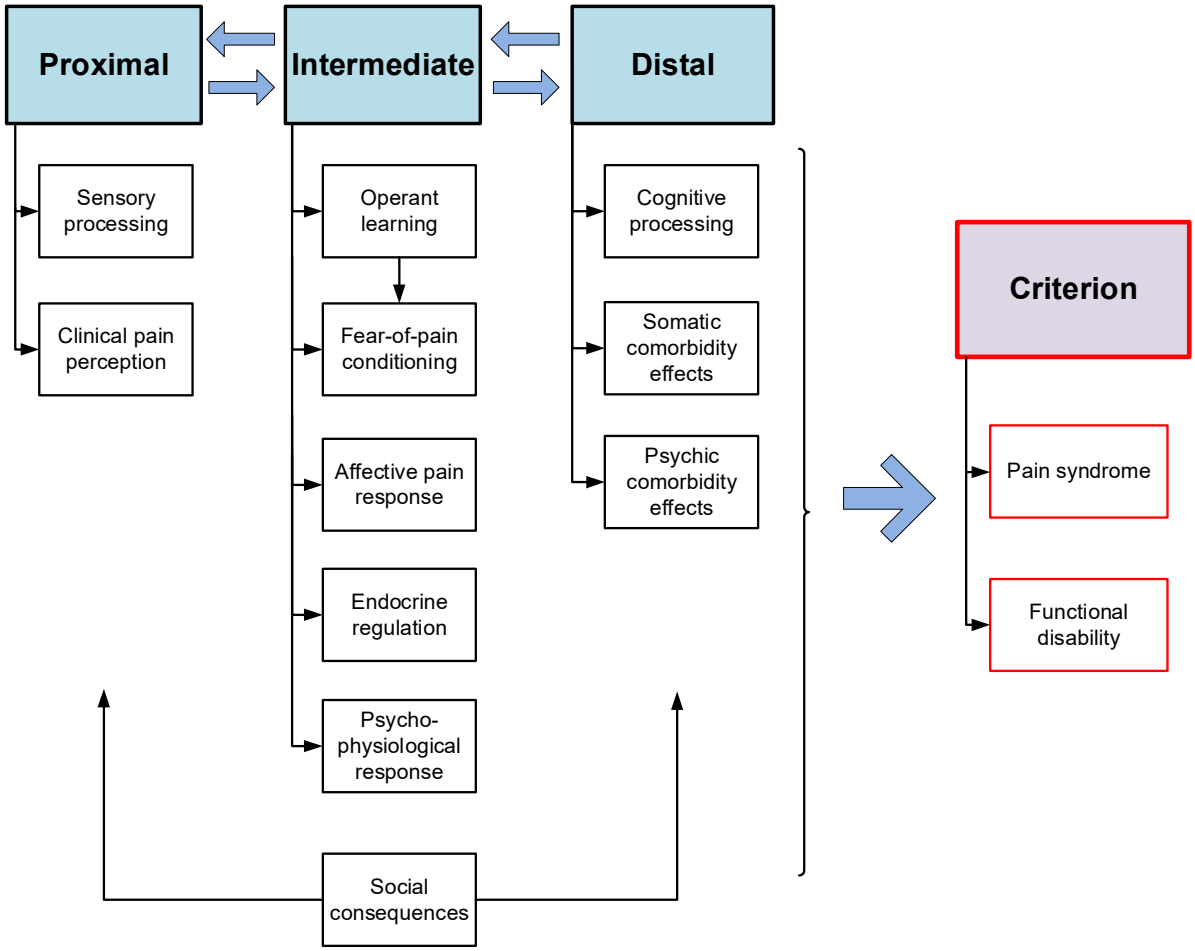

Figure 1: *Process model of core eliciting and sustaining mechanisms in MSP becoming chronic derived from the available data of the dissertation project (Figure adapted from Hölzl, Deuschle, & Benrath, 2000).*
Proximal level: peripheral (enhanced pain sensitivity) and presumably spinal/central nociception (wind-up/sensitization) as well as clinical pain; intermediate level: operant conditioning of pain escape and avoidance, but also fear of pain (cf. Leeuw et al., 2007; Vlaeyen & Linton, 2000), affective (e.g., unpleasantness of the pain experience) and psychobiological responses (cortisol level, heart rate); distal level: cognitive processing (e.g., catastrophizing), somatic symptom burden and psychic comorbidity. Social consequences are supposed to have an effect on all levels in the process of pain becoming chronic. Clinical endpoint criteria are the actual pain diagnosis (e.g., FMS in chronic primary pain, ICD-11; Treede et al., 2015) but also the functional disability classified by the International Classification of Functioning, Disability and Health with differential ICF Core Sets (Bickenbach, 2014). The ICF Core Sets comprise two core parts: The first part includes functioning and disability, whereas the second part contains contextual factors. There are pre-defined sets for chronic widespread pain and low back pain available.

The dissertation project was provided with data of sensory processes and clinical pain perception at the proximal level. Sensory processes were related to the modulation and modification of the nociceptive input as well as the development of pain hypersensitivity by neuroplastic changes in the central nervous system, e.g., impaired descending inhibitory control (Flor, 2014; Woolf & Salter, 2000). Clinical pain

perception encompassed various data on the clinical pain symptomatology, such as the pain intensity, pain location or the temporal pattern of occurrence.

The sustaining mechanisms at the intermediate level are seen as transition stage for pain becoming chronic. Research has revealed a number of such supposed transition mechanisms among the most prominent the operant learning such as the fear-of-pain conditioning (Leeuw et al., 2007; Vlaeyen & Linton, 2000). In this paradigm the pain is misinterpreted as fearful threat of potential harm for the individual well-being, resulting in negative reinforcement of safety seeking behaviors. These avoidance behaviors lead to inactivity and consequently reduced muscle activity and disordered coordination of movements prone to result in disability and more pain in a vicious circle. Another more direct transition mechanism is the aversive Pavlovian conditioning by pain stimuli itself. In this paradigm selected movements provoke pain resulting in enhanced muscular response or tension that is, in turn, more likely to be interpreted as aversive and, hence, avoided in the future (Schneider, Palomba, & Flor, 2004). Other transition mechanisms at the intermediate level are related to neuroendocrine responses for which the pathophysiology in developing chronic MSP is not entirely understood, yet. Research showed that glucocorticoids such as cortisol levels as marker for a Hypothalamic-Pituitary-Adrenocortical Axis dysregulation were higher in high risk patients for pain becoming chronic (e.g., Garofalo, Robinson, & Gatchel, 2006). The same applies to psychophysiological responses such as increased cardiovascular activity or muscle tension as a reply to (persisting) pain stimuli (Kyle & McNeil, 2014).

The distal level includes pain enhancing and modulating mechanisms, e.g., cognitive processing such as passive coping styles and catastrophic appraisals (Higgins, Bailey, LaChapelle, Harman, & Hadjistavropoulos, 2015). In addition, the overall somatic symptom complaints and psychic comorbidity such as depression was either associated with a higher risk to develop chronic pain (Pincus, Burton, Vogel, & Field, 2002) or, at least, to vary within the same diagnosis of FMS possibly resulting from different underlying subgroups (Gracely, Ceko, & Bushnell, 2012; Thieme, Turk, & Flor, 2004). Especially depressive symptomatology might enhance pain by intervening mechanisms such as helplessness, self-blaming, social withdrawal and physical inactivity.

Social consequences are supposed to have an effect on all proximal, intermediate and distal level mechanisms. The most crucial social consequence might be the way

significant others respond to the pain symptomatology thereby positively or negatively reinforcing pain behaviors, which refers to operant learning mechanisms at the intermediate level in this model (Fordyce, 1976).
The model presented here does not claim to be comprehensive, i.e., neither interdependencies of associated mechanisms are taken into account nor abnormal functional connectivity and structural changes in cortical areas, genetic or epigenetic risk factors are implemented (Flor, 2017).

1.1.3 Characteristics of musculoskeletal pain: Phenomenology

The differential consideration of mechanisms acting in different stages in the process of pain becoming chronic is partially based on the pioneering multidimensional conceptual model of pain (Melzack & Casey, 1968). This model differentiates between the sensory-discriminative, affective-motivational and cognitive-evaluative dimension and served as framework for the parametrization of marker domains given the available study data (cf. Table 1). The sensory-discriminative dimension encompassed, with respect to the available study data, peripheral nociceptor hypersensitivity, peripheral and central sensitization, endogenous pain modulation as well as clinical pain perception (cf. Figure 1; sensory and perceptual mechanisms at the proximal level). These mechanisms in pain becoming chronic were represented by quantitative markers for enhanced pain sensitivity, wind-up, impaired descending inhibitory control as well as clinical pain characteristics (cf. Table 1: experimental pain and clinical pain as markers for the sensory-discriminative domain). The affective-motivational dimension is primarily associated with central structures of the limbic system in the central nervous system. It encompasses emotional processes such as the affective pain response and the neuronal preparation of avoidance or approaching actions. These mechanisms were covered by markers for the affective quality and fear of pain (cf. Figure 1; affective pain response and fear of pain at the intermediate level). The cognitive-evaluative dimension is supposed to interact as superordinate unit with the sensory-discriminative and affective-motivational dimensions and was suggested to modulate the pain experience by meta-cognitions (Melzack & Casey, 1968). This domain was covered by pain cognitions and coping (cf. Figure 1; cognitive processing at the distal level), but also by operant learning as implied by the response of significant others (cf. Fordyce, 1976). Besides these three dimensions, comorbidity and psychosocial aspects constituted further relevant domains supposed to modulate the

pain symptomatology and intervene in the process of pain becoming chronic (cf. Figure 1; distal and intermediate level).

Table 1. Domains and characteristics of chronic musculoskeletal pain

Domain	Characteristic
Sensory-discriminative (- perceptive)	**Experimental pain** - Enhanced sensitivity - Wind-up - Impaired descending inhibitory control **Clinical pain** - Intensity - Localization - Duration and pattern of occurrence - Sensory quality
Affective-motivational	**Affective pain response** - Affective quality **Fear** - Fear of pain
Cognitive-evaluative	**Cognitions and coping** - Fear-avoidance beliefs - Catastrophizing - Coping **Learning** - Operant conditioning by social response
Comorbidity	**Somatic** - Other pain conditions - Non pain conditions **Psychic** - Mental health - Psychiatric disorders - Disposition for anxiety (trait anxiety)
Psychosocial aspects	**Stress load** - Perceived stress **Activity level** - Household, social and leisure

Domains with respective marker characteristics covered by the available data in the dissertation project. The sensory-discriminative, motivational-affective and cognitive-evaluative component are based on the multidimensional conceptual model of pain (Melzack & Casey, 1968), whereas the effects of comorbidity and psychosocial aspects stem from various experimental and observational studies as described in the text.

Somatic and psychic comorbidity is considered to add to the overall symptom burden and the severity of the pain disorder. There is strong evidence for poor physical and mental health increasing the risk to develop chronic MSP (O'Neill et al., 2018). The relatively high coincidence of chronic MSP with somatic and psychic comorbidity has motivated a line of research searching for common etiological factors (Gracely et al., 2012) and, moreover, the inclusion of aspects of gastrointestinal complains or depression as diagnostic criteria for pain disorders (e.g., Häuser, Schmutzer, Brähler, & Glaesmer, 2009; Wolfe et al., 2016). The last domain covered by data within the dissertation project comprised psychosocial aspects. This domain assembled characteristics of perceived stress (cf. Figure 1; primarily related to endocrine and psychophysical responses at the intermediate level) and activities associated with social consequences. Research has revealed that the subjective stress load affects MSP in different contradictory ways: whereas in early acute pain stages stress induced analgesia is likely, in chronic pain stress affects the homeostasis and, thus, exacerbating the pain symptomatology (Tesarz et al., 2015; Vachon-Presseau, 2018). With regard to the last characteristic related to the domain of psychosocial aspects moderate physical activities and household chores like gardening were shown to be related to lower levels of back pain and, thus, might serve as protective factor (Heneweer, Staes, Aufdemkampe, van Rijn, & Vanhees, 2011).

1.1.4 Research settings: Employees vs. clinic pain patients

To cover the range from proximal, intermediate to distal mechanisms and especially the transition stage from acute pain to chronic pain, research on risk populations for pain becoming chronic is promising. While there is a fair amount of research on patients with chronic MSP, research in occupational settings, where physical labor is performed on a daily basis, is a mean to institutionalize sub-chronic pain.

Physical load, e.g., in form of exposure to lifting or forceful movements, and work dissatisfaction has been shown to be associated with MSP disorders since decades (Bernard, 1997; Costa & Vieira, 2010) primarily identifying blue color workers as critical group. Static work load, in particular, was shown as major risk factor for MSP disorders, possibly due to disproportionate intramuscular pressure that selectively increases in low threshold motor units (Cinderella hypothesis: cf. Hägg, 1991, 2003). This selective overload is supposed to be associated with metabolic abnormalities in the muscle fiber accompanied with tension and, as consequence, MSP (Hägg, 2000). Obviously, ergonomic design has improved in occupational settings such as work at assembly

lines, driving service or office work and, hence, evidence for a relation of MSP and physical load varies across studies leveraging the effects of poor psychosocial work conditions on MSP (Lundberg, 2015). Especially low control of work, less social support, missing development opportunities and, in particular, job dissatisfaction were shown to be associated with back pain (Linton, 2001; Lundberg, 2015; Macfarlane et al., 2009).

Moreover, investigating MSP in occupational settings in comparison to patients in pain clinics offers the possibility to gain further insights in cognitive processes, related associative learning and the affective pain responses. According to the avoidance-endurance model of pain (Hasenbring, Chehadi, Titze, & Kreddig, 2014; Hasenbring & Verbunt, 2010), MSP potentially evokes two distinct kinds of pain responses: fear-avoidance responses are characterized by a decrease in physical activity due to fear-avoidance beliefs, while endurance responses refer to a suppression and distraction from the pain leading to an overuse and, consequently, injury. The endurance aspect might be especially relevant when addressing MSP in employees. It is likely that for this particular setting, the work serves as a distraction from pain, which makes them endure the pain and refrain from seeking medical advice. Contrarily, fear-avoidance beliefs might be more prevalent in patients already having chronic MSP, which are likely to be in sick leave and, consequently, are prone to physical de-conditioning and disuse syndrome.

1.2 Diagnostic and classification problems

The multidimensionality of the pain characteristics as well as the complexity of influencing factors in the process of pain becoming chronic have led to problems in diagnostics of pain syndromes, in particular, chronic pain syndromes. It was shown that chronic pain is a complex phenomenon caused by more than just somatic agents. Hence, a sound diagnostic cannot solely base on a detailed physical examination to derive somatic causes and disregard the complexity of influencing differential proximal, intermediate and distal mechanisms.

1.2.1 Diagnostic of medically unexplained pain

Clinical classification systems, i.e., the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization, 1992) and the Diagnostic and Statistical Manual of Mental Disorders (DSM- IV; American

Psychiatric Association, 1994) either classify pain as somatoform or somatic pain and, hence, inhere a cartesian dualism philosophy (Flor & Turk, 2011a). Whenever an explaining physical cause of the pain symptom is missing and there is a psychological involvement, the pain is categorized as somatoform, equivalent to psychic in nature. Consequently, the pain can be either result from pain in the body or from the mind. This exclusion diagnostic suffers from a logical problem: Falsification is not verification in turn. When a medical condition causing the pain symptoms cannot be identified, this does not automatically mean that, on the other hand, a psychological condition can be verified. There might also exist a somatic cause that cannot yet be measured with the available scientific techniques.

Adjustments were implemented in both classification manuals by the coding of “chronic pain disorder with somatic and psychological factors” in the German adaption of the ICD-10 (F45.41; Deutsches Institut für Medizinische Dokumentation und Information, 2009; Nilges & Rief, 2010) and “pain disorder associated with both psychological factors and a general medical condition” in the DSM-IV-TR (307.89; American Psychiatric Association, 2000), respectively, in which psychological and a general medical condition are described as interacting. Whereas the medical condition explains the onset, psychological factors determine the severity, the exacerbation and the maintenance of the pain symptomatology.

The latest revision of the DSM-V (American Psychiatric Association, 2013) completely abandoned the exclusion practice and does not distinguish between medically explained and medically unexplained somatic symptoms anymore (Rief & Martin, 2014). Now, one somatic symptom leading to a substantial emotional symptom burden and subjective stress load qualifies for fulfilling the criteria of the disease category “somatic symptom and related disorders” which replaces the former somatoform disorders. All patients previously diagnosed with a somatization disorder, hypochondria or conversion disorder are now subsumed under this new category. By comparison, the Task Force for the Classification of Chronic Pain within the ICD-11 has made substantial efforts to substantiate pain diagnostic by more etiology-based categories (Treede et al., 2015). However, due to the inconclusive etiology of the two most prominent chronic MSP disorders in the category “chronic primary pain”, i.e., nonspecific back pain and chronic widespread pain, current revisions of both classification systems remain far away from a diagnostic basing on positive inclusion criteria for chronic unspecific MSP. The need to classify these unspecific MSP

syndromes becomes even more relevant taking into consideration their relatively high prevalence rate (e.g., lifetime prevalence for unspecific low back pain: 85 %, Airaksinen et al., 2006; point prevalence for chronic unspecific back pain: 18 %, Gerhardt, Hartmann, Blumenstiel, Tesarz, & Eich, 2014; chronic widespread pain: 10 % Andrews, Steultjens, & Riskowski, 2018). Moreover, the differentiation between these two unspecific MSP syndromes is less clear than one might expect.

1.2.2 Widespread vs. regional pain

It has been shown that the individual assignment of regions in pain to respective body quadrants varies across studies resulting in considerable different base rates of widespread pain and concurrent fibromyalgia syndrome, FMS (Butler, Landmark, Glette, Borchgrevink, & Woodhouse, 2016). Widespread pain is defined as pain in four body quadrants plus axial skeletal pain and if there are also at least 11 out of 18 tender points sensitive to manual palpation the patient qualifies for a diagnosis of FMS according to the American College of Rheumatology (ACR) 1990 criteria (Wolfe et al., 1990). On the contrary, localized pain refers to a circumscribed region in pain, such as the lumbar spine region in low back pain (Bogduk, 2009). However, both definitions remain less explicit than implied and patients with widespread pain also report superordinate regionally distinguishable pain sites (Gerhardt et al., 2014; Natvig, Bruusgaard, & Eriksen, 2001). Several efforts have been made to improve the quantification of the pain extent, e.g., with markings in body mannequins as suggested in the “Manchester” criteria (Hunt, Silman, Benjamin, McBeth, & Macfarlane, 1999) or the Michigan Body Map (Brummett et al., 2016), but also by categorical assessments, e.g., in the Regional Pain Scale (Wolfe, 2003). The latter set the foundation for the development of the Widespread Pain Index (WPI), a checklist of pain loci, as relevant part of the revised ACR 2010/2011 criteria for FMS (Wolfe et al., 2010; Wolfe et al., 2011).

Since there is evidence for an increase of pain loci in chronic unspecific back pain (cUBP) and the gradual development of concurrent widespread pain (Forseth, Husby, Gran, & Forre, 1999; Lapossy, Maleitzke, Hrycaj, Mennet, & Müller, 1995), it is not yet clear, if both diseases stem from the same pathogenetic mechanisms. The research on a differentiation of widespread from regional MSP has much contributed to the understanding of the spatial extent, which is possibly better described on a quantitative dimension.

1.2.3 Pain induced secondary change vs. psychological comorbidity

Moreover, incidence rates of somatic and psychic comorbidity are higher in patients with widespread pain in comparison to patients with regional pain (Viniol et al., 2013). However the comorbidity with major depression is relatively high in both MSP syndromes (Bletzer, Gantz, Voigt, Neubauer, & Schiltenwolf, 2017; Roch, Follmer, & Hampel, 2017). Symptoms of a major depression, such as depressive mood, cognitions of helplessness and the decrease in activity level might be a secondary change in affect resulting from the pain symptomatology. The high coincidence led to the inclusion of depression in the ACR 2010/2011 revised criteria for FMS (Wolfe et al., 2010; Wolfe et al., 2011). In this revision a replacement of the tender point count by a composite score of self-reported pain locations (WPI) and a symptom severity scale (SSS) of characteristic additional symptoms, in particular, fatigue and depression, is suggested. This shift from sensory-perceptive pain characteristics to clinical and psychological aspects is grounded in application problems of the ACR tender point sensory testing (Cott et al., 1992; Fitzcharles & Boulos, 2003; Wolfe et al., 2016) and the above described high coincidence with psychic comorbidity. However, empirical evidence for the inclusion of secondary domains other than the primary sensory-clinical pain as cardinal criteria for FMS is limited, but urgently needed. Otherwise, including secondary criteria such as a comorbid depression would have the potential to increase heterogeneity in this diagnostic group and to hinder the identification of core mechanisms active in chronic MSP.

1.3 Chronicity concepts

In excess of the clinical pain diagnostics by sensory and clinical pain criteria, the assessment of chronic MSP was supposed to consider, in particular, the construct of chronicity itself. The quantification of chronicity is supposed to help in the differentiation of mechanisms in the process of pain becoming chronic and, as consequence, to ease the assignment of optimal treatment and rehabilitation decisions in otherwise heterogeneous patient populations. However, also in chronicity assessment the multidimensionality of pain characteristics and the complexity of the chronicity process itself presents difficulties for both comprehensive and practically viable diagnostic characterization of chronic MSP syndromes. Common questionnaires and grading instruments deal with the conflict of aims by isolating a general construct of ‘chronicity’ from other characteristics of chronic pain. However, it is questionable whether the

chronic characteristics of all chronic pain syndromes can be represented in one global index of ‘chronicity’ given the multidimensionality of the pain experience and the multifactorial causation of different syndromes (e.g., for neuropathic pain vs. MSP).

1.3.1 Multidimensionality of chronicity

There is a long tradition in conceptualizing chronic pain. Among the most significant are the research on overt pain behavior emphasizing operant aspects (Fordyce, 1976) and the research on the empirical clustering of chronic pain out of the West Haven-Yale Multidimensional Pain Inventory’s cognitive, affective and behavioral information (Kerns, Turk, & Rudy, 1985; Turk & Rudy, 1987b, 1988) highlighting the psychosocial factors in chronic pain. Several indices evaluate chronicity of MSP across clinical syndromes, etiology, psychosocial factors and comorbidity. Among the most common are the IASP Taxonomy of chronic pain (IASP Taxonomy Working Group, 2017), the Chronic Pain Grade Questionnaire (CPG; Korff, Ormel, Keefe, & Dworkin, 1992) and, in the German-speaking part, the Mainz Pain Staging System (MPSS; Pfingsten, Schöps, Wille, Terp, & Hildebrandt, 2000). These widely used chronicity indices implicate a homogeneous one-dimensional scale of chronicity in pain.

These and other indices vary in focus of conceptualization of the construct of chronicity. At the simplest, pain is defined as chronic when lasting longer than the natural time of healing (Bonica, 1990; IASP Taxonomy Working Group, 2017; Loeser & Melzack, 1999). In clinical practice, this time varies starting at a minimum of three or six months. Guidelines for systematic research reviews also recommend 12 weeks duration as minimal time period to define chronic pain (Furlan et al., 2015). The importance of the aspect of duration in chronic pain is further substantiated by research on the development of pain hypersensitivity, because neuroplastic changes in the central nervous system (pain memories) were depending on the duration of the nociceptive input, its modulation and modification (Woolf & Salter, 2000).

By comparison, the IASP Taxonomy of chronic pain applies a multiaxial representation (five axes) comprising several important dimensions of chronic pain (IASP Taxonomy Working Group, 2017). Besides duration, the fourth axis assesses the aspect of severity in a compound code. It is built of three intensity and three duration classes arranged in series to suggest an ordinal scale. However, the compound interpretation of these codes is questionable, as the relation of the intensity and duration categories to each other and to external chronicity markers are not yet known. Research of biometric criteria of the five axes of the taxonomy is limited to interrater reliability

analysis of the first and fifth axis in a consecutive sample of chronic pain patients (Turk & Rudy, 1987a).

In contrast to the IASP Taxonomy of chronic pain, the Chronic Pain Grade Questionnaire (CPG; Korff et al., 1992) emphasizes disability as essential component of chronicity. The CPG combines pain severity with disability in a compound code, too. In the final 4-step ordinal scale the higher grades do no longer depend on pain severity, as a result of a certain interpretation of the data analysis. The authors could show severity not contributing to higher levels of disability in a Guttman scale analysis. The Guttman scale analysis assumes one-dimensionality, consequently, only items fitting to a single dimension stayed in the final conceptualization of chronicity. However, this emphasis on the consequences of pain symptomatology neglects the primary aspect of suffering from enduring pain related to its actual severity and duration. Before the final release of the CPG, the items were tested in a group of pain patients with five different pain states selected from a sample of health maintenance organization enrollers; 42 - 51 % of variance in the samples could be explained with disability, average intensity and duration (Korff, Dworkin, & Le Resche, 1990). The other half of variance was not reported and, thus, remained unexplained. The authors just mentioned that persistence, activity limiting days as well as the self-evaluation of chronic or recurring pain was of minor relevance. In the later Guttman scale analysis of patients with back pain, headache and temporomandibular joint disorder items of duration and well as persistence did not follow one-dimensionality, hence were dropped in the final CPG scale construction (Korff et al., 1992). The German version of the CPG, validated in primary care back pain patients yielded a two-factor solution with the disability score (53.56 % explained variance) and the characteristic pain intensity (19.13 % explained variance) (Klasen, Hallner, Schaub, Willburger, & Hasenbring, 2004). Both factors comprise three items each, disability days as skewed variable was excluded for this factor analyses.

Another chronicity measure, popular in the German speaking area, is the Mainz Pain Staging System (MPSS; Pfingsten et al., 2000). In this multiaxial index, therapy-related aspects set up the focus in the construction of the chronicity construct. Besides the first axis measuring temporal aspects and the second axis assessing spatial aspects of pain, the third axis measures drug taking behavior and the fourth axis utilization of the health care system. The scores of each axis are measured on an ordinal level. Finally, a compound sum score ranging from 4 to 12 points is derived out

of these four dimensions (axes) resulting in three stages of pain chronicity. The higher the chronicity stage, the more persistent the pain symptomatology and the more complicating factors are presumed requiring intense interventions (Gerbershagen & Waisbrod, 1986). Obviously, the instrument measures complex heterogeneous factors of different etiology. Validation studies base on external criteria, such as psychological comorbidity, other interference scores or simply the treatment success (e.g., Sakinc, 1998; Schmitt, 1990; Wurmthaler et al., 1996).

Besides the basic pain characteristics, interference understood as functional limitation as well as disability as legal term seem be necessary to consider in a conceptualization of chronicity as implied by the International Classification of Functioning, Disability and Health ICF-Core sets (Bickenbach, 2014). The ICF-Core sets are a categorial system that assess disability with regard to two core parts: functioning and disability as well as contextual factors. The first axis functioning and disability is divided into three parts body functions (1), body structures (2) and activities and participation (3). The second axis of contextual factors consists of two parts comprising environmental factors and personal factors, respectively. The sets are pre-defined for specific disorders. The sub-category body structures, for example, is differently composed for chronic widespread pain vs. low back pain: whereas the pre-defined set for the former entails the component “musculoskeletal structures related to movement”, the set for low back pain includes “spinal cord and related structures”, “structure of pelvic region”, “structure of lower extremity” and “structure of trunk”.

In sum, the conceptualization and understanding of chronicity varies considerably across research groups. Hence, a thorough empirical analysis of distinguishable components was considered as necessary and overdue.

1.3.2 Specificity vs. generality of chronicity

A further problem driving this chronicity research concerned the question of the generality of chronicity measures: It was not known whether global indices of ‘chronicity’ such as the IASP Taxonomy’s Axis IV, the CPG or the MPSS scorings are equally applicable to different pain syndromes, e.g., for MSP syndromes and neuropathic pain alike, nor whether they are at all suitable to clinical samples with severe to very severe and incapacitating MSP as well, e.g., employees at work or clinical pain patients. Evidence was limited and inconclusive, either suggesting weak relations between the CPG and MPSS and both indices not relating to duration (Klasen

et al., 2004) or, on the other hand, high correlations between the MPSS and duration (Michalski & Hinz, 2006).

1.3.3 Critique of current chronicity assessment

Research on how the different conceptualizations of chronicity relate to each other is limited. The available chronicity indices rest on the assumption that chronicity if not pain per se is a homogeneous unidimensional characteristic. If this is not the case in specified patient populations or syndromes, grading ‘chronicity’ in this way will fail to capture important determinants of the chronic development.

1.4 Phenotypes in chronic musculoskeletal pain

Following the logical order from proximal to distal mechanisms in chronic MSP, a phenomenological classification was considered to be primarily based on characteristics related to the sensory-discriminative domain (cf. Figure 1 in chapter 1.1.2 & Table 1 in chapter 1.1.3). However, the role of sensory and clinical pain characteristics in the differentiation of chronic MSP syndromes and the relative importance of psychosocial factors and somato-psychic comorbidity is subject to controversial debate. This becomes particularly relevant against the background of recent revisions in the diagnostics of FMS as discussed in the following sections.

1.4.1 Sensory changes in musculoskeletal pain

A precise sensory characterization of the pain symptomatology was regarded as essential given the empirical findings, that the transition of acute regional into chronic widespread MSP is potentially related to the progression of peripheral to central sensitization (Graven-Nielsen & Arendt-Nielsen, 2010). Peripheral sensitization is defined as persistent nociceptor activity in deep tissues, whereas central sensitization refers to an increased response from dorsal horn neurons. Sensitization either peripheral or central produces increased pain sensitivity to noxious stimuli (hyperalgesia) as common phenomenon in both regional and widespread MSP. The spatial spread and increase in sensitization as observed in widespread pain might be the result of augmented synaptic activity in central neurons that ground imbalances between descending inhibition and facilitation of pain. Another explanation might be, according to the authors, the neural reorganization due to persistent muscle nociception (Graven-Nielsen & Arendt-Nielsen, 2010). The reorganization could produce a subsequent expansion and development of new receptive fields explaining

the spreading of pain to originally non-nociceptive loci as observed in referred pain. Central sensitization, in particular, is supposed to be associated with chronic widespread pain as compared to regional pain (Roussel et al., 2013; Staud, 2002), However, the role of peripheral nociception as necessary maintaining mechanism in primarily localized chronic pain remains inconclusive. Research applying quantitative sensory testing for pain sensitivity, temporal summation and descending control of pain is strongly recommended to better understand the transition from acute to chronic MSP and to differentiate subsyndromes between regional and widespread MSP (Graven-Nielsen & Arendt-Nielsen, 2010). The authors also repeated relevant terms and definitions of sensory testing, reported in the following paragraph.

1.4.2 Terms and definitions in pain sensitivity testing

Pain sensitivity testing refers to a stimulus-dependent technique applying psychophysics such as pain threshold testing at different loci with different stimulation intensities to detect the individual “just painful” perception (Graven-Nielsen & Arendt-Nielsen, 2010). Whereas pain sensitivity testing involves primarily peripheral nociception, temporal summation is associated with central and peripheral sensitization acting together, since both mechanisms are not separable at the measurement level with common quantitative sensory testing procedures. Temporal summation is defined as the positive or negative increase in pain perception as response to several somatosensory stimuli applied at the same site, with the same intensity and repeated in relatively short intervals. In contrast to the former, descending pain control is an entirely central pain mechanism and refers to the excitability along the neuro-spinal cord. A means to assess descending pain control is the application of a painful stimulus applied at the same time, but at a different location than a conditioned stimulus resulting in a decreased pain perception at the application site of the conditioned stimulus (diffuse noxious inhibition control, DNIC paradigm).

1.4.3 Sensory testing in fibromyalgia

The relevance of the involvement of sensory processes is in contrast to the recent development of FMS diagnostics: The 2010/11 ACR revisions abandoned the sensory testing entirely by excluding the manual probing of tender points (Wolfe et al., 2010; Wolfe et al., 2011). Given the empirical evidence for the importance of sensory characteristics to determine contributing pathophysiological mechanisms as discussed previously, it is at least regarded as questionable to exclude tender point testing. With

regard to the specific tender point testing, tenderness at tender points was repeatedly shown to be associated with sensitive myofascial trigger points (Ge et al., 2009; Ge, Wang, Danneskiold-Samsoe, Graven-Nielsen, & Arendt-Nielsen, 2010) suggesting a known peripheral etiology driving subsequent central sensitization notwithstanding characteristic differences between tender and trigger points in terms of stimulation and origin (Mense, 2011). Sensitivity to pressure pain has also been shown to be generalized to some degree across the body, hence not limited to tender points, but also to control points in FMS (Granges & Littlejohn, 1993; Wolfe, 1998). Furthermore, there is evidence that FMS are not only hypersensitive to pressure pain at the characteristic tender points, but also to other measurement modalities of evoked pain not selectively applied at tender point locations; possibly relating to a differential pattern of pain sensitivity selective for FMS diagnosis (Gracely, Grant, & Giesecke, 2003). Besides pressure pain sensitivity there is also evidence for increased heat pain sensitivity in FMS compared to patients with regional pain such as cUPB, presumed to be related to impaired descending inhibitory control (Gerhardt et al., 2016; Julien, Goffaux, Arsenault, & Marchand, 2005). Scientific findings are inconsistent, either identifying a common factor representing pain sensitivity irrespective of the stimulus modality (Neddermeyer, Fluhr, & Lotsch, 2008) or a multimodal structure of pain sensitivity (Neziri et al., 2011). In summary, the role of the specificity of the modality in quantitative sensory testing and their diagnostic significance to identify subgroups better differentiating within the spectrum from regional to widespread pain is not yet known (Uddin & MacDermid, 2016).

1.4.4 Relations of sensory and clinical pain characteristics

Moreover, a linear relation of hypersensitivity to pressure pain with clinical pain characteristics such as self-reported pain loci or pain intensity has not yet been shown either. Validation studies of the 2010/11 revised criteria for FMS concentrate on detecting FMS with sensitivity and specificity analysis, but the actual relation of the tender point count or the pressure pain sensitivity with the self-reported regions in pain has not been in focus before (Wolfe et al., 2016). Adding up to this, a meta-analysis revealed only weak associations of clinical pain intensity with pressure and heat pain sensitivity (Hübscher et al., 2013). There is, thus, strong support that sensory and clinical pain characteristics are better described on two separate dimensions.

1.4.5 Comorbidity and psychosocial factors in fibromyalgia

Some authors argue that psychic comorbidity constitute a major determinant of FMS (Häuser et al., 2009; Wolfe & Michaud, 2009). The number of tender points, in this regard, might serve as marker for psychological distress. This assumption is based on high correlations of sensitive tender points with markers for poor mental health, such as, screening questionnaires for anxiety and depression but also worse sleeping quality (Brown et al., 2016) Obviously, there is a coincidence of psychosocial factors and somato-psychic comorbidity especially in FMS. Research revealed widespread pain patients with concurrent FMS scoring higher on these factors in contrast to patients without concurrent FMS possibly related to a distinct qualitatively different group of patients (White, Nielson, Harth, Ostbye, & Speechley, 2002). There might also exist subgroups within FMS patients as shown by distinctive psychophysiological patterns of stress-related parameters (e.g., blood pressure and skin conductance level) associated with differences in psychological coping and prevalence rates of mental disorders (Thieme, Turk, Gracely, Maixner, & Flor, 2015). Interestingly, although classified with FMS, this study revealed one cluster labeled as “adaptive copers” without any psychic comorbidity, challenging the inclusion of psychic characteristics in FMS diagnostic.

Moreover, pertinent research dismantled the frequent association of FMS and depressive symptomatology by comparing FMS to controls with major depression without FMS (Gracely et al., 2012). Both shared the same pathophysiology but with different alterations in involved processes such as the dysregulation of the hypothalamic-pituitary-adrenal (HPA) function, which is supposed to be mediated by cytokine only in FMS. The authors also point out measurement problems, since many items in questionnaires for depression relate to somatic symptoms of hurt confounding the associations of the FMS pain disorder with depression. They concluded, that the diagnostic value of psychosocial factors is of minor importance relative to primary sensory-pain aspects and the somatic symptom burden.

1.4.6 Critique of the revised diagnostic criteria for fibromyalgia

Although strong evidence for the importance of nociceptive sensory processes in MSP, the new ACR 2010/11 criteria abandoned the manual probing of tender points primarily because of application problems by non-rheumatologists in conventional physician practice (Wolfe et al., 2016). FMS obviously show characteristics such as sleeping

abnormalities or depressive symptoms. However, diagnostics suffer from circular reasoning if these characteristics are included as cardinal criteria for FMS without a thorough systematic empirical basis. The shift from sensory to clinical pain characteristics and psychic comorbidity in the recent ACR 2010/11 criteria has possibly created a different pool of patients now classified with FMS. This effects the research on proximal mechanisms closely related to the pain pathophysiology because variance not related to the primary sensory pain processing potentially intervenes.

1.5 PhD project realization

The diagnostic and classification problems of chronic MSP presented above provided the basis to start this PhD project. The two original contributions investigated the dimensional structure of the chronicity construct (study #1) and isolated sensory-clinical pain phenotypes in chronic MSP (study #2). The following section describes how this research was realized.

1.5.1 Research aims

Purpose of study #1 was to analyze the structure and composition of chronicity operationalized by established chronicity indices, in particular, Axis IV of the IASP Taxonomy of chronic pain, the widely used Chronic Pain Grade (CPG), compared to a national system of evaluating pain chronicity, the Mainz Pain Staging System (MPSS). The dimensionality of these indices was analyzed, aiming to isolate the construct of chronicity from possible additional clinically relevant aspects of pain in becoming chronic. The dimensional structure was analyzed within an occupational sample of working employees and a sample of chronic pain patients.

Study #2 aimed to find sensory and clinical pain phenotypes that differentiate within the spectrum from chronic widespread pain to regional pain exemplarily for a sample of patients with FMS vs. cUBP. The phenotypes were supposed to be evaluated with respect to clinical significance relative to chronicity and functionality, psychosocial stress load and psychosomatic comorbidity.

1.5.2 Data basis and work program

Data of this PhD thesis stem from two different studies: The pain patient sample was part of a multicenter study: “Neuroplasticity and Learning in Chronic Pain” (Projects HO 904/11 & FL 156/26) funded by the Deutsche Forschungsgemeinschaft (Clinical Research Group 107), whereas the occupational sample was provided by the German

Occupational Health Association, Section Nutrition and Gastronomy Business (Berufsgenossenschaft Nahrungsmittel & Gaststätten, BGN).

Pain patients of the former sample were assigned to subprojects at different institutes, that were each investigating pain mechanisms of their own accord. A pharmacological central project was established under contribution from all of these subprojects. This central project performed a randomized placebo-controlled clinical trial testing the efficiency of an extinction training combined with a low dose of dose of the cannabinoid receptor agonist Delta-9-Tetrahydrocannabinol. Data come from this central project as well as two subprojects (P3 and P4). Subproject P3 investigated learning processes involved in the acquisition and extinction of pain and their neuronal correlates (Thieme et al., 2006; Yilmaz et al., 2010). Subproject P4 focused on implicit operant learning of pain sensitization and the role of psycho-somatic comorbidity as well as stress in pain becoming chronic (Becker, Kleinböhl, Klossika, & Hölzl, 2008).

The occupational sample was acquired within a study on the prevention of work-related MSP disorders and concentrated on risk evaluation of employees working in jobs that involved a seating or standing activity with a high musculoskeletal load and an assumed high a priori risk to develop MSP disorders. The funders allowed access to sensitive, in other circumstances confidential, data of active workers within their associated companies. An overview of the work program is provided in Table 2.

Before the two original contributions were written, several pre-studies had to be done (some of them prior to the enrollment as PhD in December 2013). Besides proof of principle analyses by checking minimal sample sizes in the combined data sets, an additional sample of patients with neuropathic and cancer pain from a pilot study on multidimensional sequential risk assessment was recruited at the Clinic of Anaesthesia and Intensive Care at the University Medical Cent in Mannheim. Moreover, a large sample acquired within a multidimensional diagnostic risk assessment of stress and somato-psychic comorbidity was prepared to serve as additional study sample because of the rich content on endocrine and psychobiological data. These two datasets were dropped in the final stage of this dissertation project due to a lack of primary pain-related data (especially psychophysical variables) in the a priori applied Multidimensional Sequential Risk Assessment for Stress, MSRA-S (Hölzl et al., 2010).

As further part of the preparatory work, all study data had to be checked for the same item content and labeling to allow merging. Moreover, the IASP Taxonomy of chronic pain was mapped on all datasets as starting phenotypic approach to classify MSP

(IASP Taxonomy Working Group, 2017). The data, hence, had to be recoded to fit the categories suggested in five axes (Axis I: pain region, Axis II: system, Axis III: temporal characteristics of pain, i.e., the pattern of occurrence; Axis IV: intensity and the time since onset of pain; Axis V: etiology of pain).

Subsequently, all parameters in the datasets had to be checked for their potential applicability within the multidimensional model of selective marker domains in chronic MSP (cf. Table 1 in chapter 1.1.3). Incongruences due to different parametrization of core domains in different datasets had to be corrected by analytic and theoretical data comparisons. The final parameters were then thoroughly selected according to the research aims defined in both articles.

Table 2. Work program with timeline of the PhD thesis

Year	2012	2013	2014	2015	2016	2017	2018	2019
Pre-studies Conceptualization, data collection, sample selection, data preparation								
Research paper #1 Deconstructing chronicity of musculoskeletal pain: intensity-duration relations, minimal dimensions and clusters of chronicity								
Research paper #2 Reclassifying patients with widespread and regional MSP by sensory and clinical phenotypes; principal components and latent class analyses								
Write PhD thesis General introduction and discussion								

PhD thesis subprojects with respective timeline. There were two research papers written (research paper #1 published in 2018 in the Scandinavian Journal of Pain, research paper #2 under review by co-authors for submission to PAIN).

Research paper #1, reanalyzed the construct of chronicity for discriminable dimensions and generality across different samples with MSP. Subsequently, research paper #2 identified sensory-clinical pain phenotypes according to a proximal to distal search strategy of necessary and sufficient dimensions of chronic MSP (cf. Figure 1 in chapter 1.1.2). After sensory-clinical pain phenotypes were isolated, relevant markers for somato-psychic comorbidity and psychosocial aspects at domains at the intermediate and distal level were compared for differences on these sensory-clinical pain phenotypes.

1.5.3 Research questions and hypothesis

In study #1 we asked what are the core components of chronicity and is it justified to apply one global index in different groups with MSP? We expected variation in content and structure of chronicity across pain syndromes, durations, severity ranges and diagnostic groups.

In study #2 we questioned the recent diagnostic shift in FMS diagnostics by re-examining the role of altered pain sensitivity and primary clinical pain characteristics in a selected sample of widespread and regional pain (FMS and cUBP patients, respectively). The dimensional structure of pain sensitivity and clinical pain was assessed and sensory-clinical phenotypes were derived. Moreover, the generalization of sensory pressure hypersensitivity to heat pain was checked by asking for discernible phenotypes as modalities change. Finally, we were interested in the role of comorbid psycho-somatic pathology and stress and asked if there are any differences between the sensory-clinical pain phenotypes. We expected a better differentiation of the prior diagnostic groups by sensory-clinical pain phenotypes, discernible clusters of enhanced heat pain sensitivity and differences in comorbid psycho-somatic pathology and stress.

1.5.4 General methods

The following studies applied an empirical phenotypic approach throughout as an example for a dimensional assessment of MSP with quantitative data provided from responses in questionnaires and psychophysics. Based on a framework of the multidimensional model of chronic pain well-established marker domains and respective characteristics were selected and parameterized (cf. Figure 1 in chapter 1.1.2 and Table 1 in chapter 1.1.3). The search followed the theoretical cascade of domains involved in MSP becoming chronic. The marker domains were selected

starting from proximal to distal mechanisms in the process of pain becoming chronic. After a thorough descriptive characterization of marker parameters in the respective domain, linear (factor analyses) and probabilistic (latent class analyses) structure finding methods were applied to elaborate on the dimensional structure of MSP syndromes.

2 ORIGINAL CONTRIBUTIONS

2.1 Deconstructing chronicity of musculoskeletal pain: Intensity-duration relations, minimal dimensions and clusters of chronicity[1]

[1] Finnern, M.M., Kleinbohl, D., Flor, H., Benrath, J., Hölzl, R. (2018). Deconstructing chronicity of musculoskeletal pain: intensity-duration relations, minimal dimensions and clusters of chronicity. *Scandinavian Journal of Pain,18*(3), 363-377. doi: 10.1515/sjpain-2018-0021

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Abstract

Background and aims: Evaluating the degree to which pain has become chronic beyond mere duration poses several problems. The IASP Pain Taxonomy Axis IV employs intensity and duration combined to 9 ordered categories. The Chronic Pain Grade links intensity and disability, but only the latter contributes to higher grades. The Mainz Pain Staging System includes temporal and spatial aspects, medication and health care utilization. Their interrelations, scale properties and construct validity are not always known or debatable. The study challenges the generality and homogeneity of the chronicity construct of musculoskeletal pain aiming at necessary and sufficient sub-constructs identified by separable marker clusters. We show chronicity to vary in content and structure with severity and duration and between different populations. This raises the question of validity conditions of general chronicity indices and requires further work on adequate chronicity measures.

Method: Diagnostic entrance data of 185 patients with chronic regional vs. widespread musculoskeletal pain (unspecific back pain, fibromyalgia) from regional pain clinics and 170 active employees in a nationwide prevention program were included in a retrospective cross-sectional analysis of the combined marker sets of the three chronicity indices above. The samples of patients and employees provided intensity, duration and disability degrees over the whole range of the assumed chronicity. Intensity-duration relations were quantified by correlations and frequency distributions of successive duration classes. The dimensional structure of pain and chronicity variables was assessed by factor and cluster analyses.

Results: Pain intensity distributions showed inhomogeneous courses from short to long durations - lowest intensities predominating at longer durations in patients and at shorter in employees. Moreover, pain intensity and duration related nonlinearly to Chronic Pain Grade and Mainz Pain Stage and differently in patients compared to employees, and these indices correlated only moderately to each other. Factor and cluster analyses revealed different dimensions and clusters of chronicity markers for patients and employees. In the former, three dimensions with four clusters were identified with clinical characteristics (intensity, temporal and spatial aspects) separated from direct consequences (disability/interference with activities, medication usage) and chronic development (duration, healthcare utilization). In employees, only two dimensions with three clusters were obtained and clinical pain characteristics clustered with direct consequences both separated from chronic development. Similar

differences were shown between unspecific back pain and fibromyalgia but were less well defined.

Conclusions: There appears to be no coherent ‘chronicity’ entity over the entire range of severity and duration for all pain populations with different clinical pictures and social contexts. Statements about chronicity must be differentiated with respect to those aspects relative to patient career.

Implications: General indices do not capture the complex and changing composition of chronicity. There is evidence for at least three weakly coupled core domains of chronicity, i.e., the primary clinical characteristics, the direct consequences of current interference with activities, and aspects of the patient history. Hence, multivariate assessment is recommended. The particular syndrome, the diagnostic context and the population under investigation should likewise be considered.

Keywords: Chronicity; Chronic Pain Grade; Mainz Pain Staging System; IASP Taxonomy of Chronic Pain; Musculoskeletal Pain; Validity

1. Introduction

The multidimensionality of pain and the complexity of chronicity factors have led to varied approaches to quantify the general degree to which pain has become chronic beyond the normal healing time, across different populations and syndromes. The latest consensus for ICD-11 has fixed this time at three months [1]. However, further aspects of chronic pain, for example, the time course of intensity, quality and location, are important. In addition, cognitive, affective and behavioral characteristics have been related to chronicity [2]. Not all of these aspects may be necessary core variables for a general construct of chronicity and more comprehensive measures have been proposed. For instance, Axis IV of the IASP Taxonomy of chronic pain [3] employs a combination of 3-point intensity and duration scales yielding a composite scale of nine ordinal chronicity categories leaving biometric properties undefined. The internationally used Chronic Pain Grade (CPG; [4]) combines intensity with disability, but only the latter contributes to higher grades due to the item response theory-based scale construction. The multiaxial Mainz Pain Staging System (MPSS; [5, 6]) used in German speaking countries includes temporal and spatial aspects, medication and health care utilization. The relations between different indices and subscales vary, scale metrics are often unclear, and validation studies are based on external criteria like comorbid psychopathology, treatment success or return to work [5]. This raises the question of necessary and sufficient components, the internal structure of the chronicity construct and the stability over time, across different severities, populations and syndromes (internal and construct validity).

We report pertinent results including only the primary properties of duration and intensity at different times and the subscales of extant chronicity indices (CPG, MPSS) in the retrospective analysis of a large data-set from patients of pain clinics and a non-patient group of employees with musculoskeletal pain (MSP). Combining these groups ensured coverage of the full range of pain severity, duration, and impairment. We hypothesized:

(1) Pain intensities develop over time in non-linear ways differing between patients and employees: Monotonic (uniform) increases prevail in employees with lower intensity and shorter duration, whereas this relation gets lost in patients with a longer pain history, levelling off at higher severity.

(2) Intensity increases monotonically with duration in relatively localized (regional) pain, in particular, in chronic unspecific back pain (cUBP). In contrast, widespread pain,

in particular, fibromyalgia (FMS), shows variable symptom development, from continuous spreading and higher severity to no change at all.
(3) Combined structural analyses of the chronicity markers (Axis IV of IASP Taxonomy with the subscales of CPG and MPSS) do not reveal one common but multiple factors of chronicity. These differ between patients and employees and between syndromes. In patients, clinical picture, severity, and patient career are most important, while severity and disability constitute the main components in employees.
Analyzing the internal structures of the core marker set of extant indices, we aimed to obtain a minimal set of scales to quantify the necessary chronicity aspects specific to the model populations and syndromes while excluding secondary cofactors and consequences.

2. Material and methods

2.1. Study sample

The present cross-sectional analysis is based on the initial assessment data of (1) patients participating in a collaborative multicenter project on plasticity and learning in pain becoming chronic and (2) employees taking part in a nationwide prevention program for work-related stress and musculoskeletal disorders in the nutritional and gastronomy businesses. Both studies were approved by the Local Ethics Committee. Patient data were partially acquired in connection with a clinical trial of combined behavioral and cannabinoid treatment for chronic pain (ClinicalTrials.gov Identifier: NCT00176163). Patients were eligible for the study if they reported musculoskeletal pain (MSP) for at least three months, and employees were included also when they reported pain for shorter durations. Healthy controls were not considered as the research questions required only comparisons within MSP pain populations. General exclusion criteria collected on first contact and confirmed in the initial medical screening were psychotic disorders and substance abuse, disorders of the central nervous system (epilepsy, craniocerebral injury, stroke, Parkinson's disease, multiple sclerosis), infectious diseases (HIV, hepatitis), autoimmune diseases (untreated thyroid disease), and/or the current use of neuroleptics, benzodiazepines or mood-stabilizers. Pregnant and nursing women and persons with insufficient German language competence (written and spoken) were also excluded.
Neither patients nor employees were selected for representativeness but systematically recruited according to the quasi-experimental study designs in the

original intervention and prevention projects. Thus, frequencies in subcategories varied widely due to different base rates and acquisition quota of pain clinics and occupational health centers. However, age, sex and other variables pertinent to the present research questions were matched where possible. Main analyses focused on within-group associations of chronic pain markers more or less neutral against selection effects. Further details on recruiting, exclusions and dropouts (CONSORT flow diagram), sociodemographic and diagnostic data are provided in supplementary material (Table S1 and Fig. S4).

Table 1. Sociodemographic characteristics of participants

	Pain patients: N = 185 [a]			Employees:	All:
	FMS: N = 78	**cUBP: N = 107**	**All MSP**	**N = 170 [b]**	**N = 355**
Age [yrs.]					
Mean +/- SD	50.8 +/- 9.5	48.3 +/- 12.2	49.3 +/- 11.1	40.5 +/- 11.9	45.1 +/- 12.3
Range	23 – 68	18 – 68	18 – 68	18 – 64	18 – 68
Female	73 (93.6) [c]	69 (64.5)	142 (76.8)	103 (60.6)	245 (69.0)
Male	5 (6.4)	38 (35.5)	53 (23.2)	67 (39.6)	110 (31.0)
Work situation					
Student	3 (3.8)	6 (5.6)	9 (4.9)	0 (0.0)	9 (2.5)
At work	23 (29.5)	40 (37.4)	63 (34.1)	170 (100.0)	233 (65.6)
Sick leave	1 (1.3)	4 (3.7)	5 (2.7)	0 (0.0)	5 (1.4)
Pension/pendg.	9 (11.5)	5 (4.7)	14 (7.6)	0 (0.0)	14 (3.9)
Retired	23 (29.5)	25 (23.4)	48 (25.9)	0 (0.0)	48 (13.5)
Unemployed	14 (17.9)	17 (15.9)	31 (16.8)	0 (0.0)	31 (8.7)
Missings	5 (6.4)	10 (9.3)	15 (8.1)	0 (0.0)	15 (4.2)
Not working [d]	47 (60.3)	51 (47.7)	98 (53.0)	0 (0.0)	98 (27.6)

[a] Fibromyalgia (FMS) and chronic unspecific back pain (cUBP) in chronic musculoskeletal pain (MSP) patients of regional pain clinics; [b] occupational health program; [c] absolute N, percentage in brackets; [d] total numbers of persons currently not at work. Note. Widely varying Ns in subcategories due to different base rates and acquisition quota of pain clinics and occupational health centers.

2.1.1. Patients of regional pain clinics

For the present study, initial assessment data of all N = 261 patients eligible for the multicenter study suffering from clinically relevant chronic unspecific back pain (cUBP) or widespread muscle pain were considered. Of the 261 data sets 60 were incomplete or inconsistent leaving 201 patients qualifying. Further 16 patients met additional exclusion criteria so that 185 patients (107 cUBP, 78 FMS) entered the final analysis (CONSORT flow chart in the supplementary material). Additional exclusion criteria were relevant drug taking or change in medication within 3 months prior to data collection; cardiovascular disease or hypertension not treatable with drugs, and renal insufficiency requiring dialysis assessed by doctor's checklist (supplementary material, Fig. S5). Entry assessment for mental disorders was done with the Structured Clinical Interview for DSM IV Axis I Disorders (SKID-I; [7]). Patients with major depression or anxiety disorders remained in the sample because affective comorbidity was a research question of the source projects. Comorbidity relations of chronicity as such were not subject of the present analysis and will be reported elsewhere.

cUBP criteria required that pain in upper or lower back was the primary problem and was not related to acute trauma, inflammatory or neurologic disease; radicular and neuropathic signs were also excluded on final medical investigation (Fig. S5: Doctor's checklist in supplementary material). Chronic widespread pain criteria corresponded to earlier ACR fibromyalgia (FMS) criteria based solely on muscle pain (11 of 18 tender points; [8]). This left 107 patients with cUBP and 78 with FMS diagnoses. Of the latter 63 matched also the FMS criteria suggested in 2010/2011 [9].

2.1.2. Employees at risk for musculoskeletal pain

Data of employees currently at work were acquired according to an adapted protocol of the patient study. The cooperating occupational health service centers collected the data, guaranteeing full anonymity of individualized data against employers as well as study partners. Employees were eligible for participating when in jobs requiring a seating or standing activity with high musculoskeletal load and established risk and prevalence of work-related musculoskeletal pain (detailed information on field of work and work schedule in supplementary material, Table S1). Initially, nine companies in the program were interested and allowed contacting employees. One-hundred-and-forty employees fulfilling the inclusion criteria German language comprehension, age 18 – 65 years, actively working and reporting musculoskeletal pain at present,

continuing or repeatedly during the last years were recruited this way; another 32 participants were acquired through advertisements in the press and brochures displayed in local practitioners' offices. After exclusion of 2 persons without pain related to the musculoskeletal system 170 employees remained in the analysis (Table 1).

2.2. Diagnostic Instruments

All assessments were performed using the multidimensional battery of validated instruments initially assembled for the patient multicenter study. The complete battery included established pain questionnaires as well as scales on coping and functional level, quantitative sensory testing, von Korff's Chronic Pain Grade (CPG; [4]) questionnaire as well as checklists of anxiety, depression, life quality and general health. A subset of this battery was adapted for the occupational group with identical instruments for the core variables of the present study. In the occupational health project additional instruments were included in further diagnostic steps to assess perceived stress at work, psychosocial and physical work factors as well as biological stress markers (MSRA-P; [10]). Only data of the common variable set for both groups at study entry are included here as described below.

2.2.1. Pain assessment

Assessment of pain and related variables comprised the West Haven-Yale Multidimensional Pain Inventory (German version, MPI-D; [11]), the German Pain Questionnaire (Deutscher Schmerzfragebogen, DSF; [12, 13]) and the questionnaire for the Mainz Pain Staging System (MPSS; [14, 15]). The latter was only applied in the employee sample; for pain patients, MPSS variables were recoded from corresponding items of the DSF.

2.2.2. Chronicity measures

Chronicity was first coded according to Axis IV of the IASP Taxonomy of chronic pain [3, 16] using current pain intensity derived from the MPI-D [11]; item #1: present pain intensity) and the duration parameter of the DSF ([13]; item #25: time since onset). Secondly, von Korff's Chronic Pain Grade questionnaire (CPG, German version; [17]) and the Mainz Pain Staging System (MPSS; [5]) were included as global chronicity indices and analyzed at item and subscale level. Only the results of the latter are reported here for brevity.

The CPG consists of item response theory based subscales [18-20] comprising three items on pain intensity (present, average, worst), three items on disability (interference with daily, recreational, social and family and work-related activities) using 11-point Likert scales to derive a disability score. An additional question concerns the number of days the person was not able to perform at work or carry out other relevant activities due to pain.

The MPSS is a multiaxial system for staging pain chronicity used in the German speaking area. Three stages of pain chronicity are derived from a compound sum score ranging from 4 to 12 points out of four “axes” of 3-point items. Axis I evaluates “temporal characteristics” of pain (occurrence pattern, episode duration, changes in intensity). Axis II codes “spatial aspects” of pain (number of painful areas). Axis III evaluates “medication use” (drug intake, previous withdrawal treatments). Axis IV concerns current and previous “utilization of the health care system/patient career” (number of physician changes, pain-related hospitalizations, pain-related operations, pain-related stays in a spa, rehabilitation center or pain center). Scores of 4 – 6 points on these items correspond to pain chronicity stage I, 7 – 8 points code as stage II, and 9 – 12 as stage III. The higher the “pain stage”, the more persistent the pain symptomatology and the more intense therapeutic intervention is needed for complicating factors [21].

2.2.3. Control variables

Control variables were pain medication and psychological comorbidity assessed with the DSF [13], the Center for Epidemiological Studies Depression (German version: ADS; [22]) and the State-Trait Anxiety Inventory (German version: STAI-T; [23]).

2.3. Data analyses

Data were analyzed with the program packages IBM SPSS Statistics (version 23; Armonk, NY, USA) and R (version 3.2.0; The R Foundation for Statistical Computing, Vienna, Austria). Main analyses covered the internal relations between chronicity attributes within the two groups of participants, separately as well as combined to control for Simpson effect-like dependencies [24]. A multimethod strategy was applied, which comprised correlational, contingency and frequency analysis, dimensional analyses with exploratory and confirmatory factor analyses as well as maximum likelihood estimation of latent class models of marker clustering.

2.3.1. Correlation and frequency analyses

Relations of intensities to duration, CPG grades and MPSS stages were calculated as nonparametric correlations (Spearman's Rho, Kendall's Tau) or contingency coefficients (Pearson's contingency coefficient C_{corr}, adjusted for number of categories [25]). Specific intensity characteristics at different durations and chronicity levels were further explored by analyses of frequency distributions across single duration classes and chronicity grades. Differences of pain intensity-duration characteristics and global chronicity indices were assessed by non-parametric planned post-hoc tests. Effects of control variables were checked by correlation and median-split analyses. Significance levels were Bonferroni-Holm corrected for multiple testing, familywise and separately for each chronicity index and dataset of patients and employees. The significance level was set at $p < 0.05$ throughout; exact probabilities are reported where appropriate.

2.3.2. Dimensional analyses at scale and item level

The dimensional structure of the IASP Taxonomy Axis IV coding, CPG and MPSS was explored by principal component analysis (PCA) and principal axis factoring (PAF) with varimax rotation and pairwise exclusion of cases with missing data for both samples separately and combined. The Kaiser and scree criteria were applied to determine the number of components to be extracted. Confirmatory factor analyses (CFA) were conducted with the *lavaan* package in R [26] to evaluate the dimensions derived from exploratory factor analyses by descriptive fit indices [27].

2.3.3. Latent class analyses

To substantiate the dimensional relations found and to identify specific variable groupings possibly obscured in conventional factor analyses, hierarchical latent class analysis (LCA, R program pvclust; [28–30]) was employed as second structure finding method. LCA generates variable groupings by a maximum likelihood model. It is apt to support and inform the results of classic dimensional analysis from a different perspective operating on the same data set. In addition, pvclust provides tests of robustness of cluster solutions. Probability values were calculated for each cluster with non-parametric bootstrap probability (BP) and approximately unbiased (AU) p-values in % ranging from 0 (not robust) to 100 (highly robust). To reduce a type 2 error, AU and BP values were uncorrected for multiple testing and used only for descriptive assessment of cluster dendrograms, not for inferential difference testing. Correlations

between observed IASP Axis IV, CPG and MPSS marker values entered the cluster analysis with the average linkage method. Data were permuted 1,000 times to assess the stability of cluster solutions.

3. Results

3.1. Sample characteristics: pain intensity, duration and chronicity

As expected, due to different recruiting paths and source populations, patients and employees with musculoskeletal pain differed significantly in all chronicity markers included (Table 2): On average, patients reported pain intensities in the medium range and long-term durations; only two indicated no pain at present. In contrast, pain intensities were generally low in employees, none reported the strongest intensity and 54 (31.8%) had no pain at present. Again, long durations > 5 years dominated although less frequent than in the patients.

Table 2. Pain symptoms, medication, and chronicity indices

	Pain patients: N = 185 [a]			Employees:	All:
	FMS: N = 78	**cUBP: N = 107**	**All MSP**	**N = 170 [b]**	**N = 355**
Pain intensity [c]					
Mean +/- SD	3.3 +/- 1.3	2.9 +/- 1.3	3.1 +/- 1.3	1.4 +/- 1.3	2.3 +/- 1.5
Median +/- IQD	3 +/- 0.5	3 +/- 1.0	3 +/- 0.5	1 +/- 1.0	2 +/- 0.5
Range	0 – 6	0 – 6	0 – 6	0 – 6	0 – 6
	Difference patients vs. employees: $p < 0.001$ (t-test, U-test, K-S test)				
Duration [mths] [d]			N (%)		
]0-6]	0 (0) [e]	0 (0)	0 (0)	18 (10.6)	18 (5.1)
]6-12]	2 (2.6)	7 (6.5)	9 (4.9)	28 (16.5)	37 (10.4)
]12-24]	4 (5.1)	8 (7.5)	12 (6.5)	30 (17.7)	42 (11.8)
]24-60]	14 (18.0)	15 (14.0)	29 (15.7)	44 (25.9)	73 (20.6)
> 60	53 (68.0)	68 (63.6)	121 (65.4)	50 (29.4)	171 (48.2)
Missings	5 (6.4)	9 (8.4)	14 (7.6)	0 (0)	14 (3.9)
Mean +/- SD	50 +/- 25	48 +/- 32	48 +/- 29	24 +/- 16	42 +/- 22
Median +/- IQD	60 +/- 18	60 +/- 18	60 +/- 18	42 +/- 27	60 +/- 24
	Difference patients vs. employees: $p < 0.001$ (U-test, K-S test, t-test not applicable)				
Chronic Pain Grade					
Grade 0	0 (0.0) [e]	0 (0)	0 (0)	2 (1.2)	2 (0.6)
Grade I	13 (16.7)	32 (29.9)	45 (24.3)	124 (72.9)	169 (47.6)
Grade II	6 (7.7)	7 (6.5)	13 (7.0)	24 (14.1)	37 (10.4)

[Table 2, continued]

	Pain patients: N = 185 [a]			Employees:	All:
	FMS: N = 78	**cUBP: N = 107**	**All MSP**	**N = 170 [b]**	**N = 355**
Grade III	14 (18.0)	19 (17.8)	33 (17.8)	13 (7.7)	46 (13.0)
Grade IV	23 (29.5)	16 (15.0)	39 (21.1)	7 (4.1)	46 (13.0)
Missings	22 (28.2)	33 (30.8)	55 (29.7)	0 (0.0)	55 (15.5)
Mean +/- SD	2.8 +/- 1.2	2.3 +/- 1.2	2.5 +/- 1.2	1.4 +/- 0.8	1.9 +/- 1.2
Median +/- IQD	3 +/- 1.0	2 +/- 1.0	3 +/- 1.5	1 +/- 0.5	1 +/- 1.0
	Difference patients vs. employees: $p < 0.001$ (U-test, K-S test, t-test not applicable)				
Mainz Pain Stage			N (%)		
Stage I	0 (0.0) [e]	0 (0)	0 (0)	122 (71.8)	122 (34.4)
Stage II	10 (12.8)	16 (15.0)	26 (14.1)	38 (22.4)	64 (18.0)
Stage III	25 (32.1)	14 (13.1)	39 (21.1)	4 (2.4)	43 (12.1)
Missings	43 (55.1)	77 (72.0)	120 (64.9)	6 (3.5)	126 (35.5)
Mean +/- SD	2.7 +/- 0.5	2.5 +/- 0.5	2.6 +/- 0.5	1.3 +/- 0.5	1.7 +/- 0.8
Median +/- IQD	3 +/- 0.5	3 +/- 0.5	3 +/- 0.5	1 +/- 0.5	1 +/- 0.5
	Difference patients vs. employees: $p < 0.001$ (U-test, K-S test, t-test not applicable)				
Medication usage [f]			N (%)		
None	26 (33.3) [e]	46 (43.0)	72 (38.9)	56 (33.0)	128 (36.1)
Seldom-several/week	1 (1.3)	7 (6.5)	8 (4.3)	105 (61.8)	113 (31.8)
Daily	39 (50.0)	24 (22.4)	63 (34.1)	7 (4.1)	70 (19.7)
Missings	12 (15.4)	30 (28.0)	42 (22.7)	2 (1.2)	44 (12.4)

[Table 2, continued]

	Pain patients: N = 185 [a]			Employees:	All:
	FMS: N = 78	**cUBP: N = 107**	**All MSP**	**N = 170** [b]	**N = 355**
	Difference patients vs. employees: $p < 0.001$ (K-S test, U- and T-test not applicable)				

[a] Fibromyalgia (FMS) and chronic unspecific back pain (cUBP) in chronic musculoskeletal pain (MSP) patients of regional pain clinics; [b] occupational health program; [c] present pain intensity ratings in MPI-D [11]; [d] duration categories]…] in left-open/right-closed intervals (without first, including second limit). [e] Absolute numbers, % in brackets; varying N due to missings. [f] Frequency of taking pain-relevant drugs at present (item 38 in DSF;[13]); " seldom - several/week" , as required.

*Notes: IQD, inter-quartile distance = 0.5 * [Q(75) – Q(25)]; means and medians for CPG and MPSS included for completeness, but not reliable because of few scale categories resulting in many ties; U-tests are of limited value. Results descriptions refer to Kolmogoroff-Smirnow 2-sample tests (K-S) if not stated otherwise.*

On average, global chronicity grades were also higher in patients than employees (medians: CPG = III vs. I; MPSS = III vs. I) for the same reasons; no patient was classified with CPG 0 or MPSS stage I. Average chronicity was higher for FMS as in cUBP (medians: CPG III vs. II; MPSS: III for both; modal values: CPG IV vs. III, MPSS: III vs. II). Interestingly, patients' chronicity indices showed second modes at CPG I and MPSS stage II indicating a mixed composition of low and high chronicity. In employees' chronicity indices declined consistently in frequency at higher grades. The apparent qualitative differences in distribution are further explored in the following sections.

3.2. Intensity-duration relations

3.2.1. Correlations of intensity and duration

As expected, pain intensities were only weakly although significantly associated with duration for the combined sample of patients and employees (Spearman's $\rho = 0.24$; Kendall's $\tau = 0.20$; coefficient of association, corrected for number of categories, $C_{corr} = 0.39$; $p < 0.01$, adjusted).

Table 3. Associations between pain intensity, duration, and chronicity indices [a]

		Pain Intensity	***Pain Duration***	***CPG***
FMS	***Pain Duration***	-0.194+/-0.166+ [a] (98)	---	---
	CPG Grade	0.478***/0.396***/0.628*** [a] (74)	-0.412***/-0.374***/0.450* [a] (74)	---
	MPSS Stage	0.273/0.245/0.537* [a] (30)	0.230/0.222/0.421 [a] (30)	0.718** [b] (27)
cUBP	***Pain Duration***	-0.127/-0.109 [a] (72)	---	---
	CPG Grade	0.442**/0.373***/0.687* [a] (55)	0.077/0.068/0.486 [a] (56)	---
	MPSS Stage	0.311+/0.280+/0.547* [a] (35)	-0.032/-0.033/0.482+ [a] (35)	0.185 [b] (31)
All MSP	***Pain Duration***	-0.156*/-0.136* (170)	---	---
	CPG Grade	0.472***/0.390***/0.580*** (129)	-0.203*/-0.181*/0.322 (130)	---
	MPSS Stage	0.275*/0.247*/0.487 (65)	0.087/0.084/0.428+ (65)	0.391 [b] (58)

[Table 3, continued]

		Pain Intensity	*Pain Duration*	*CPG*
Employees	***Pain Duration***	0.135+/0.109+ (170)	---	---
	CPG Grade	0.392***/0.345***/0.662*** (170)	0.103/0.087/0.317 (170)	---
	MPSS Stage	0.334***/0.302***/0.544*** (164)	0.250**/0.223**/0.363** (164)	0.451*** [b] (164)
All	***Pain Duration***	0.244***/0.199*** (340)	---	---
	CPG Grade	0.572***/0.480***/0.612*** (299)	0.191**/0.163***/0.310+ (300)	---
	MPSS Stage	0.544***/0.472***/0.632*** (229)	0.471***/0.408***/0.538*** (229)	0.615*** [b] (222)

*[a] Non-parametric correlation or contingency coefficients, respectively, as appropriate: Spearman's ρ / Kendall's τ / C_{corr} adjusted for number of categories; ordinal scales throughout (7, 5, 5 and 3 levels). Variable N due to missings after pairwise exclusion. [b] C_{corr} only. + p < 0.1; * p < 0.05; ** p < 0.01; *** p < 0.001; 2-tailed, Bonferroni-Holm corrected (k = 6 per coefficient family). Note. Correlations within the syndrome groups Fibromyalgia (FMS) and chronic unspecific back pain (cUBP) are not significantly different from those in all chronic musculoskeletal pain (MSP) patients of regional pain clinics.*

However, the low overall correlation is misleading because correlations differed qualitatively and in sign between the subgroups (Table 3). In patients, pain intensity correlated weakly negatively with duration (ρ = - 0.156; τ = - 0.136; N = 170; $p < 0.05$, adjusted) for both cUBP and FMS patients. In contrast, pain intensity correlated weakly positively although insignificantly with duration in employees with MSP (ρ = + 0.135; $p = 0.079$; τ = + 0.109; $p = 0.069$ adjusted; N = 170; C_{corr} = n. s.).

3.2.2. Frequency distribution analyses

The inconsistent intensity-duration correlations found are likely due to nonlinear and group-dependent relations in accordance with hypothesis 1. This was confirmed by significant differences in cumulative intensity distributions between particular duration classes in the total sample, i.e., between shorter and longer durations ($p < 0.01$; 2-sample K-S, U-test,). Further, intensity distributions across duration classes differed between patients and employees in specific ways (Fig. 1): In patients, lower, not higher intensities prevailed at longer durations above five years, whereas in employees, lower intensities dominated in shorter durations ($p < 0.001$ and 0.05; 2-sample K-S, U-test; Figs. 1 C and D).

The two-dimensional temperature-plots of intensity-duration distributions corrected for base rates are apt to further clarify these specific relations in patients and employees (Figs. 1 E, F): In patients, contrary to hypothesis 1, pain intensities decreased with increasing duration only up to 5 years and leveled out above (Fig. 1 E). The picture differed completely in employees (Fig. 1 F): Pain intensities first increased with duration at shorter durations (according to hypothesis 1) but decreased again at longer durations (see also in supplementary material, Figs. S6 and S7).

Finally, contradicting hypothesis 2 and according to the correlational analysis above, there were neither significant syndrome-specific intensity-duration characteristics between cUBP and FMS patients nor significant differences in absolute intensities or durations. However, the negative result may be due to low power, particularly, in males and FMS subgroups.

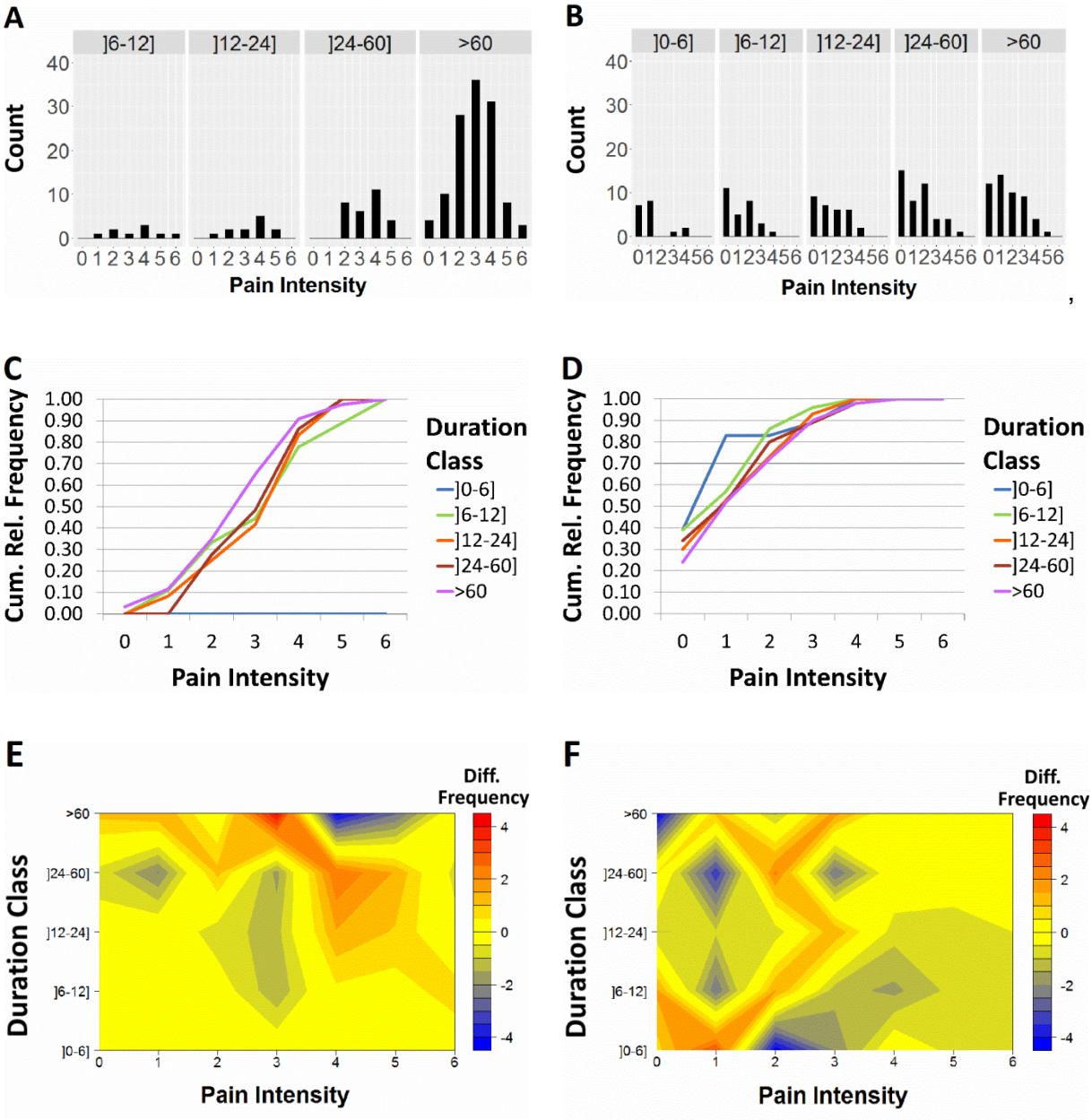


Figure 1: *Different of intensity-duration characteristics in clinic patients and employees. First and second rows: Histograms (**A**, **B**) and cumulative relative frequency distributions (**C**, **D**) of pain intensities per duration class in patients and employees (N = 170, each). Duration classes d]i … j]: i < d ≤ j months; no durations ≤ 6 months in patients. Differences: (1) Intensity histograms of patients (**A**) and employees (**B**) at all durations (p < 0.001; K-S and U-tests, corrected). (2) Cumulative relative intensity frequencies at long durations > 60 mths shifted to lower intensities in patients (**C**, violet; p < 0.05), which tend to dominate at short durations ≤ 6 mths. in employees (**D**, blue; p < 0.08). Third row: Temperature plots of the relative intensity frequencies per duration class with marginal distributions controlled: colour-coded differences between observed (**f_{obs}**) and expected (**f_{exp}**) frequencies; **f_{exp}** = $f_{i.} * f_{.d} / N_{total}$; $f_{i.}$ = N of intensity i; $f_{.d}$ = N of duration d. (**E**) patients; (**F**) employees. Intensity-duration contours generated with statistical package R, function filled.contour. Note. (1) In patients, difference frequencies concentrated in the red-to-orange area starting from low to medium intensities at very long and long durations and decreasing to high and very high intensities at medium to short durations at the lower right. This indicates a general tendency of lower pain intensities at shorter times since onset consistent with the negative overall-correlation (Table 3 and text). (2) In employees, the difference plane shows a different picture concordant with the zero overall-*

correlation of intensity and duration. In addition to the low intensity main group with short durations (red, bottom left), subgroups with different intensity-duration relations appeared: one with pain intensity increasing with longer durations, another with decreasing intensity after one year since onset and a third subgroup again worse at durations longer than 2 years (bifurcation at pain intensity 2).

3.3. Dimensions and clusters of chronicity markers

To investigate whether these variable relations between intensity and duration of pain in patients and employees are connected to the changing composition of chronicity indices, dimensional and cluster analyses including the marker sets of CPG and MPSS were calculated. In an initial step, overall correlations of intensity and duration with the source indices were considered.

3.3.1. Correlations of pain intensity and duration with CPG and MPSS

Pain intensity correlated moderately positively with both chronicity indices (Table 3). These associations were much lower when patients and employees were considered separately, and held also at the syndrome level for both cUBP and FMS patients. Table 3 illustrates that, contrary to expectation, duration correlated negatively with CPG and zero with the MPSS in patients, while CPG correlated zero and the MPSS correlated positively in employees. Similar inconsistent and weak correlations of pain duration with chronicity indices were repeated for the patient sample at the syndrome level, separately for cUBP and FMS patients. Corresponding intensity and duration frequency characteristics underlined these different relations to the chronicity indices in patients and employees. For instance, in patients, lower intensities were more frequent at grade III than at II and the intensity frequencies of grade II did not significantly differ from that of grade IV (supplementary material, Figs. S8 - S10). In employees, in contrast, intensity characteristics progressed with increasing CPG.
Complex relations of the chronicity indices held also for duration: In patients, contra-intuitively, longer durations were more frequent at the lowest CPG and shorter at the highest. In employees, however, duration characteristics across CPG grades resembled the expected sequence of longer durations with increasing grades more closely. The intensity and duration distributions for the MPSS showed a more systematic sequence from lower to higher intensities and from shorter to longer durations with progressive MPSS stages.

The different relation of CPG and MPSS to the primary pain properties intensity and duration shown above raised the question of their relation to each other. Accordingly, correlations differed largely between subgroups and were not significant in patients (Table 3). Frequency distribution analyses specified this (supplementary material, Figs. S11 and S12).

3.3.2. Exploratory factor analyses of the combined chronicity markers

When data of patients and employees were combined, exploratory factor analyses of pain intensity, duration and CPG/MPSS subscale values produced two principal components and principle axis factors accounting for 58.5% of the total variance (Table 4 C). The dominant first component (46.3%) was characterized by disability (CPG *disability score* and *disability days*), *pain intensity* (CPG intensity scale and MPI-D), MPSS scales *temporal characteristics* and *medication use*. The second component (12.3%) related closely to chronic development itself indicated by *duration* and MPSS scales *health care utilization/patient career* and *spatial aspects* (number of painful areas). The remaining 41.5% of the variance were distributed over seven non-significant components.

Table 4. Factor analyses of chronicity markers

(A) Pain clinic patients: 3-factor solution, 62.3% of total variance

Variable	Factor 1: 32.3% *Direct Consequences*		Factor 2: 15.5% *Clinical Characteristics*		Factor 3: 14.5% *Chronic Development*	
	PCA	PAF	PCA	PAF	PCA	PAF
CPG DD	**0.825**	0.768	–0.037	0.006	0.072	0.062
CPG DS	0.81	**0.778**	0.284	0.298	–0.077	–0.083
CPG PI	0.582	0.505	0.637	**0.703**	–0.125	–0.108
MPS MU	0.566	0.376	–0.091	0.023	0.059	0.023
MPI PI	0.454	0.356	0.678	0.7	–0.140	-0.097
MPS HC	0.353	0.296	0.029	0.056	0.763	0.588
DSF TO	–0.206	–0.162	0.027	–0.007	**0.819**	**0.591**
MPS SA	–0.097	–0.016	0.62	0.356	0.168	0.083
MPS TC	–0.065	–0.019	**0.742**	0.505	–0.005	0.006

(B) Employees: 2-factor solution, 47.12% of total variance

Variable	Factor 1: 33.6% *Clinical Characteristics & Direct Consequences*		Factor 2: 13.6% *Chronic Development*	
	PCA	**PAF**	**PCA**	**PAF**
CPG DS	**0.803**	**0.784**	0.123	0.132
CPG PI	0.785	0.751	0.172	0.195
MPI PI	0.748	0.654	0.182	0.252
CPG DD	0.64	0.5	-0.026	0.075
MPS TC	0.508	0.377	0.219	0.253
MPS MU	0.445	0.292	-0.014	0.12
MPS HC	0.211	0.147	0.69	**0.657**
DSF TO	0.053	0.085	**0.725**	0.447
MPS SA	0.025	0.109	0.616	0.258

(C) Patients and employees combined: 2-factor solution, 58.52% of total variance

Variable	Factor 1: 46.25% *Clinical Characteristics & Direct Consequences*		Factor 2: 12.27% *Chronic Development*	
	PCA	**PAF**	**PCA**	**PAF**
CPG DS	**0.837**	0.779	0.152	0.21
CPG PI	0.831	**0.827**	0.228	0.243
MPI PI	0.797	0.748	0.249	0.287
CPG DD	0.635	0.519	0.287	0.342
MPS TC	0.521	0.383	0.067	0.15
MPS MU	0.502	0.417	0.368	0.36
MPS SA	0.37	0.367	0.673	0.572
MPS HC	0.337	0.301	0.743	**0.732**
DSF TO	0.004	0.11	**0.836**	0.566

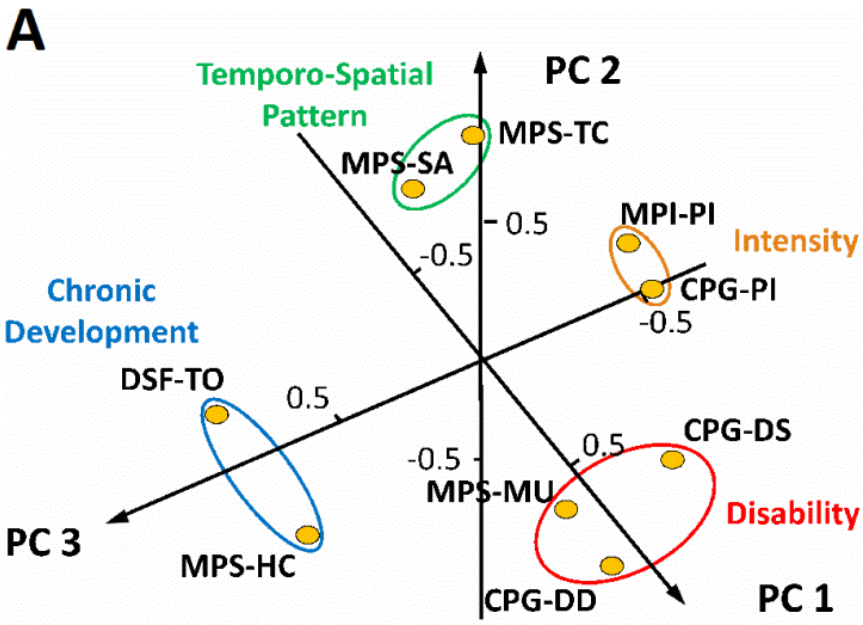
Notes: PCA = principal component analysis, PAF = principal axis factoring; VARIMAX rotated factor loadings. CPG DD = Chronic Pain Grade (CPG; [17]) disability days; CPG DS = CPG disability score (interference); CPG PI = CPG characteristic pain intensity; DSF DU = German Pain Questionnaire (DSF; [13]) duration (time since onset); MPI PI = West Haven-Yale Multidimensional Pain Inventory (MPI-D; [11]) present pain intensity; MPS MU = Mainz Pain Staging System (MPSS; [5]) medication usage; MPS HC = MPSS utilization of the health care system/patient career; MPS SA = MPSS spatial aspects; MPS TC = MPSS temporal characteristic. Shaded cells: the three highest loading items/scales used in CFA; bold numbers: highest loading for the factor.

The two-factors structure was replicated in the separate analysis for the employee sample (Table 4 B); a general common chronicity factor was not detected. However, when the patient data were analyzed separately, three rather than two significant principal factors explaining 62.3% of the variance were necessary (Table 4 A). Again, the dominant first component (32.3%) was best characterized by *disability*, *pain intensity* and *medication use*, but not by *temporal characteristics* of the pain symptoms. Moreover, *pain intensity* (CPG, MPI-D) loaded most on the second component (15.5%) together with *temporal characteristics* and *spatial aspects* (number of painful areas) independently of disability. The third component (14.5%) resembled the chronic development marked by duration (*time since onset*) and *health care utilization/patient career* similar to factor 2 in the pooled sample except for the *spatial aspects* (number of painful areas), which loaded mainly on the second component in the clinical sample. The stability of these principal dimensions at the syndrome level was checked by separate analyses for cUBP and FMS patients excluding the MPSS scale *spatial aspects* because of maximal values (≥ 3) in the latter (supplementary material, Table S2). The FMS data yielded three significant components explaining 69.2% of the variance mapping well onto the 3-factors structure for all patients. In contrast, the corresponding factor analysis for the cUBP group revealed four significant components accounting for 80.8% of the variance. Three of them were concordant with the previous analyses. An important exception consisted in *disability* scales forming a separate factor (extracted second) on their own.

The 3- and 2-factor models suggested by the exploratory factor analyses for patients and employees were tested by confirmatory factor analyses (CFA) using the three diagnostic markers with the highest PCA and/or PAF loadings (shaded cells in Table 4). The 3-factor model for patients was confirmed for non-orthogonal (correlated) factors with acceptable fit indices (corrected chi-square, $\chi^2/df < 3$). The 2-factor model for employees showed excellent fit (corrected chi-square, $\chi^2/df < 2$; RMSEA = 0.00; CFI = 1.00; supplementary material, Table S3).

In summary, no common factor of chronicity was found and dimensional structures of MSP chronicity patterns differed between patients and employees. The composition of the third factor in patients and the second factor in employees suggests that the dimensional structure of the related chronicity was varying with duration. Syndrome-specificity within the patient sample was only partially supported by the 4- vs. 3-factor solutions for cUBP and FMS patient data, respectively.

Qualitative inspection of mutual variable distances in factorial space suggested three conspicuous and clinically meaningful tentative clusters of chronicity markers (Figs. 2A, B; supplementary material, Fig. S13), which differed in important aspects between patients and employees. In patients, disability and intensity markers from the CPG and IASP Axis IV, on the one hand, and *spatial* and *temporal characteristics* from the MPSS, on the other hand, formed three separate groups of closely related variables. Duration (*time since onset*) and the MPSS variables *medication use* and *health care utilization/patient career* remained relatively isolated. In employees, in contrast, markers of the chronic development (*duration*, *healthcare utilization*/*patient career*) formed a cluster with *spatial aspects* (number of painful areas) while *temporal characteristics* grouped with *medication usage*. Interestingly, in the still active employees pain intensity clustered with the disability markers from the CPG (Fig. 2B, at the right).



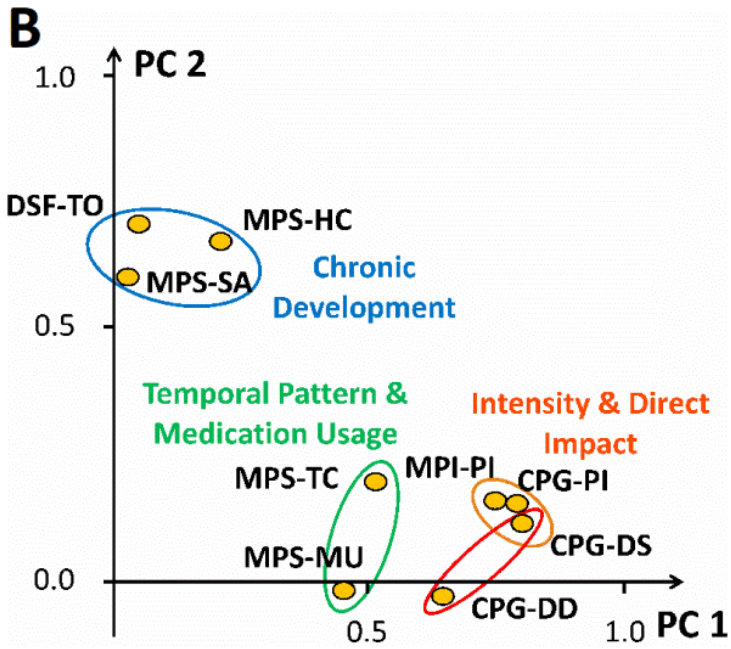
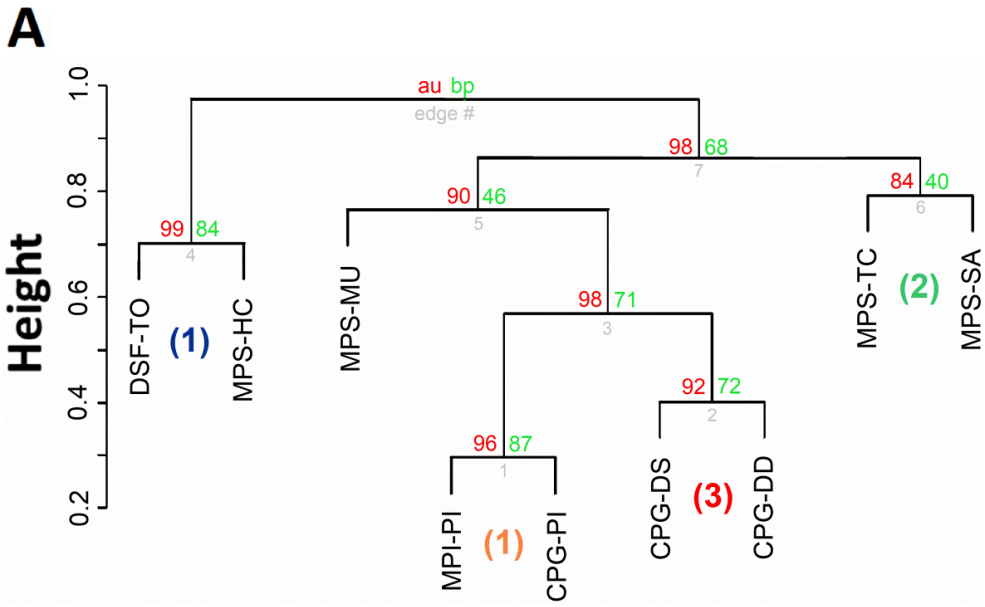


Figure 2: *Dimensions of pain and chronicity markers in clinic patients and employees.*
*(**A**) Patients: Three principal components in relation to main markers and associated variables, symbols as in Table 4: PC 1, Direct Consequences, marked by "disability days" and "disability score (interference)" of the CPG; PC 2, Clinical Characteristics, marked by "pain intensity" and "temporal" and "spatial aspects" (number of painful areas) of the MPSS; PC 3, Chronic Development, marked by "duration (time since onset)" of the DSF and "health care utilization" from the MPSS. Descriptively, four clusters (elliptic frames) of variables may be identified by their distances in the 3D vector space including associated variables with moderate loadings on more than one principal component, labelled tentatively as (1) "intensity cluster", (2) "temporo-spatial pattern cluster", (3) "disability cluster" and (4) "chronic development". (**B**) Employees: Two principal components in relation to main markers and associated variables, symbols as in Table 4: PC 1, Direct Consequences & Clinical Characteristics, marked equally strong by pain intensity and disability variables of the CPG and MPI-D; PC 2, Chronic Development, marked by "duration (time since onset)" of the DSF and "health care utilization/patient career" from the MPSS as in patients. Three descriptively defined clusters of variables differing from those in patients: (1) intensity and disability variables now closely related except for "disability days" of the CPG, all mainly loading on PC 1; (2) "temporal pattern and medication usage", also near PC 1; (3) a cluster "chronic development" including duration and health care utilization related to the MPSS variable "spatial aspects" (number of painful areas).*

3.3.3. Hierarchical Latent Class Analysis of Chronic Pain Markers

The clinically meaningful clustering of variables apparent in the distance mapping of principal pain markers in two- and three-dimensional factor space was cross-examined by hierarchical latent class analyses (LCA) for patients and employees, separately and combined. In the LCA two super-clusters of variables could be distinguished in both patients and employees analyzed separately (Fig. 3) according to the 95%-AU criterion.

Cluster 1 comprised scales related directly to the chronic development as such (*duration/time since onset*, *healthcare utilization/patient career*), while Cluster 2 contained clinical characteristics (*intensity*, *temporal* and *spatial aspects*) and direct consequences of the pain (*disability score* and *disability days*) together with *medication usage* (Figs. 3A, B). Intensity and the direct consequences (disability) were strongly interconnected within a coherent sub-cluster itself connected only weakly with *medication use*. *Temporal characteristics* and *spatial aspects* formed a second less coherent sub-cluster (AU criterion > 80%). This cluster structure was replicated in single analyses for cUBP and FMS patients and for employees analyzed alone, although the cluster pattern for the latter was somewhat less differentiated and *spatial aspects* did not cluster (supplementary material, Fig. S14).



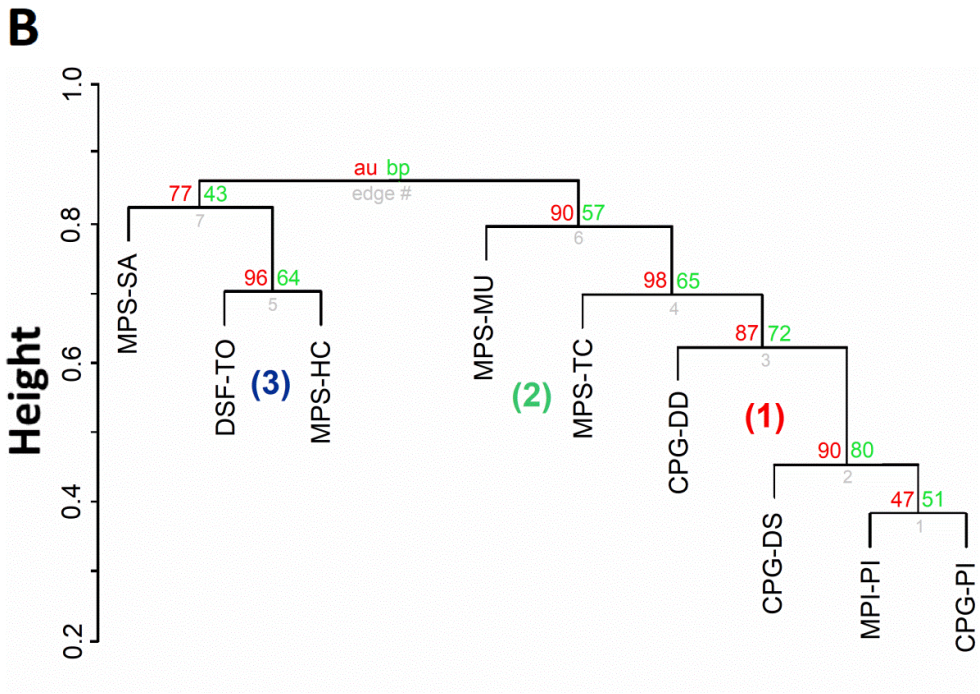


Figure 3: *Clusters of chronic pain markers of clinic patients and employees at the subscale level. Dendrograms of variable clusters according to latent class analyses of all pain markers of present pain intensity, duration (time since onset) and chronicity scales (CPG, MPSS); multiscale bootstrap resampling technique [33]. Red and green numbers AU/BP (arbitrary unbiased/bootstrap probability) values of significant clusters (AU ≥ 95% significant). Symbols as in Table 4 and Fig. 2; numbers in parentheses refer to tentative descriptive clusters in Fig. 2. (**A**) Patients: Two super-clusters representing (1) Chronic Development (left dendron) separated from (2) Pain Intensity, Clinical Characteristics and Direct Consequences which related more closely to each other (right dendra): The MPSS marker "healthcare utilization/patient career" (MPS-HC) clustered with "duration (time-since-onset)" (left dendron; AU/BP = 99/84) as in the PCA (Fig. 2). Within the second dendron at the right sub-clusters of Pain Intensity and of Disability were detected (AU/BP = 98/71). "Temporal characteristic" (MPS-TC) and "spatial aspects" (MPS-SA) were separated from all other variables of supercluster (2) (AU/BP = 84/40). (**B**) Employees: Two super-clusters of variables appeared also in the data of employees similar to those in patients, but less clearly defined and some variables grouping differently: (1) As in patients, "duration (time since onset)" and "healthcare utilization/patient career" clustered strongly together, but "spatial aspects" (MPS-SA, left-most) complicated the picture. (2) The second dendron (right) represents a super-cluster of pain severity with Clinical Characteristics similar to that in patients as well as with Direct Consequences. The general cluster structure is less well defined, mainly because of instable groupings of MPSS variables, but disability and intensity variables remained closely related as in the factor analyses.*

4. Discussion

The reported studies applied a multimethod approach to reappraise the generality of the pain chronicity construct in musculoskeletal pain by characterizing the composition and internal structure of frequently used chronicity indices (IASP Axis IV, CPG, MPSS). Two exemplary samples from model populations of patients and a nationwide sample of employees at risk for chronic MSP and currently in pain from two multicenter studies were compared in a cross-sectional retrospective study. The combined entrance data of established instruments for the assessment of chronic pain were analyzed by frequency distribution, correlational, factor and cluster analyses. Three hypotheses were tested assuming intensity-, duration-, population- and syndrome-dependent internal relations between chronicity characteristics with variable composition and dimensional structures.

Hypothesis 1: Non-linear, population-specific relations between *intensity and duration*

Intensity-duration correlations differed qualitatively and had opposite signs in patients (negative) as compared to the employees (positive). Patients reported lower pain intensities after longer rather than shorter pain duration, while employees recorded the lowest intensities at durations below six months. Non-monotonic shifts of intensity distributions over successive duration categories suggest that the process of pain becoming chronic is not uniform at all times and that it depends on individual circumstances. The inverse relation of pain severity to duration in patients could not have been due to more effective medication with longer treatment because the current medication was limited by the strict inclusion criteria and controlled by medication records. Instead, we assume that non-medical factors like long-term adaptation to prevailing pain, anchoring effects on scale responses, and/or change in coping caused this state of affairs. In contrast, a monotonic intensity-duration relation prevails in employees at lower intensity and shorter pain durations but this relation disappears at longer pain durations in a subgroup.

Hypothesis 2: Monotonic relations of pain intensity-duration are more pronounced in chronic unspecific back pain compared to widespread pain.

Contrary to hypothesis 2, syndrome-specific intensity-duration relations were not found in patients. This may be partially due to generally low overall intensity-duration correlations and/or low power because of low and unbalanced frequencies in several

intensity and/or duration categories. However, the general trend of lower pain intensities with longer durations in patients was stronger in FMS than in cUBP (negative correlations, shift to lower intensities). This suggests a difference in the intensity-duration relation in widespread pain compared to regional pain possibly due to more pronounced long-term adaptation. However, the variability in symptom pattern and development and, in particular, of comorbidities of the FMS group may have obliterated the differences. Furthermore, there is evidence for an increase in pain loci in cUBP and gradual development of concurrent widespread pain over time [32, 33], but this would require a longitudinal analysis to clarify. As there is evidence for different underlying mechanisms in both syndromes [33], it remains to be seen whether specific intensity trajectories can be differentiated between MSP subsyndromes.

The complex picture of pain intensity developing unevenly with duration had not been in focus previously and mostly global correlations with variable duration categories have been considered. In part, this may explain the inconsistent intensity differences found between different times since onset (e.g., [34]) and weak or absent relations of intensity as well as duration to global chronicity indices (CPG, MPSS: [4, 5, 35-37]).

Our results add to these findings demonstrating that the correlation of intensity and duration with each other and with chronicity indices depend on the group considered and possibly also on the MSP syndrome. The results indicate a dynamic interrelation between severity and duration changing from early to later stages and over the life span. This dynamic interaction may not be completely captured by the chronicity indices we examined. In the case of the CPG, this may be due to its scale construction based on IRT, which selects items to form a weakly monotonous (homogeneous) scale [4]. In consequence, pain intensity is not scoring above grade II. However, we showed that the prevailing pain intensity may still have a significant impact on the patient's degree of suffering during the further chronic development although manifest disability may grow over time decoupled from severity [38]. The chronicity aspect of suffering, although clinically important, may be overlooked by using one-dimensional chronicity indices emphasizing disability. We assume that the extent of *suffering* expressed in the pain intensity report remains a relevant dimension of pain becoming chronic also in later stages, for treatment decisions and success or relapse through reconditioning [39]. This was further specified by the factor and cluster analyses.

Hypothesis 3: There is no common factor of chronicity but multiple dimensions differing between populations and syndromes.

The convergent results of the structure finding approach with factor and cluster analyses demonstrate that chronicity is indeed not a homogeneous construct, but composed of the clinically relevant components of pain, that is, severity, clinical picture and history apart from disability, which are not easily condensed in one single scalar score. Furthermore, the composition is not invariant across subgroups with MSP and may differ between localized and widespread pain. This further limits the scope of global pain chronicity indices despite indirect validation by reports of significant correlations with other health domains such as, general health and well-being (e.g., SF- 36; [40]).

Our data suggest that a minimum of three independent marker sets is necessary to grasp the chronicity spectrum of chronic MSP in different subpopulations. This includes (1) primary clinical characteristics, at least, intensity and spatial and temporal extension; (2) direct consequences of current interference with daily functioning; (3) characteristics of the chronic development such as duration, health care utilization and patient career including medication and treatment history. However, it remains unclear where instrumental aspects, like pending compensation and/or early retirement would fit in, because sufficient data were not available. Based on previous studies [41] we expect that these variables would either cluster with the third major component or form a separate cluster of characteristics.

Thus, it is not surprising that different indices reconstruct chronicity differently and we find generally weak and population-specific intercorrelations between the CPG and MPSS. This is in accordance with previous research emphasizing qualitative differences between various chronicity indices [42]. We expect that other indices not considered here such as those derived from the Örebro Musculoskeletal Pain Questionnaire [43] or the Heidelberg Short Questionnaire [44] might show similar deviations.

Limitations

The generalizability of our results is limited because of the special samples and their recruitment. They were not drawn randomly from the underlying population, but selected by the consent to collaborate of the outpatient clinic or center and the patient or participant. The sample of employees was restricted to the nutritional industries and

gastronomy businesses. However, this should not compromise the core results nor the soundness of the conclusions since these were exemplary cases.

A more serious limitation concerns the necessarily different base distributions of intensity and duration in patients and employees, but it was central for the study to obtain datasets covering the full range of severity, duration and impairment. This was partially compensated by sufficient overlap in intensities but less so in durations. These limitations preclude representativeness for the general MSP population and the syndromes selected, but this was not an aim of this study. The primary aim of the study to differentiate intrinsic structural properties of extant indices and their population-specific composition should not have been impaired by these limitations.

5. Conclusions

The study shows that Chronicity of musculoskeletal pain is no coherent general construct, inherently multifactorial and composed of independent components varying in weight with severity and duration, in different groups and, possibly, in different pain syndromes.

6. Implications

Our results have implications for research and clinical applications as they underline that there is no unique way of assessing chronicity, over the entire range of severity and durations of the pain disorder for all pain populations. The conceptualizations of “chronicity“ implied by current indices underestimate the complexity of the development of chronic pain. Chronicity evaluation should be designed specific to the population, the diagnostic context, clinical or occupational, and the particular syndrome of musculoskeletal pain, in particular, of regional vs. widespread pain. We recommend 3- to 4-dimensional (multivariate) instead of global scalar indices in assessing the chronicity of musculoskeletal pain. They should comprise the core components of chronic pain that have emerged as essential aspects from our and previous analyses of extant indices, i.e., the primary clinical characteristics with severity, spatial and temporal extension, the direct consequences of current interference with daily activities, as well as aspects of the chronic development, in particular, duration, health care utilization and patient career including medication and treatment history. Further analyses of time- and population-specific compositions of chronicity are needed, which include characteristics of pain processing, for example, altered pain sensitivity and

topography at later stages. The result of our cross-section analysis of three chronicity-coding schemes is suggestive, but requires further support with longitudinal data from a cross-validation sample including other pain syndromes with distinctly different clinical pictures and high chronicity potential such as neuropathic pain.

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Author’s statements

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Conflicts of interest

The authors declare that there are no conflicts of interest associated with this manuscript.

Informed consent

All participants were informed of the purpose of research and gave their informed consent.

Ethical approval

The study was approved by the Local Ethics Committee. Patient data were partially acquired in connection with a clinical trial of combined behavioral and cannabinoid treatment for chronic pain (ClinicalTrials.gov Identifier: NCT00176163). The prevention program for the employees was conducted by the nutritional business and gastronomy section of the German employers' liability insurance association (Berufsgenossenschaft Nahrungsmittel & Gaststätten, BGN) according to legal regulations.

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2.2 Reclassifying patients with widespread and regional musculoskeletal pain by sensory and clinical phenotypes: Principal components and latent class analyses of multimethod data from pain clinic patients with prior FMS and cUBP diagnoses[2]

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Abstract

Background: Differentiating chronic unspecific widespread and regional musculoskeletal pain syndromes has been plagued by controversial discussions of pathognomonic clinical criteria and sensory phenotypes related to mechanisms of chronic pain. The problem has crystallized recently particularly around the repeated revisions of fibromyalgia criteria since the first ACR version of 1990. In the latest versions, sensory characteristics such as number of “tender points” have been discarded and additional symptoms such as fatigue and depression were added to distinguish the syndrome from other widespread pain and chronic unspecific regional pain with several pain loci. The present study examined the justification of these diagnostic shift, re-examines the diagnostic value of altered pain sensitivity and aims to identify circumscribed pain sensory-clinical phenotypes in patients with classical fibromyalgia syndrome (FMS) and chronic unspecific back pain (cUBP). We hypothesized that intermediate states exist between these exemplary syndromes of widespread and regional pain with different combinations of sensory and clinical phenotypes.

Methods: Sensory and clinical characteristics of 185 patients with prior diagnoses of FMS and cUBP having participated in a multicenter study on chronic pain mechanisms were reanalyzed retrospectively. Combined sensory-clinical phenotypes were derived by a stepwise data-reduction through descriptive statistical, correlational, principal components and latent class analyses of primary data (PCA, LCA). Patients were reclassified according to their sensory-clinical phenotypes of pressure pain sensitivity combined with severity and spatial spread of the clinical pain. LCA clusters were cross-validated by linear discriminant analysis. The resulting clusters were compared with respect to further pain characteristics, chronicity, somato-psychic comorbidity and psychosocial factors.

Results: Four clusters of patients with different sensory characteristics and clinical markers were identified requiring four pressure pain sensitivity markers (number of sensitive ACR tender and control points, test pain intensity and pressure pain threshold) and two clinical pain characteristics (pain regions, present pain intensity). Two clusters were closely related to the prior diagnoses of classical FMS and cUBP, respectively. The other two clusters represented clusters with intermediate pressure sensitivity and mixed pain related to FMS and cUBP. Subsequent discriminant analysis revealed that three discriminant functions of pressure sensitivity markers sufficed to

discriminate between these coherent clusters with a high correct rate. These sensory-clinical phenotypes differed mainly in functional somatic symptoms and impairment but neither in psychopathology nor in psychosocial co-factors.
Conclusions: An indicator set of four sensory and two clinical essential markers is apt to identify subgroups of patients with distinguishable sensory-clinical pain phenotypes. Sensory phenotyping should be retained in the diagnostic assessment in addition to the clinical pain picture while secondary psychopathology and psychosocial chronicity factors do not add to differential diagnosis of widespread pain.

Keywords: Pain Phenotypes; Widespread Pain; Fibromyalgia; Musculoskeletal Pain; Latent Class Analysis.

1 Introduction

1.1 Multiple pain loci, chronic widespread pain (CWP) and fibromyalgia (FMS)

Differentiating syndromes of chronic unspecific musculoskeletal pain has been subject to controversial discussions since decades (Clauw, 2015; Mense & Gerwin, 2010). This problem has not been addressed so far by the superordinate category of “chronic primary pain” of the IASP classification of chronic pain for ICD-11 (Nicholas et al., 2019). Distinguishing patients diagnosed with “fibromyalgia syndrome” (FMS) from others suffering of “chronic widespread pain” (CWP) and persons with regionally confined pain at multiple loci, in particular, chronic unspecific back pain (cUBP), is still subject to debate despite intensified large scale epidemiological research (Gerhardt et al., 2016; Hardt, Jacobsen, Goldberg, Nickel, & Buchwald, 2008; Mease, 2005; Viniol et al., 2013)

Recent revisions of the classical ACR criteria of FMS (Wolfe et al., 2010; Wolfe et al., 2011; Wolfe et al., 2016) have centered on CWP as the obligatory core characteristic of FMS and abandoned the sensory criterion of enhanced pressure sensitivity in a minimum of 11 of 18 “tender points” (Wolfe et al., 1990). CWP was originally defined as persisting pain in all four body quadrants plus the axis and is now operationalized by the Widespread Pain Index (WPI) developed out of the Regional Pain Scale (Wolfe, 2003). For the FMS diagnosis pain in four sites in at least four out of five body regions covered by a WPI ≥ 7 or 4 – 6 is required depending on the symptom severity measured by the Symptom Severity Score (SSS; Wolfe et al., 2016). Both scores are combined in the Fibromyalgia Symptom scale (FS; 0 – 31). A cutoff of FS ≥ 12 was found to discriminate patients meeting the ACR 1990 criteria from those with regional musculoskeletal pain without recourse to the original sensory indicator of spatially distributed pressure hypersensitivity (Häuser et al., 2012). Notably, the SSS addresses abdominal pain and additional symptoms of unrefreshing sleep, fatigue, cognitive symptoms as well as depression.

It is debatable whether the resulting purely clinical FMS criteria are apt to define a clinically coherent and pathogenetically meaningful diagnostic entity. For instance, many cUBP patients show an increase in pain loci and the gradual development of concurrent widespread pain (Forseth, Husby, Gran, & Forre, 1999; Lapossy, Maleitzke, Hrycaj, Mennet, & Müller, 1995). There appears to be a continuum between “regional”

and “widespread pain” rendering categorical distinctions by empirical cutoffs problematic, not to speak of comorbid combinations of both.

Moreover, it may be argued that this development has created a different, incoherent nosological FMS entity altogether, with a number of problematic consequences such as symptom overlap with psychiatric disorders (Gracely, Ceko, & Bushnell, 2012) and secondary shift in gender prevalence (Vincent et al., 2013). The inclusion of comorbid depression and depression equivalents like sleep disorders is apt to compound chronic unspecific musculoskeletal pain with circumscribed psychiatric disorders and stigmatizes patients whose primary problem is the chronic pain disease which should be the center of diagnostic evaluation and treatment. The problem of inflation of comorbid diagnoses by inhomogeneous diagnostic criteria is well-known from other disease classification (American Psychiatric Association, 2013; World Health Organization, 1992) and has hindered the development of differential diagnosis on the basis of pathogenetic mechanisms (cf. the recent discussion of the IASP category of chronic primary pain: Henningsen, Layer, Fink, & Häuser, 2019; Rief et al., 2019).

In fact, the current controversies on diagnostic criteria (“Are the ACR 2010 diagnostic criteria for fibromyalgia better than the 1990 criteria?”; Sarzi-Puttini et al., 2018) support the suggestion of subgroups of CWP including FMS with different underlying pathogenesis which cannot be discriminated by clinical indicators from each other and from patients with chronic musculoskeletal pain in multiple regions and additional somatic symptoms. This is corroborated by well documented differences between FMS patients with and without functional disorders other than pain, e.g., cardiac or gastrointestinal complaints. This cautions against using comorbid disorders of other domains to differentiate between CWP syndromes (Becker, Kleinböhl, Baus, & Hölzl, 2011; Cole, Rothman, Cabral, Zhang, & Farraye, 2006; Georgescu et al., 2018).

1.2 Diagnostic significance of sensory aspects of CWP and the specificity for FMS

Focusing on non-sensory facets of the pain response such as suffering, coping and immediate consequences of the pain to differentiate a core syndrome of FMS avoids the comorbidity trap (Thieme, Turk, Gracely, Maixner, & Flor, 2015) but may be of limited value in uncovering changes in primary pain perception as an underlying causal factor. From a mechanistic view, therefore, abandoning direct sensory assessment could lead to overlook genuine peripheral and/or central nociceptive sensitization

leading to enhanced deep pain sensitivity in at least part of the FMS patients (cf. Mense, 2008; Oaklander, Herzog, Downs, & Klein, 2013). Besides, the early studies suggesting specific changes in pressure sensitivity in “tender points” proximal to muscle-tendon junctions to be related to peripheral myofascial hypersensitivity have not been disproved so far (Simons, 1975, 1976; Smythe & Moldofsky, 1978). Thus, the involvement of sensory enhancement in a core group of FMS and the relation of regional hypersensitivities to pain loci in CWP in general remain open questions.

1.2.1 Hyperalgesia to pressure stimulation

Therefore, dispensing with assessment of pressure hypersensitivity at the ACR “tender points” because practitioners may have neglected or assessed them not reliably by the manual probing (Cott et al., 1992; Fitzcharles & Boulos, 2003; Wolfe et al., 2016) may have been premature. The diagnostic relevance of the spatial distribution of hypersensitivity to pressure stimuli in addition to the number of spontaneously painful body sites can only be decided on the basis of adequate sensory testing as established in the last decades exemplarily for neuropathic pain (Baron et al., 2017) and relating the sensory parameters to current clinical diagnostic criteria. Patients at the transition between regional and widespread pain not fulfilling FMS criteria could not be classified correctly without considering sensory aspects of their pain and the spatial distribution of their sensitivity to pressure stimulation.

The relevance of precise sensory characterization of the pain symptomatology and the related pain sensitivity in different body regions is supported by the finding that “tender points” are often associated with myofascial trigger points (Ge et al., 2009; Ge, Wang, Danneskiold-Samsoe, Graven-Nielsen, & Arendt-Nielsen, 2010) suggesting a related peripheral etiology possibly driving subsequent central sensitization in FMS despite some differences between tender vs. trigger points in terms of response to stimulation and origin (Mense, 2011). Enhanced sensitivity to pressure pain of FMS patients can be distributed to some degree across the whole body, is not limited to ACR “tender points” and may occur also in control points (Granges & Littlejohn, 1993; Wolfe, 1998). It is not clear whether such distributed enhanced pressure sensitivity is limited to FMS or whether it may be observed also in patients with chronic pain in multiple regions but not fulfilling the FMS criteria (Gerhardt et al., 2016).

1.2.2 Modality specificity of hyperalgesia in widespread and regional pain

There is evidence that FMS patients are hypersensitive not only to pressure, but also to other stimulus modalities, e.g., heat, and this was not limited to ACR tender points (Gracely, Grant, & Giesecke, 2003). Whether such generalized hyperalgesia would differentiate regional and widespread pain is not known (Uddin & MacDermid, 2016). Multimodal quantitative sensory testing (QST) has produced inconsistent findings on a common (cross-modal) factor of pain sensitivity (Neddermeyer, Fluhr, & Lotsch, 2008) in contrast to multiple modality-specific sensitivities (Neziri et al., 2011). However, FMS patients have shown increased heat pain sensitivity possibly related to impaired descending inhibitory control when compared to regional pain such as chronic unspecific back pain (Gerhardt et al., 2016; Horn-Hofmann, Kunz, Madden, Schnabel, & Lautenbacher, 2018; Julien, Goffaux, Arsenault, & Marchand, 2005).

1.3 Psychosocial factors and somato-psychic comorbidity of widespread pain

The role of psychosocial factors in chronic unspecific musculoskeletal pain has long been established, social stress and the response of significant others being important (Flor, 2017; Flor, Kerns, & Turk, 1987; Thieme, Gromnica-Ihle, & Flor, 2003; Thieme, Spies, Sinha, Turk, & Flor, 2005). Affective comorbidity and associated distress play a key role in the determination of functional impairment of CWP/FMS compared to patients with regional pain (Häuser, Schmutzer, Brähler, & Glaesmer, 2009). Patients with CWP have repeatedly shown to have higher rates of somatic symptoms and depression than patients with regional pain (Viniol et al., 2013). Poor mental and physical health increases the risk to develop chronic musculoskeletal pain in general (O'Neill et al., 2018). In FMS, but also in cUBP depressive symptoms contitute the major part of psychic comorbidity, anxiety being less important (Bletzer, Gantz, Voigt, Neubauer, & Schiltenwolf, 2017; Roch, Follmer, & Hampel, 2017). It had been shown earlier that adding fatigue symptoms, also a marker of major depression, to pain symptoms improved the differentiation of clinically defined FMS from rheumatic arthritis (White, Harth, Speechley, & Ostbye, 1999). However, it is difficult to disentangle the role of these important comorbidity factors from that of basic mechanisms of enhanced pain sensitivity after including them into the defining criteria of the “FMS” entity in the first place. Relying on a more differentiated clinical picture of CWP alone, however, may also not lead to pathogenetically discernable subsyndromes of chronic unspecific musculoskeletal pain. For example, including “pain or cramps in lower abdomen” as in

the recent revision of the FMS criteria (page 326; Wolfe et al., 2016) creates a high, partly spurious, comorbidity with functional gastrointestinal disorders as repeatedly reported. Moreover, this hampers the differentiation of MSP from visceral pain syndromes and the identification of common pathogenetic factors such as central sensitization (Costantini, Affaitati, Wesselmann, Czakanski, & Giamberardino, 2017). Mechanism-oriented diagnostic classification would rather require a systematic comparative assessment of sensory and clinical characteristics of exemplary syndromes of widespread and regional pain and the structural analysis of their interrelations with comorbid symptoms and well-known psychosocial determination factors.

1.4 Aims, research questions and hypotheses

We assume that there is a continuum from regional to widespread pain in chronic unspecific musculoskeletal syndromes with respect to numbers of regions in pain and degrees of severity and impact. Trying to differentiate the distinct syndrome of fibromyalgia from other chronic musculoskeletal pain with multiple pain loci by combining these gradually varying indicators with secondary, not directly pain-related properties, particularly, psychosocial factors and somatic or psychic comorbidity may be insufficient. Ignoring sensory aspects of pain sensitivity and its spatial distribution across body regions may, in fact, obscure phenotypical subgroups with different underlying pain mechanisms for which different treatments should be appropriate.

The present study aims to clarify these issues by reclassifying patients from two model populations for widespread vs. regional pain with prior diagnoses of FMS or cUBP into subgroups with distinguishable pain phenotypes by combining the clinical picture with comprehensive sensory characterization and structure finding statistical methods. Subsequently, these phenotypes were to be compared to each other and to prior diagnoses with respect to clinical significance relative to chronicity and functionality, psychosocial stress load and psychosomatic comorbidity.

Clinical pain was assessed in terms of intensity and spatial spread supplemented by sensory testing of pressure and heat pain sensitivity including temporal summation to identify modality- and/or region-specific phenotypes in relation to prior diagnosis groups. For this purpose, the complete arrays of sensory indicators of 32 sites in 9 body regions and 10 clinical pain variables were statistically reduced to optimal sets of

discriminators by principal components and cluster analysis aiming at sufficient power for reclassification.

We hypothesized:

(1) FMS and cUBP patients may be further differentiated into subgroups with characteristic sensory phenotypes with respect to the intensity and spatial distribution of pressure pain sensitivity as measured by manual probing and/or quantitative sensory testing.

(2) The total number of hypersensitive body sites and their spatial spread or regional restriction indicates a more or less generalized pressure (mechano-/muscle-nociceptor) hypersensitivity which is characteristic for pathogenetically different subgroups of FMS and cUBP. Specific “tender points”, the previous cardinal indicators of FMS, are not qualitatively different from “control points” at other muscle or soft tissue body sites and provide no better differentiation than the total number of hypersensitive body sites.

(3) There is a substantial overlap in degree and spread of hypersensitivity to pressure stimuli which can be related to a “transition” stage between FMS and cUBP with overlapping numbers of pain loci and differentiable by combined sensory and clinical phenotyping.

(4) Combined sensory and clinical phenotypes identified by structure-finding classification methods (latent class analyses) differentiate subgroups of widespread and regional pain with different pain mechanisms, somatic and psychic comorbidity and psychosocial co-factors better than the global diagnostic categories of FMS and cUBP.

(5) Generalization of sensory hypersensitivity to other modalities such as heat pain forms a discernible phenotype of enhanced secondary pain processing within the diagnostic groups.

(6) Cross-modal generalization of pressure pain sensitivity to heat pain may characterize a subgroup of FMS patients with impaired descending inhibitory control marked by the dynamic wind-up response (temporal summation) to tonic stimulation.

2 Method

2.1 Participants

The present study is based on the initial assessment of sensory and clinical pain characteristics of patients with musculoskeletal pain participating in a collaborative

multicenter project on plasticity and learning in pain becoming chronic. Our group has previously reported results of the project with respect to the composition of pain severity and duration, interference and chronicity specific to musculoskeletal pain (details on sample in: Finnern, Kleinböhl, Flor, Benrath, & Hölzl, 2018). As for the previous study, patient data were partially acquired in connection with a clinical trial of combined behavioral and cannabinoid treatment for chronic pain (ClinicalTrials.gov Identifier: NCT00176163). The reanalysis was approved by the Local Ethics Committee. Patients were eligible for the study if they reported musculoskeletal pain for at least three months. Exclusion criteria were current psychotic disorders and substance abuse, disorders of the central nervous system, infectious and autoimmune diseases as well as current use of neuroleptics and benzodiazepines or mood-stabilizers. Patients with major depression or anxiety disorders remained in the sample because affective comorbidity was a research question. Self-reported life-time medical diagnoses were recorded for control purpose showing a relative preponderance of past somatic diagnoses in FMS patients but apparent differences were not related to their pain symptoms (cf. Table S1 in Supplemental).

According to the inclusion criteria of the previous study, 185 patients with clinically relevant pain in at least one body region for longer than six months were included. The majority (65.4 %) had pain for longer than 5 years. At entrance, 78 patients had a prior diagnosis of fibromyalgia (FMS ACR criteria: 11 out of 18 tender points; Wolfe et al., 1990); 107 patients fulfilled criteria for chronic unspecific pain (cUBP) which required that pain in upper or lower back was the primary problem and was not related to acute trauma, inflammatory or neurologic disease, radicular and neuropathic signs absent. Table 1 gives an overview of the sociodemographic and chronicity data of patients.

Table 1. Sociodemographic, clinical and chronicity data

(A) Sociodemographic characteristics

	FMS: N = 78	cUBP: N = 107	Healthy controls: N = 41
Age [yrs.]			
Mean ± SD	50.8 ± 9.5	48.3 ± 12.2	48.9 ± 8.8
Range	23 – 68	18 – 68	23 – 69
Sex		N (%)	
Female	73 (93.6)	69 (64.5)	30 (73.2)
Male	5 (6.4)	38 (35.5)	11 (26.8)
Education		N (%)	
up to college level	62 (79.5)	77 (72.0	26 (63.4)
University	11 (14.1)	19 (17.8)	13 (31.7)
Missing	5 (6.4)	11 (10.3)	2 (4.9)
Work		N (%)	
Working	26 (33.3)	46 (43.0)	25 (61.0)
Not working	47 (60.3)	51 (47.7)	6 (4.9)
Missing	5 (6.4)	10 (9.3)	10 (24.4)

Notes. Absolute numbers, % in brackets; varying N due to missings

(B) Chronicity data

	FMS: N = 78	cUBP: N = 107
Duration]mths] [a]	N (%)	
]0-6]	0 (0.0)	0 (0.0)
]6-12]	2 (2.6)	7 (6.5)
]12-24]	4 (5.1)	8 (7.5)
]24-60]	14 (18.0)	15 (14.0)
> 60	53 (68.0)	68 (63.6)
Missings	5 (6.4)	9 (8.4)
Mean ± SD	50 ± 25	48 ± 32
Median ± ½ IQD	60 ± 18	60 ± 18
Chronic Pain Grade [b]	N (%)	
Grade I	13 (16.7)	32 (29.9)
Grade II	6 (7.7)	7 (6.5)
Grade III	14 (18.0)	19 (17.8)
Grade IV	23 (29.5)	16 (15.0)
Missings	22 (28.2)	33 (30.8)
Mean ± SD	2.8 ± 1.2	2.3 ± 1.2
Median ± ½ IQD	3.0 ± 1.0	2.0 ± 1.0

[a] *Duration categories in left-open/right-closed intervals]…] (excluding first, including second limit).*
[b] *Chronic Pain Grade (CPG; Korff, Ormel, Keefe, & Dworkin, 1992).*
Differences between FMS and cUBP (U-test & K-S test): duration n. s.; CPG n. s.

Sex ratio differed between FMS and cUBP according to the base rates in the clinical population consecutively recruited by the regional pain clinics participating in the collaborative research focus program. However, the frequency of prior diagnoses of FMS and cUBP were balanced in females to control sex bias. Other variables pertinent to the present research questions such as education and work situation were also matched. In particular, duration and Chronic Pain Grades (CPG; Korff et al., 1992) did not differ significantly between FMS and cUPB patients in the clinical population (cf. Finnern et al., 2018). Structural main analyses focused on within-group associations of sensory and clinical pain indicators and are neutral against selection effects. Data of N = 41 healthy controls (gender and age matched) with no clinically relevant pain assessed in the clinical trial served as reference for the sensory data of patients.

Further details on recruiting, exclusions and dropouts, sociodemographic and diagnostic data were reported in the previous study.

2.2 Clinical pain assessment

Clinical pain was assessed with a comprehensive battery of validated questionnaires. It consisted of the German version of the Westhaven-Yale Multiphasic Pain Inventory (MPI-D; Flor, Rudy, Birbaumer, Streit, & Schugens, 1990), the German Pain Questionnaire (Deutscher Schmerzfragebogen, DSF; Nagel, Gerbershagen, Lindena, & Pfingsten, 2002), the Pain Perception Scale (Schmerzempfindungsskala, SES; Geissner, 1996), the Fibromyalgia Impact Questionnaire (FIQ; German version: Offenbächer, Waltz, & Schöps, 2000; original version: Burckhardt, Clark, & Bennett, 1991) and the Hannover Functional Ability Questionnaire (FFbH-R; Kohlmann & Raspe, 1996). In addition, pain-related cognitions and coping with pain were assessed by the German version of the Pain-Related Self-Statements Scale (FSS; Flor, Behle, & Birbaumer, 1993) and fear-avoidance-beliefs with the Fear-Avoidance-Beliefs Questionnaire (FABQ; subscales “work as cause”, “return to work prognosis”, “physical activity”; Pfingsten et al., 1997).

Pain loci were extracted from the DSF with respect to current pain sites (item #20) and major pain (item #21). Reported pain localizations were aggregated into 9 regions according to Axis I of the IASP Taxonomy of chronic pain (IASP Taxonomy Working Group, 2017) and into 19 regions for the Widespread Pain Index (WPI, regions as stated in the Fibromyalgia Survey Questionnaire, FSQ; Häuser et al., 2012), the survey version of the FS scale (Wolfe et al., 2016; cf. Table S2 for the concordance of locularity and regionality definitions in Supplemental). A further question applied concerned “pain all over my body” for non-localized pain.

2.3 Sensory testing

2.3.1 Pressure pain sensitivity

2.3.1.1 Manual tender point probe

Sensitivity to pressure stimuli was assessed semi-quantitatively by a standardized manual probe at 18 “tender points” and 14 control sites adapted from Wolfe et al. (1990) and Okifuji, Turk, Sinclair, Starz and Marcus (1997) applied by trained physicians adhering to about 1 kp/cm2/s up to 4 kp/cm2 maximum pressure (Figure

S3 in Supplemental). Subjective pain intensity at endpoint was rated by a numerically anchored visual analogue scale from no to worst pain (VAS, 0 – 10). In order to represent the complete sensitivity range all over the body, the lean criterion of VAS ≥ 1 was applied to define a sensitive point.

In addition, the spatial distribution of pressure sensitivity was evaluated per body region by aggregated measures. For this purpose, the 32 single ratings of pressure pain intensity (VAS, 0-10) in the manual probe were averaged for 5 body regions adapted from the Heidelberg pain drawing mask (head-cervical, thoracic, lumbar, upper and lower limb region; Gerhardt, Hartmann, Blumenstiel, Tesarz, & Eich, 2014; cf. Table S6 correspondence for Heidelberg pain drawing mask).

2.3.1.2 Quantitative algometer test

Pressure sensitivity was quantitatively assessed by an algometer (Algometer; Wagner, Inc.) with 8 mm diameter stimulation area. Phasic pressure pain thresholds (“just painful”) were obtained bilaterally with the method of limits at the tender point in the center of the trapezius and the control point on the thenar eminence (0.5 kp/s ramps; mean of 3 trials). In addition, pain intensity ratings (VAS 0 – 10) for each completed series were recorded as a subjective scale anchor.

2.3.2 Heat pain sensitivity

A rectangular Peltier thermode with a contact surface of 1.6 × 3.6 cm was used for the assessment of heat pain sensitivity (PATH Tester MPI 100; Galfe, Lautenbacher, Hölzl, & Strian, 1990, accuracy 0.05 °C; 0.7 °C/s heating and 2.0 °C/s cooling rate). All test procedures were controlled by computer and subject’s responses were acquired automatically by a keyboard for yes/no, up/down and a trackball for rating responses, respectively. Instructions, control signals and graphic rating scales were presented on a computer screen in front of the subject (for details of apparatus and procedures: cf. Kleinböhl et al., 1999; Kleinböhl, Trojan, Konrad, & Hölzl, 2006).

2.3.2.1 Heat pain thresholds

Phasic heat pain thresholds were obtained from the center of the trapezius (dominant side) and the thenar eminence (non-dominant hand) with continuous versions of the method of limits and the method of adjustment (means of 5 trials). The tonic heat pain threshold was defined as the “just painful” temperature adjusted by the subject after 30 s constant heat stimuli above and below the self-adjusted threshold.

2.3.2.2 Supra-threshold heat pain sensitivity

Absolute magnitude estimates (AME) of the perceived heat pain were recorded at the end of the tonic stimulation on a numerically and verbally anchored visual analogue scale ranging from 0 (warm sensation) to 100 (very strong pain) with the pain threshold set at 40 (just painful). The linear regression of AMEs on stimulus temperature was used as estimate of the psychophysical function (Steven's coefficient) for heat pain.

2.3.2.3 Short-term sensitization to heat: Temporal summation

Short-term sensitization to heat was measured with the previously established dual sensitization method (Kleinböhl et al., 1999) based on temporal summation. The method provides both a behavioral re-adjustment measure (ΔT) as well as a subjective estimate (ΔE) of perceived temperature change over 30 s of tonic heat as a function of the initial temperature (temperature gradient). Nine initial temperatures, 3 below and 6 above the previously self-adjusted pain threshold, were applied in steps of 0.33°C in a pseudo-randomized order. At the end of the tonic stimulation period subjects were to rate the perceived temperature change (ΔE) and the perceived heat pain intensity (absolute magnitude estimation, AME) on numerically anchored visual analogue scales and, finally, to re-adjust the thermode to the (assumed) initial temperature (ΔT).

2.4 Assessment of comorbidity and psychosocial co-factors

2.4.1 Somatic symptoms and well-being

In addition to the general medical entrance diagnostics and anamnestic data, somatic well-being and subjective body complaints were specified by established and validated questionnaires. The general somatic symptom burden was evaluated by the SF-12, physical component (short-form of the SF-36, Health-Related Quality of Life Questionnaire; Bullinger & Kirchberger, 1998) and the global symptom score of the Giessen Symptom Questionnaire (GBB-24; Brähler, Hinz, & Scheer, 1995). Specific symptoms were quantified by the GBB subscales for exhaustion, gastric symptoms, heart complaints and limb pain (German "Gliederschmerzen", equivalent to musculoskeletal pain). The presence of specific functional gastrointestinal disorders was checked by the questionnaire for functional gastrointestinal disorders (FGID; Drossman et al., 1992; Herschbach, 1996). Sleep quality was evaluated by the Pittsburg Sleeping Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

2.4.2 Psychopathology

General mental health was assessed by the mental health component of the SF-12; depressive and anxiety symptom burden was quantified by the Center for Epidemiological Studies Depression Scale (German version: ADS; Hautzinger & Bailer, 1993) and the Trait Anxiety Scale of the State-Trait Anxiety Inventory (German version: STAI-T; Laux, Glanzmann, Schaffner, & Spielberger, 1981), respectively. An ADS score ≥ 24 indicates a risk for major depression and allows for a tentative diagnosis while the STAI-T score indicates only a general anxious disposition. Untransformed sum scores were used in all calculations instead of population-dependent percentile ranks or T-values.

2.4.3 Psychosocial co-factors

The Short Stress Questionnaire (German “Kurzer Fragebogen zur Erfassung von Belastungen, KFB; Flor, 1991, a short stress scale adapted from the Daily-Hassles-Scale; Kanner, Coyne, Schaefer, & Lazarus, 1981) for chronic pain, was applied to determine self-reported stress burden on four subscales (partnership, daily problems, social contacts, trouble at work) and the sum-score as indicator of overall strain.

2.5 Data analyses

The sequential multimethod strategy consisted of initial descriptive statistical, correlational and contingency analysis followed by structure-finding methods. Data were analyzed with the program packages IBM SPSS Statistics (version 25; Armonk, NY, USA), R (version 3.4.1; The R Foundation for Statistical Computing, Vienna, Austria) and LatentGOLD® (version 5.1.0.17248; Statistical Innovations Inc., Belmont, MA, USA).

Main analyses comprised principal component (SPSS program), hierarchical cluster analyses (R program pvclust; Shimodaira, 2002; Suzuki & Shimodaira, 2006, 2015) and latent class analyses (LatentGOLD®, program LC cluster) to identify sensory phenotypes with respect to pressure pain sensitivity separately and combined with heat pain sensitivity and short-term sensitization. Heat pain served as non-mechanoceptive control for the modality-specificity of phenotypes.

Preparatory correlation analyses served as basis for identifying common variable groupings. Principal components analyses were calculated to uncover dimensions and spatial relations of pressure sensitivity indicators of the semi-quantitative manual probe

and the quantitative algometer test to derive an optimal set of indicators for the latent class analysis (LCA) defining coherent sensory phenotypes of the target modality. A similar analysis was run for the heat pain sensitivity and sensitization parameters and for both sensory modalities combined. These initial exploratory steps implied repeated, statistically dependent analyses on the same dataset. Thus, the extracted principle components and clusters of sensory indicators served merely for a descriptive selection of the reduced set of best sensory markers to be combined with clinical pain characteristics while minimizing sample attrition in the database.

The selected indicator set was included in the final step of sensory-clinical phenotyping by robust LCA at the individual level and reclassifying the patients with prior FMS or cUBP diagnoses (LatentGOLD®, program LC cluster). The identified transdiagnostic sensory-clinical profile clusters were cross-validated by a stepwise linear discriminant function analysis applying Wilks' lambda for variable selection.

Finally, the identified sensory-clinical phenotypes were compared to prior FMS and cUBP groups with respect to clinical pain characteristics, comorbidity and psychosocial co-factors not included in the previous LCAs. Parametric t-tests and nonparametric U-tests for ordinal data were used for comparisons between clusters throughout, K-S 2-samples tests were calculated for control when appropriate. Cross-classifications of prior diagnoses and clusters were evaluated by contingency analysis using the corrected contingency coefficient (C_{corr}). In view of current controversies about the validity of conventional significance levels (cf. Amrhein, Greenland, & McShane, 2019) exact probabilities are reported up to $p = 0.001$ where possible; else, classical significance was set at $p < 0.05$ with p-values corrected familywise.

3 Results

In the following the main results of the 3-step analysis of sensory and clinical phenotypes of patients with prior FMS and cUBP diagnoses serving as exemplary samples of widespread and (more or less) regional pain with no known organic origin are described. First, the clinical picture, in particular, spatial extension of pain sites and regions, current pain intensity, quality and severity of the prior diagnosis groups were re-evaluated according to the comprehensive entrance assessment. Second, the extraction of a minimal set of sensory classifiers from the initial indicators of enhanced pain sensitivity in the database by PCA and LCA was delineated (cf. the Supplemental for details). Third, combining the minimal classifier with selected clinical pain

characteristics four distinguishable sensory-clinical phenotypes were identified differing in spatial patterns of pressure sensitivity and clinical pain, forming two extreme subgroups with high and low pressure pain sensitivity associated with widespread and regionally confined pain, respectively, and two intermediary clusters. Finally, patients with prior FMS and cUBP diagnoses were reclassified into these sensory-clinical phenotypes revealing partially overlapping subgroups at the transition between cUBP to FMS. These were related to the clinical pain picture, psychic and somatic comorbidity and psychosocial co-factors specifying their role in differential diagnosis of widespread and regional musculoskeletal pain syndromes.

3.1 Re-evaluation of clinical pain

3.1.1 Spatial extension and regions in pain

Table 2. Re-evaluation of spatial extent and severity of current pain

Pain Characteristic	Prior Diagnosis at study entrance	
	FMS ACR 1990 [a]: N = 78	cUBP: N = 107
"Widespread pain" [b]		
4 quadrants + axis	71 (91.0)	28 (26.2)
< 5 regions	2 (2.6)	70 (65.4)
FS scale [c]		
FMS criterion ≥ 12	63 (80.8)	23 (21.5)
FMS criterion < 12	15 (19.2)	84 (78.5)
Mean ± SD	16.3 ± 6.3	8.2 ± 4.5 ***
Median ± ½ IQD	17.0 ± 4.5	8.0 ± 3.0 ***
Range	0 – 20	0 – 20
Widespread Pain Index, WPI [d]		
Mean ± SD	11.8 ± 3.8	5.5 ± 2.9 ***
Median ± ½ IQD	12 ± 3.0	5 ± 1.5 ***
Range	4 – 19	0 – 15
No. present pain sites [e]		
0	0 (0.0)	1 (0.9)
1	0 (0.0)	2 (1.9)
2	0 (0.0)	7 (6.5)
3	1 (1.3)	10 (9.3)

[Table 2, continued:]

Pain Characteristic	Prior Diagnosis at study entrance	
	FMS ACR 1990 [a]: N = 78	cUBP: N = 107
4	2 (2.6)	29 (27.1)
5	12 (15.4)	22 (20.6)
6	15 (19.2)	12 (11.2)
7	21 (26.9)	9 (8.4)
8	12 (15.4)	5 (4.7)
9	10 (12.8)	1 (0.9)
Mean ± SD	6.8 ± 1.4	4.7 ± 1.7 ***
Median ± ½ IQD	7 ± 1	4.5 ± 1 ***
No. major pain sites [f]		
1	19 (24.4) [e]	35 (32.7)
2	12 (15.4)	33 (30.8)
3	14 (17.9)	17 (15.9)
4	9 (11.5)	7 (6.5)
5	8 (10.3)	0 (0.0)
6	4 (5.1)	4 (3.7)
7	0 (0.0)	0 (0.0)
8	1 (1.3)	1 (0.9)
9	0 (0.0)	0 (0.0)
Mean ± SD	2.79 ± 1.72	2.19 ± 1.36 *
Median ± ½ IQD	3.0 ± 1.5	2.0 ± 1 *
Pain all over my body [g]	15 (19.2)	1 (0.9)
Present pain intensity [h]		
Mean ± SD	3.3 ± 1.3	2.9 ± 1.3
Median ± ½ IQD	3 ± 0.5	3 ± 1.0
Range	0 – 6	0 – 6
Pain severity [i]		
Mean ± SD	3.7 ± 1.1	3.4 ± 1.1 *
Median ± ½ IQD	3.7 ± 0.9	3.3 ± 1.2 *
Range	1.3 – 6.0	1.0 – 6.0
Missings	8	12

[Table 2, continued:]

Pain Characteristic	Prior Diagnosis at Study Entrance	
	FMS ACR 1990 [a]: N = 78	cUBP: N = 107
Pain quality [j]		
Sensory scale SS10		
Mean ± SD	21.7 ± 7.0	17.7 ± 6.5 **
Median ± ½ IQD	20.0 ± 4.9	16.0 ± 3.5 **
Range	10.0 – 39.0	10.0 – 40.0
Affective scale AS14		
Mean ± SD	34.3 ± 9.9	30.7 ± 9.3 *
Median ± ½ IQD	33.0 ± 8.0	29.0 ± 7.3 *
Range	18.0 – 56.0	14.0 – 53.9

[a] ACR criteria: 11 out of 18 tender points (Wolfe et al., 1990).
[b] "Widespread pain" according to Wolfe, 1990 (ACR criteria for fibromyalgia): present pain in 4 body quadrants plus axis; N cases (%).
[c] Fibromyalgia Symptom Scale, FS scale ≥ 12 (Wolfe et al., 2016); N cases (%).
[d] Widespread Pain Index, (WPI, range 0 - 19) according to the Fibromyalgia Survey Questionnaire (FSQ, Häuser et al., 2012), the survey version of the FS scale (Wolfe et al., 2016).
[e] All present pain sites reported by patients corresponding to Axis I, IASP Taxonomy of chronic pain (IASP Taxonomy Working Group, 2018); N cases (%); responses to item #20 in DSF (Nagel et al., 2002), cf. Table S2 in Supplemental for correspondence of pain regions.
[f] Responses to item #21 in DSF (Nagel et al., 2002), which includes max. 3 separate sites for back pain; N cases (%).
[g] Responses to item #21: "pain all over my body", in DSF (Nagel et al., 2002); N cases (%).
[h] Intensity ratings of present pain, MPI-D item #1 (Flor et al., 1990).
[i] Pain severity: MPI-D, section I, scale 1 score (Flor et al., 1990).
[j] Raw sum scores of the affective and sensory subscales (AS: 14 and SS: 10 items, respectively) of the German Pain Perception Scale (Schmerzempfindungs-Skala, SES, Geissner, 1996); for comparisons between subscales values were corrected for different item numbers; 17 missing patient values imputed according to test manual.
*Differences between FMS and cUBP (U-test, K-S test and t-test where applicable): FS scale: *** $p < 0.001$; WPI: *** $p < 0.001$; present pain sites: *** $p < 0.001$; major pain sites: * $p < 0.05$; present pain intensity: n. s.; pain severity: * $p < 0.05$; sensory scale: ** $p < 0.01$; affective scale: * $p < 0.05$.*

Seventy-one FMS patients of 78 with complete data sets reported pain in four body quadrants and along the axis consistent with the ACR 1990 criteria of "widespread pain", but 28 (26.2 %) patients previously diagnosed with chronic unspecific back pain reported also pain in all body quadrants in addition to their primary pain area at the back (Table 2). The FS criterion ≥ 12 was fulfilled by comparable quota (63 FMS, 23 cUBP patients). The WPI values of the FS scale of FMS patients was twice as high

than for cUBP patients (U-test; $p < 0.001$). However, the WPI of the latter ranged up to 15 and the distributions of both groups overlapped substantially (Figure 1).

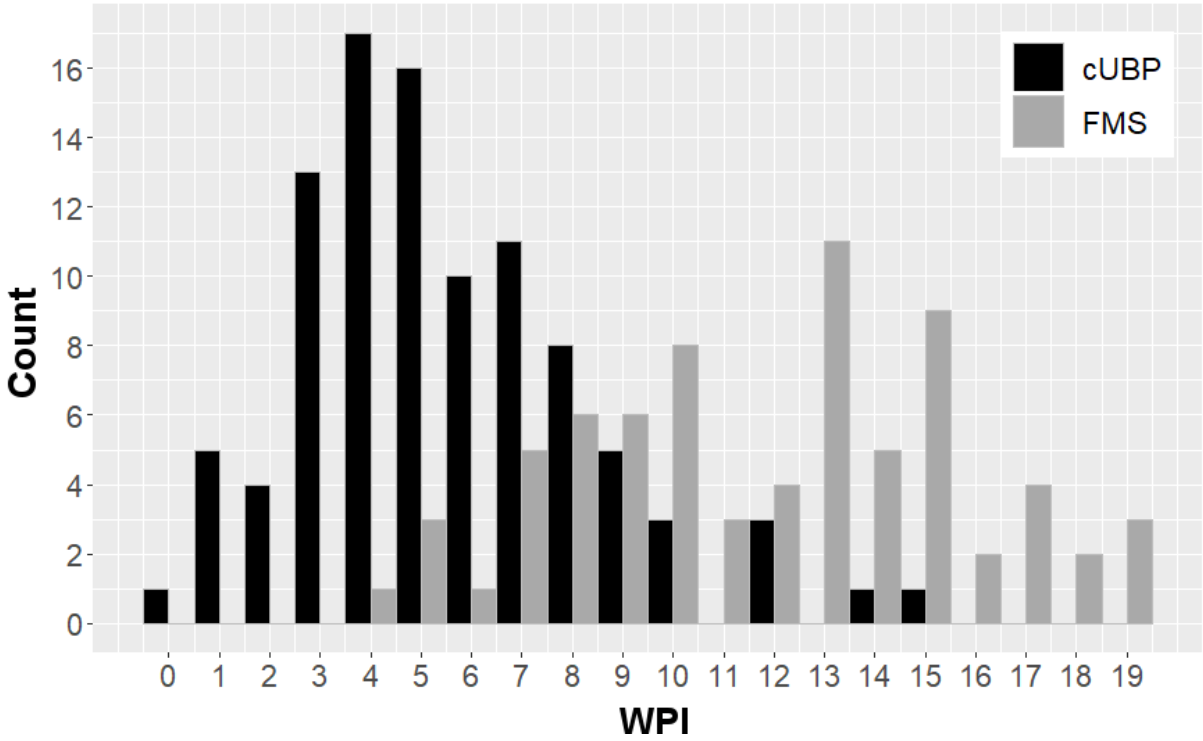


Figure 1: *Absolute frequencies of self-reported pain loci according to the Widespread Pain Index, WPI (Wolfe et al., 2010; Wolfe et al., 2011). By definition, patients with prior FMS diagnoses indicated more pain loci than cUBP but many reported only 10 or less pain loci at re-assessment. WPI distributions of FMS and cUBP patients overlapped between 4 and 15 indicating a subgroup of patients in a transition stage neither fulfilling entirely FMS criteria nor having only regionally restrained pain as in cUBP proper.*

The number of body sites currently in pain named by patients when presented with the nine IASP Taxonomy regions corroborate and specify this finding (Table 2): The FMS patients indicated generally more IASP regions “currently in pain” than cUBP patients and the distribution was dominated by higher numbers (5 – 9) while the number of pain regions of UBP patients were symmetrically distributed around 4 and 5. Similar overlaps of the spatial extent of pain symptoms were reported when patients were asked for the region of their “major pain” (DSF item #21): 48 FMS patients indicated “major pain” in more than one IASP region (median = 3; max = 8) while 19 FMS patients localized their “major pain” in only one region, 11 reporting “pain all over my body” in addition. Four FMS patients were not able to indicate a distinct major pain region and felt pain all over their body. For comparison, 62 cUBP patients reported also more than one major pain region and 54 one to five additional, not back-related major pain regions. One cUBP patient also indicated “pain all over my body”. In summary, the

spatial extent and pattern of pain sites and/or regions showed distinct differences between the FMS and the cUBP group but a high variability and substantial overlap between the prior diagnoses prevailed.

3.1.2 Pain severity

In contrast, the severity of pain symptoms did not differ consistently between prior FMS and cUBP groups: The intensity ratings of present intensity (MPI-D, item #1) of the major pain were marginally higher in FMS patients (U-test, $p = 0.060$, n. s.; Table 2) covering the whole range from 0 – 6 with the same median at 3.0 in both groups. Global pain severity summarizing present and recent pain with subjective suffering (MPI-D Scale 1, section I) was only moderately higher by FMS than cUBP patients (t-test, $p = 0.033$; Table 2).

3.1.3 Pain quality: sensory and affective descriptors

Sensory and affective qualities of the major pain measured by the SES scored significantly higher in FMS compared to cUBP patients (t-tests; affective descriptors: $p = 0.017$; sensory: $p < 0.001$). FMS patients differed from cUBP most pronouncedly in sensory rather than affective pain descriptors (standardized differences: 0.59 SD vs. 0.38 SD; Figure S4 in Supplemental). Moreover, the differences between sensory and affective evaluations were equivalent in both groups indicating that FMS patients did not emphasize the affective stronger than the sensory aspect of their pain.

3.2 Sensory phenotyping: Experimental measures of pain sensitivity

The measures of enhanced sensitivity to provoked pressure pain available in the database showed important but complex relations to each other and to the heat pain control modality. Therefore, extensive descriptive and structural analyses including PCA and LCA were needed in order to extract a parsimonious marker set for coherent sensory phenotypes to be finally combined with clinical pain characteristics and related to chronicity factors. A detailed description of the procedure is available in the Supplemental. Here we report only the main results of (1) the descriptive analysis of the spatial distribution of pressure sensitivity to standardized manual and algometer stimulation of ACR “tender” and control points in FMS and cUBP patients and (2) the final sensory profiles used in phenotyping.

3.2.1 Spatial distribution of pressure pain sensitivity

The standardized manual probe of pressure sensitivity at 32 body sites confirmed the pronounced enhancement of sensitivity to pressure stimulation in FMS patients established by previous research, both in terms of number of hypersensitive body sites as well as provoked pain intensities compared to cUBP patients (U-tests, $p < 0.001$; Table 3); with one exception healthy controls had neither sensitive tender nor control points in the manual probe.

Table 3. Spatial distribution of pressure sensitivity in 18 ACR "tender" and 14 control points

(A) Number and pain intensity of standardized manual stimulation

	FMS: N = 78	**cUBP: N = 107**
No. sensitive tender points [a, b]		
Mean ± SD	15.0 ± 2.8	5.0 ± 4.6
Median ± ½ IQD	15.5 ± 3.0	4.0 ± 4.0 ***
Range	7.0 – 18.0	0.0 – 18.0
Missings	2	5
No. sensitive control points [a,b]		
Mean ± SD	4.4 ± 4.0	1.1 ± 2.0
Median ± ½ IQD	3.0 ± 3.3	0.0 ± 1.0 ***
Range	0.0 – 14.0	0.0 – 10.0
Missings	1	6
No. all sensitive points [a,b]		
Mean ± SD	19.2 ± 6.1	6.1 ± 6.6
Median ± ½ IQD	19.0 ± 4.8	4.0 ± 4.3 ***
Range	0.0 - 32.0	0.0 – 26.0
Missings	1	5
Intensity tender points [b,c]		
Mean ± SD	5.755 ± 1.684	4.2 ± 1.8
Median +- ½ IQD	5.7 ± 1.3	4.0 ± 1.2 ***
Range	2.6 – 10.0	1.0 – 10.0
Missings	2	5
Intensity control points [b,c]		
Mean ± SD	4.9 ± 1.9	3.8 ± 1.9

[Table 3 A, continued:]

	FMS: N = 78	cUBP: N = 107
Median ± ½ IQD	4.8 ± 1.3	3.0 ± 1.1 **
Range	1.5 – 9.0	1.0 – 10.0
Missings	15	74
Intensity tender and control points [b,c]		
Mean ± SD	5.5 ± 1.6	4.10 ± 1.7 ***
Median ± ½ IQD	5.6 ± 1.2	3.7 ± 1.2 ***
Range	2.7 – 9.6	1.0 – 10.0
Missings	2	26
VAS pain intensity average of head-cervical region [d]		
Mean ± SD	5.1 ± 1.9	4.1 ± 1.8
Median ± ½ IQD	5.0 ± 1.5	4.0 ± 1.4 **
Range	1.8 – 9.4	1.0 – 10.0
Missings	4	53
VAS pain intensity average of thoracic region [d]		
Mean ± SD	5.6 ± 1.8	4.1 ± 1.8
Median ± ½ IQD	5.6 ± 1.4	4.0 ± 1.4 ***
Range	1.3 – 10.0	1.0 – 8.1
Missings	2	44
VAS pain intensity average of lumbar region [d]		
Mean ± SD	5.8 ± 2.3	4.1 ± 1.8
Median ± ½ IQD	5.9 ± 2.0	4.0 ± 1.0 ***
Range	1.0 – 10.0	1.0 – 10.0
Missings	2	69
VAS pain intensity average of upper limb region [d]		
Mean ± SD	5.5 ± 2.0	4.1 ± 2.1
Median ± ½ IQD	5.5 ± 1.5	4.0 ± 1.3 ***
Range	1.9 – 10.0	1.0 – 10.0
Missings	10	73
VAS pain intensity average of lower limb region [d]		
Mean ± SD	5.6 ± 1.9	4.0 ± 2.3
Median ± ½ IQD	5.8 ± 1.6	3.3 ± 2.0 ***
Range	2.0 – 9.5	1.0 – 8.5
Missings	4	62

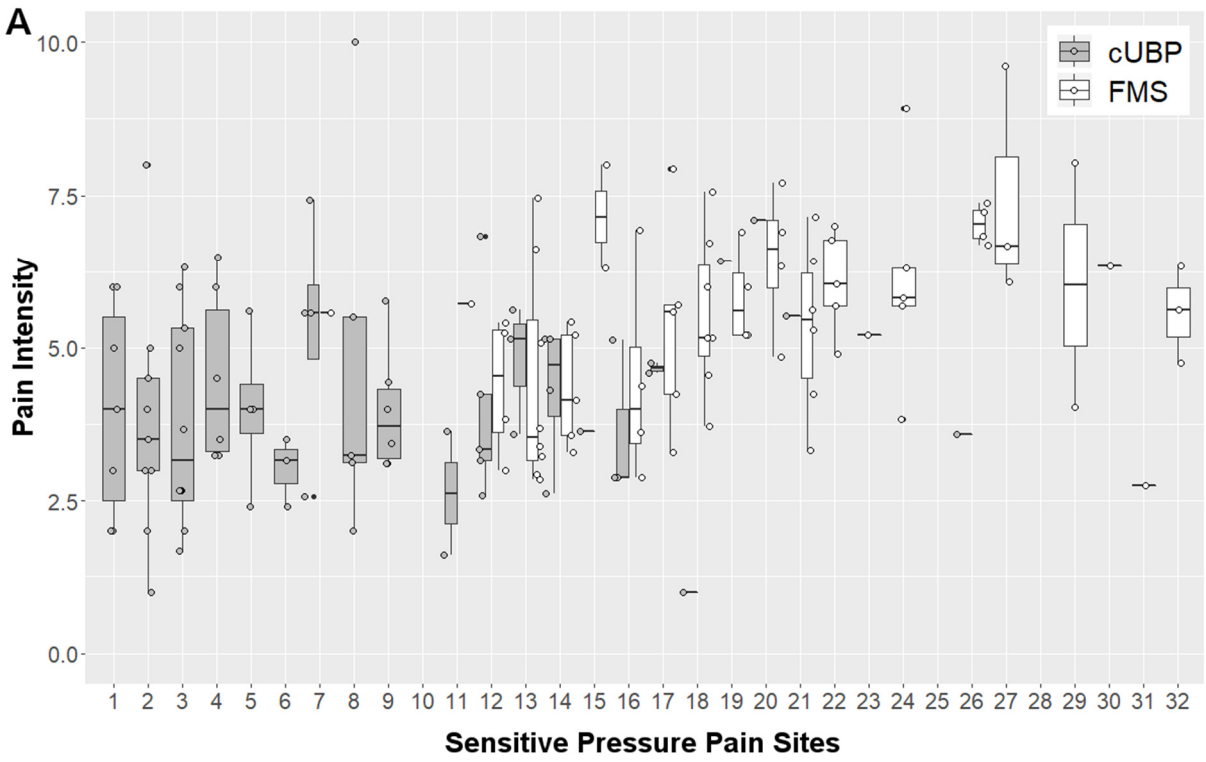
[a] Number of tender and control points on both sides with VAS ratings ≥ 1 (max. 18 tender and 14 control points) corrected for individual maximum number of test sites. Differences between left and right n. s. (t-test, Wilcoxon).
[b] One healthy control with sensitive ACR tender points > 0 (TP at left and right knee/ lower limb region); no healthy control indicated sensitive control points. Average pain intensity for control points not calculated for healthy controls.
[c] Means of intensity ratings > 0; zero values predominating at the thenar control point in both FMS and cUBP, but not at the trapezius "tender point" in FMS (cf. histograms in Figure S5 in Supplemental).
[d] Average pressure pain intensity ratings (VAS, 0-10) of the manual probes in the five body regions of the Heidelberg pain drawing mask (Gerhardt et al., 2014), zero-values excluded. Average pain intensity for pain regions (head-cervical, thoracic, lumbar, upper limbs) in healthy controls and comparisons with patients not calculated.
Notes. ½ IQD, ½ inter-quartile distance = 0.5 × [Q(75) – Q(25)].
**** p < 0.001; ** Difference FMS vs. cUPB, Intensity control points: p = 0.003; and VAS pain intensity average of head-cervical region p = 0.005 (U-test).*

(B) Pressure pain thresholds and intensity in algometer test

	FMS: N = 78	cUBP: N = 107	Healthy controls: N = 41
Pressure threshold: Trapezius with algometer [a]			
Mean ± SD	2.45 ± 1.46	4.18 ± 1.71 ***	3.55 ± 0.97 ***
Median ± ½ IQD	2.05 ± 1.33	4.00 ± 0.83	3.50 ± 0.47
Range	0.10 – 7.00	0.75 – 9.90	1.55 – 7.25
Missings	0	4	1
Pressure threshold: Thenar with algometer [a]			
Mean ± SD	2.85 ± 1.26	3.71 ± 0.99 ***	3.30 ± 1.00 *
Median ± ½ IQD	3.30 ± 1.11	4.00 ± 0.40	3.35 ± 0.79
Range	0.10 – 5.00	0.95 – 6.75	1.30 – 5.50
Missings	0	4	1
Pain intensity VAS rating trapezius [b]			
Mean ± SD	5.99 ± 2.12	3.92 ± 2.81 ***	4.26 ± 2.83 **
Median ± ½ IQD	6.00 ± 1.75	4.00 ± 2.63	5.00 ± 2.50
Range	1.00 – 10.00	0.00 – 9.00	0.00 – 8.00
Missings	1	6	3
Pain intensity VAS rating thenar [b]			
Mean ± SD	3.14 ± 3.00	2.84 ± 2.93	4.26 ± 2.74
Median ± ½ IQD	3.00 ± 2.75	2.50 ± 2.75	4.00 ± 2.5
Range	0.00 – 9.00	0.00 – 9.00	0.00 – 8.00
Missings	1	5	2

[a] Phasic pressure pain thresholds were obtained using ramps of 0.5 kp/s. After initial trials the threshold ("just painful") was recorded three times at each site. Differences between left and right n. s. (t-test, Wilcoxon).
[b] Mean pain intensity ratings (VAS 0 – 10) for completed series after the phasic pressure pain threshold testing. Differences between left and right n. s. (t-test, Wilcoxon).
Notes. ½ IQD, ½ inter-quartile distance = 0.5 × [Q(75) – Q(25)].
**** p < 0.001; ** Difference FMS vs. HC: p = 0.001, cUBP vs. HC: p = 0.518; * Difference FMS vs. HC: p = 0.037, cUBP vs. HC: p = 0.031 (t-test).*

As shown in Table 3, however, the pressure hypersensitivity was not limited to the 18 "tender points" specified by the ACR 1990 protocol but applied also to control points if fewer and less pronounced. The number of hypersensitive ACR tender points of FMS patients ranged from 7 to 18 (median = 15.5) three patients not fulfilling the criterion of ≥ 11 tender points at second testing. Moreover, 16 cUBP patients (15 %) showed also 11 or more hypersensitive ACR tender points indicating substantial overlap between prior FMS and cUBP diagnoses on second testing. Moreover, 63 (81 %) FMS and 33 (31 %) cUBP patients reported also one or more hypersensitive control sites numbers ranging respectively from 0 to 14 and from 0 to 10. The total number of hypersensitive body sites, irrespective of ACR tender or control position, differed also significantly between FMS and cUBP (median = 19 vs. 4) but ranges overlapped considerably (0 – 32 vs. 0 – 26). At the same time, pain intensity ratings of the manual stimulation were consistently higher at ACR tender points than at control points in both groups (U-test; FMS: $p < 0.001$; cUBP: $p = 0.003$). This and the higher numbers of sensitive tender points suggest enhanced pressure sensitivity at classical "tender points" to be specific to FMS. The question is further explored in the next section by considering the variation of pain ratings as a function of numbers of hypersensitive body sites, overall and separately for tender and control points (Figure 2).


A
cUBP
FMS
Pain Intensity
10.0
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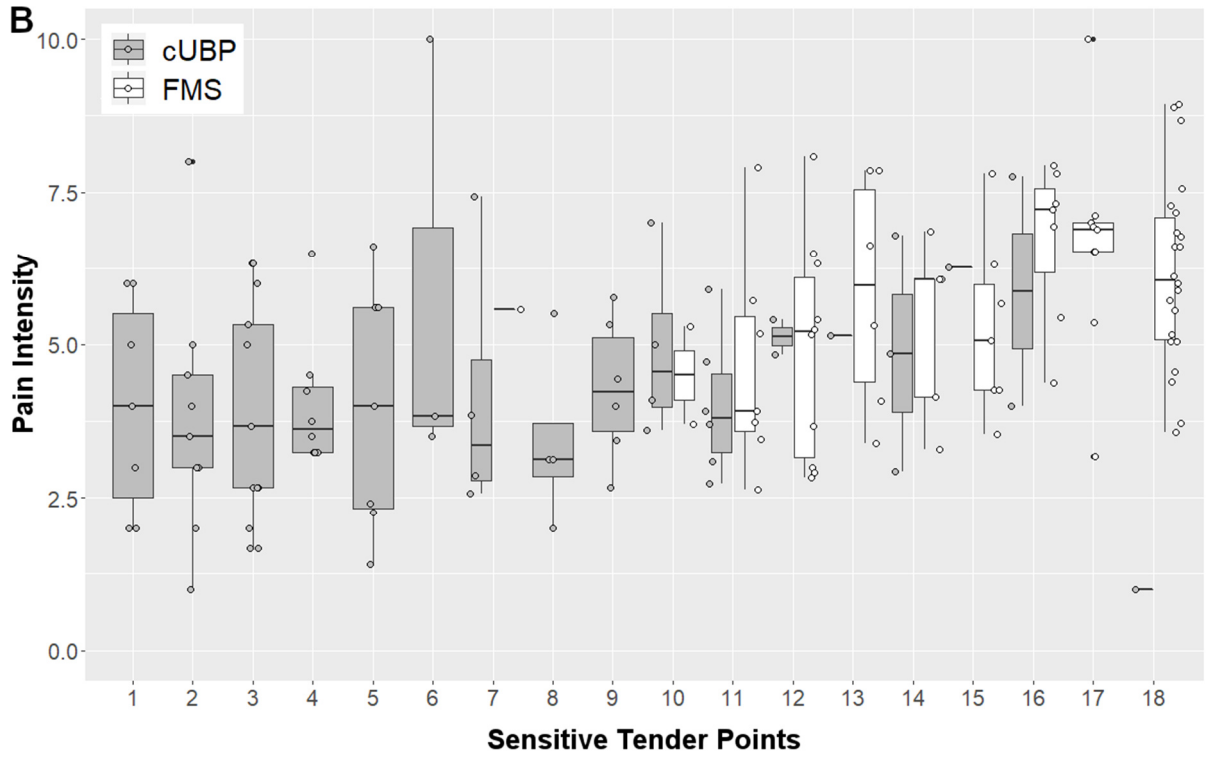
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32
Sensitive Pressure Pain Sites


B
cUBP
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Pain Intensity
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Sensitive Tender Points

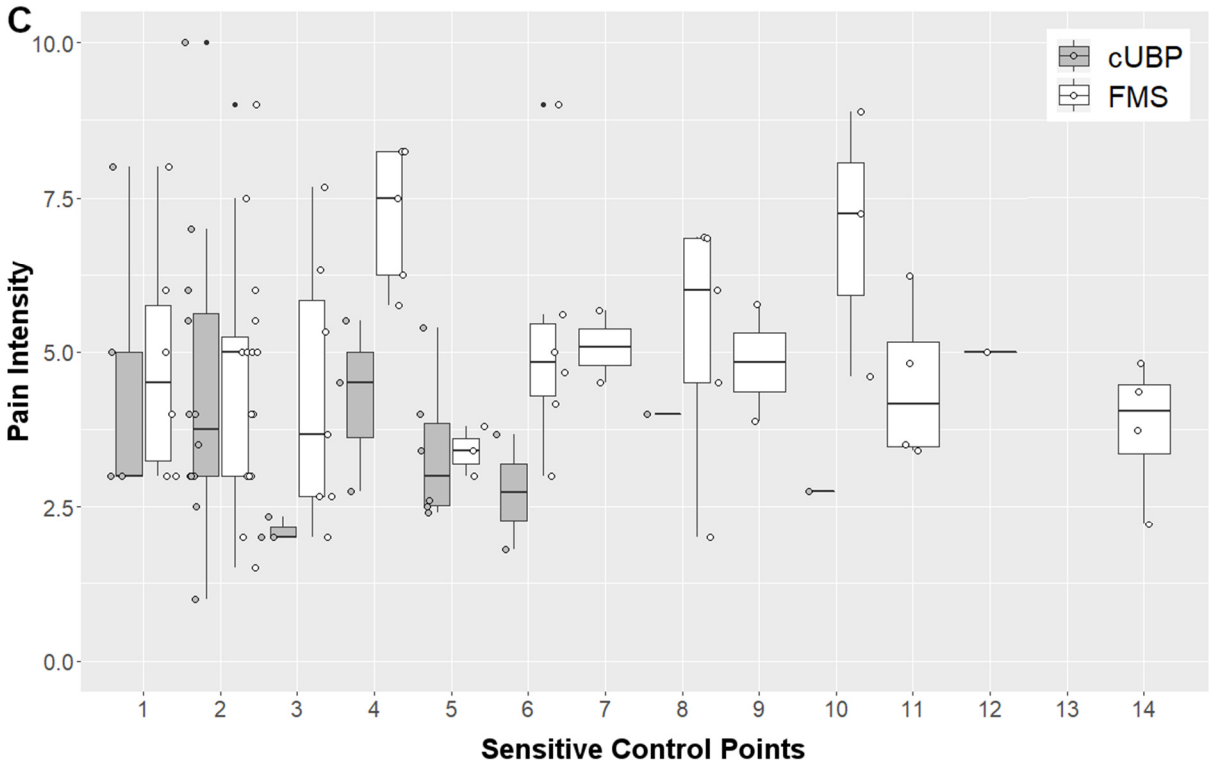


Figure 2: *Average pain intensities of standardized manual probing as a function of number of pressure-sensitive body sites; pain intensity: NRS 0 – 10; sensitive site: NRS > 0 (just clearly painful or more); number of sensitive sites corrected for missings. (**A**) All sensitive points; (**B**) sensitive ACR "tender points"; (**C**) sensitive control points. Box-plots: group median ± P25/P75; circles = individual values; whiskers: range windsorized at 1.5 × IQR ± P75/P25.*
*Average pain intensity ratings of painful thumb probes (classic "tender" and control point locations taken together) were significantly higher in FMS than in cUBP patients and increased with the number of sensitive sites in FMS, but not in cUBP patients (right vs. left half of diagrams (**A** – **C**). In FMS, evoked pain intensity correlated with the actual number of sensitive tender points (**B**: ρ = 0.347, p < 0.065), but not with the number of sensitive control points (**C**: ρ = 0.048, n. s.); no correlation in cUBP.*

Figure 2 A demonstrates that test pain intensity increases systematically with numbers of sensitive points in both FMS and cUBP; there is a more or less continuous transition from the regional to the widespread pain syndrome with a large overlap between the two syndromes. Closer inspection shows that the relation is mainly due to the FMS group confirmed by group-specific correlations (FMS: ρ = 0.363, p = 0.001; cUBP: ρ = 0.116, p = 0.302, n. s.; respective correlation-regression analysis in Table S7 and Figure S8 in Supplemental). Moreover, the high number × intensity correlation in FMS was limited to the 18 ACR tender points (Figure 2 B) whereas pressure pain intensity did not increase systematically with the number of sensitive control points (Figure 2 C). This increase could also be found in cUPB patients with more than 7 classical ACR tender points (right half of Figure 2 B). Thus, local pressure sensitivity appears to be associated with the spatial extent of sensitive areas across the whole body. This was

particularly pronounced when ACR tender points were considered for which the relation held also in those cUBP patients in the transition to widespread hypersensitivity above 7 sensitive ACR tender points.

This supports the notion of a sensory difference between classical tender and control points as suggested by earlier research. Note, however, the ceiling effect due to scale clipping at the maximum of 18 tender points tested in FMS causing the accumulation of observations at the rightmost category 18 in Figure 2 B. Accordingly, provoked pain intensity correlated maximally with the number of sensitive ACR points when only subjects with 16 or less sensitive ACR points were taken into account; the partial correlation above cannot be evaluated reliably. Therefore, the FMS subgroup with 17 or more sensitive test points (max = 32) and the corresponding frequency distributions of provoked pain intensity deserve further consideration as they may represent a different population. Accordingly, the highest pain intensities were found in FMS patients with 25 - 28 sensitive points out of 32 tested, the lowest intensities in patients with 13-16 sensitive points. The intensity distributions of patients with 17 - 20, 21 – 24 and 29 - 32 sensitive points exhibited the most systematic shift from lower to higher intensities with increasing numbers irrespective of “tender” or “control” sites (cumulative frequency distributions of intensities in Figure S9 in Supplemental).

Note also, that these specific patterns of spatially spread pressure sensitivity were lost when the site-specific manual probes were aggregated for macro-anatomic functional body regions, e.g., the five body regions of the Heidelberg pain drawing mask. cUPB patients indicated generally lower pain intensities than FMS patients (multiple U-tests, $p < 0.001$, corrected; Table 3) but the aggregated intensity ratings lay in the medium range for both patient groups irrespective of region, tender or control points.

Cross-examination of the results of the semi-quantitative manual assessment by comparisons with selected quantitative algometer tests at respective marker loci on the trapezius muscle (“tender point”) and the thenar eminence (extra-spinal control point) reproduced the sensitivity differences between FMS and cUBP patients. Algometer pressure pain thresholds were significantly lower at both sites in FMS than in cUBP (multiple t-tests, $p < 0.001$). The corresponding pain intensity ratings of FMS patients were higher only at the trapezius tender point marker (trapezius: $p < 0.001$; thenar: $p = 0.512$, n. s.; Table 3 B). cUBP data were generally less consistent and, for instance, differed from healthy controls (HC) by higher thresholds, particularly on the trapezius, and lower provoked pain intensity. Moreover, the correlations between these

algometer measures of near- and supra-threshold pressure sensitivity differed between the selected “tender point” on the trapezius and the control site in both groups (cf. Table S10 in Supplemental). Therefore, the algometer pain threshold and intensity were included from both test sites in the final measurement model for sensory phenotyping of patients.

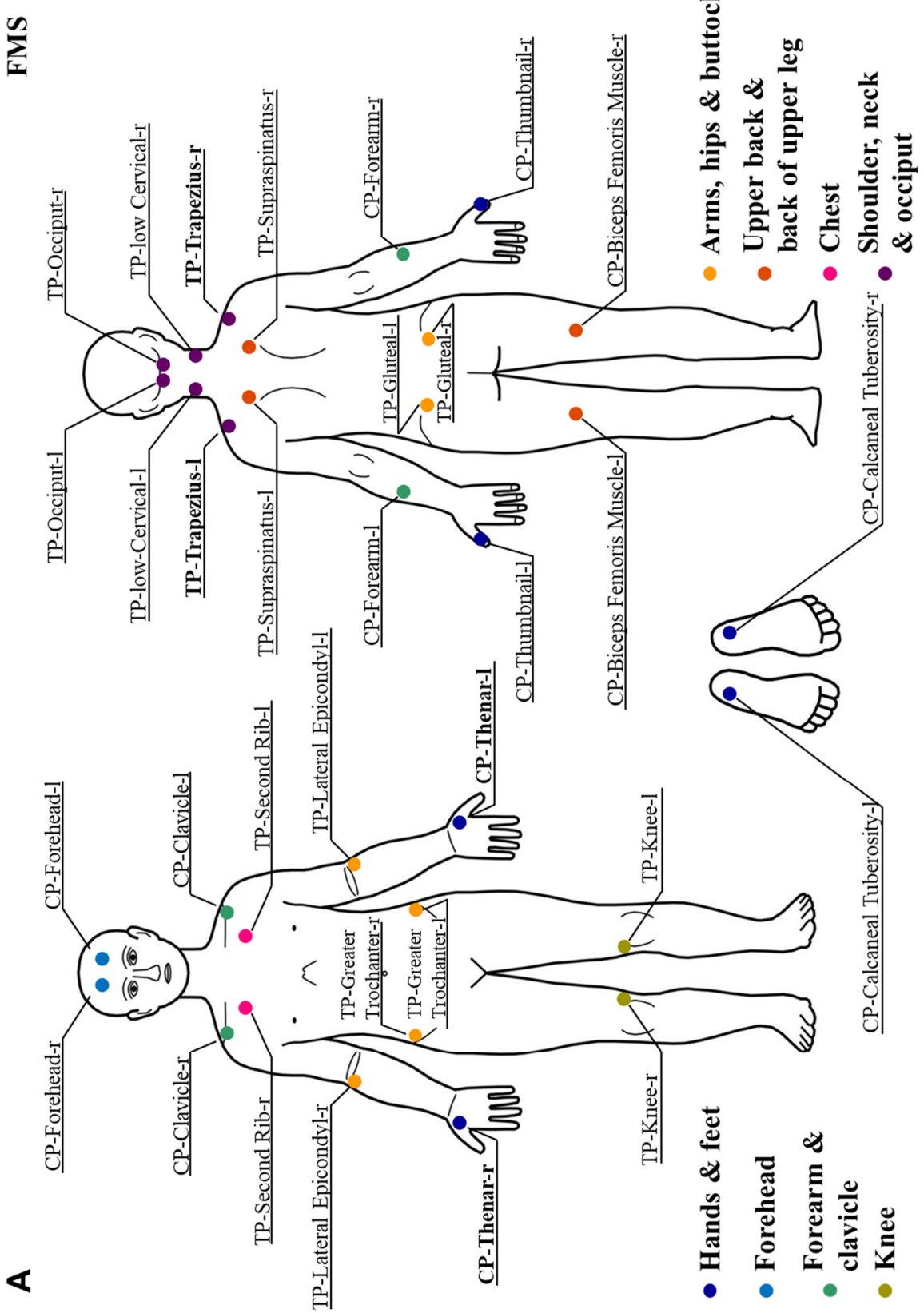
3.2.2 Regional clusters of pressure sensitivity

For this purpose, the initial set of 32 pain intensity ratings from bilateral manual pressure stimulation at 18 tender (TP) and 14 control points (CP) was first reduced by PCA revealing bilateral and regional redundancies. Nine significant components were sufficient to describe the spatial distribution of the test pain in both FMS and cUBP (Kaiser criterion; 79.5 % and 80.4 % variance) with 5 dominant components (loadings ≥ 0.50) collecting most of the variance (64.1 % and 60.7 %). These components represented systematic relations to the functional body regions on head, neck, shoulder, trunk and extremities as defined in Table 3. The ninth component was selective for the extremities (tender and control points on arms, legs and foot; PCA in Table S11 in Supplemental). Notably, tender and control points loaded on separate components only in FMS while the cUBP intensity ratings showed 3 composite TP-CP components. In general, loading patterns reflected the functional difference between TP and CP in FMS patients apparent in the sensory differences described in the previous section. Moreover, CP loadings were distributed all over the body without left-right asymmetries. The first dominant component (28 %) consisted only of TPs from the head, neck, shoulder and upper back in both FMS and cUBP with minor gluteal loading in the latter. The second, third and fourth components, in contrast, differed in composition between FMS and cUBP with separation of tender and control points in the former and TP-CP combined in the latter. The fifth dominant component was mainly thoracal in both groups extending to the cervix in FMS. The other components 6 to 9 explained neglectable further 3 – 4 % of the variance from different sites on the extremities.

The group-specific dimensional structure of pressure pain sensitivity was principally reproduced in additional PCAs including the pressure pain thresholds and intensity ratings from the quantitative algometer test at the exemplary ACR tender and control points (cf. Table S12 in Supplemental). In FMS, in particular, the algometer pain intensities at the trapezius tender point and the thenar control point loaded on the corresponding tender and control point components of the manual test as well as TP

and CP were separated on different components. This well-defined structure represents the functional differences between tender and control points in FMS. This was different in the cUBP group where algometer and manual measures created different, method-specific components irrespective of their functional relation to “tender” vs. “control points”.

The distinct functional and regional dimensional structures of pain intensities provoked in the manual pressure probe and the quantitative algometer test allowed the reduction of the final parameter sets to define economic sensory phenotypes by appropriate cluster analyses at the parameter level. The first set covered the pain intensities of the manual test at all tender and control points related to body regions; the second set combined the algometer pain thresholds and supra-threshold intensities at the trapezius “tender” and the thenar control point with the corresponding manual probe measures. The described dimensional differences in FMS and cUBP argued for separate cluster analyses. Their results are shown in the body maps and corresponding cluster dendrograms of Figure 3, A – D.


A
FMS
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TP-low Cervical-r
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TP-Supraspinatus-r
TP-Supraspinatus-l
CP-Forearm-r
CP-Forearm-l
CP-Thumbnail-r
CP-Thumbnail-l
TP-Gluteal-l
TP-Gluteal-r
CP-Biceps Femoris Muscle-r
CP-Biceps Femoris Muscle-l
CP-Calcaneal Tuberosity-r
CP-Calcaneal Tuberosity-l
CP-Forehead-l
CP-Forehead-r
CP-Clavicle-l
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TP-Second Rib-l
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TP-Lateral Epicondyl-r
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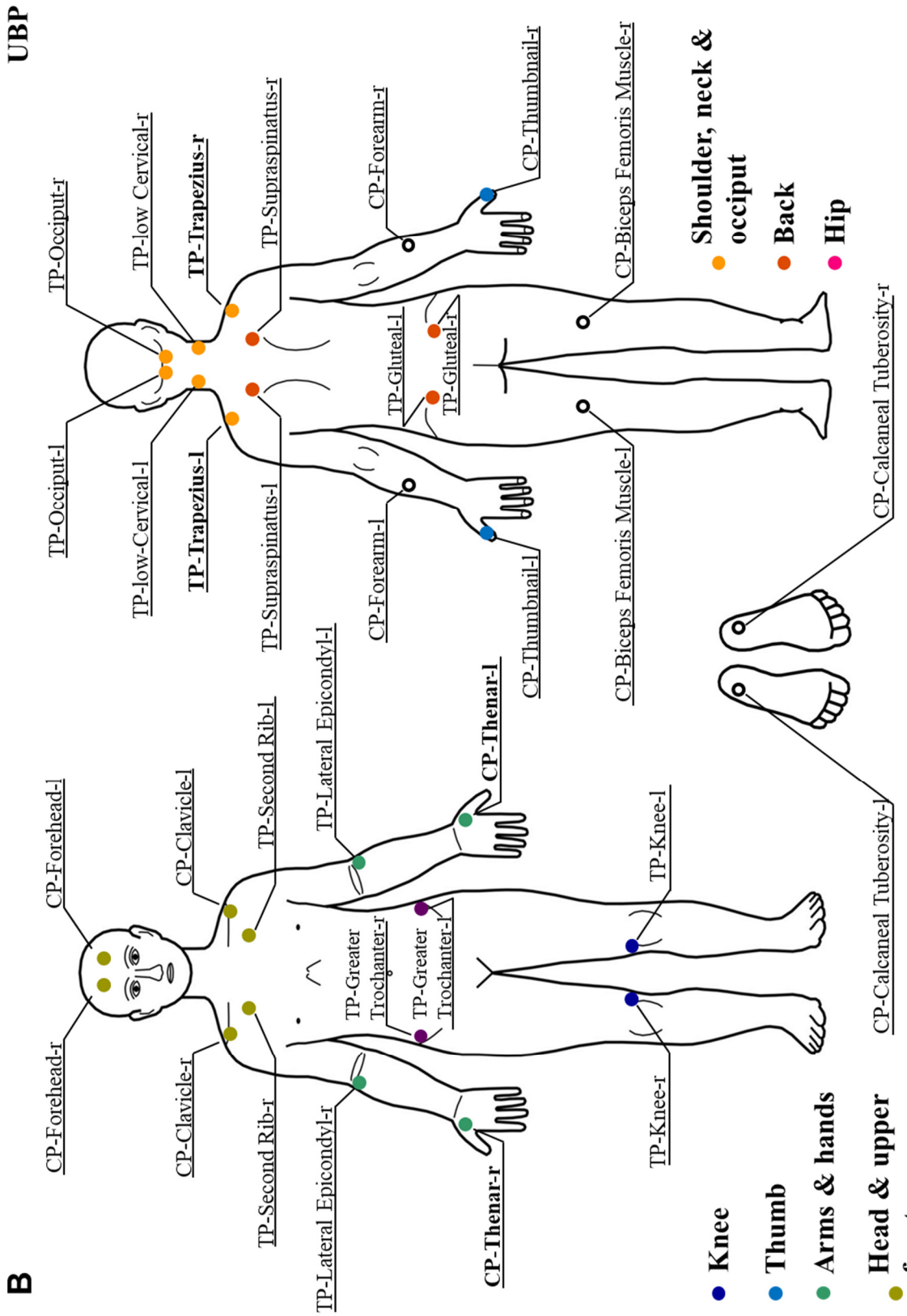
B
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TP-Trapezius-r
TP-Supraspinatus-r
CP-Forearm-r
CP-Thumbnail-r
CP-Biceps Femoris Muscle-r
TP-Occiput-l
TP-low-Cervical-l
TP-Trapezius-l
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TP-Lateral Epicondyl-l
CP-Thenar-l
TP-Greater Trochanter-r
TP-Greater Trochanter-l
TP-Knee-l
CP-Calcaneal Tuberosity-l
CP-Forehead-r
CP-Clavicle-r
TP-Second Rib-r
TP-Lateral Epicondyl-r
CP-Thenar-r
TP-Knee-r
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Shoulder, neck & occiput
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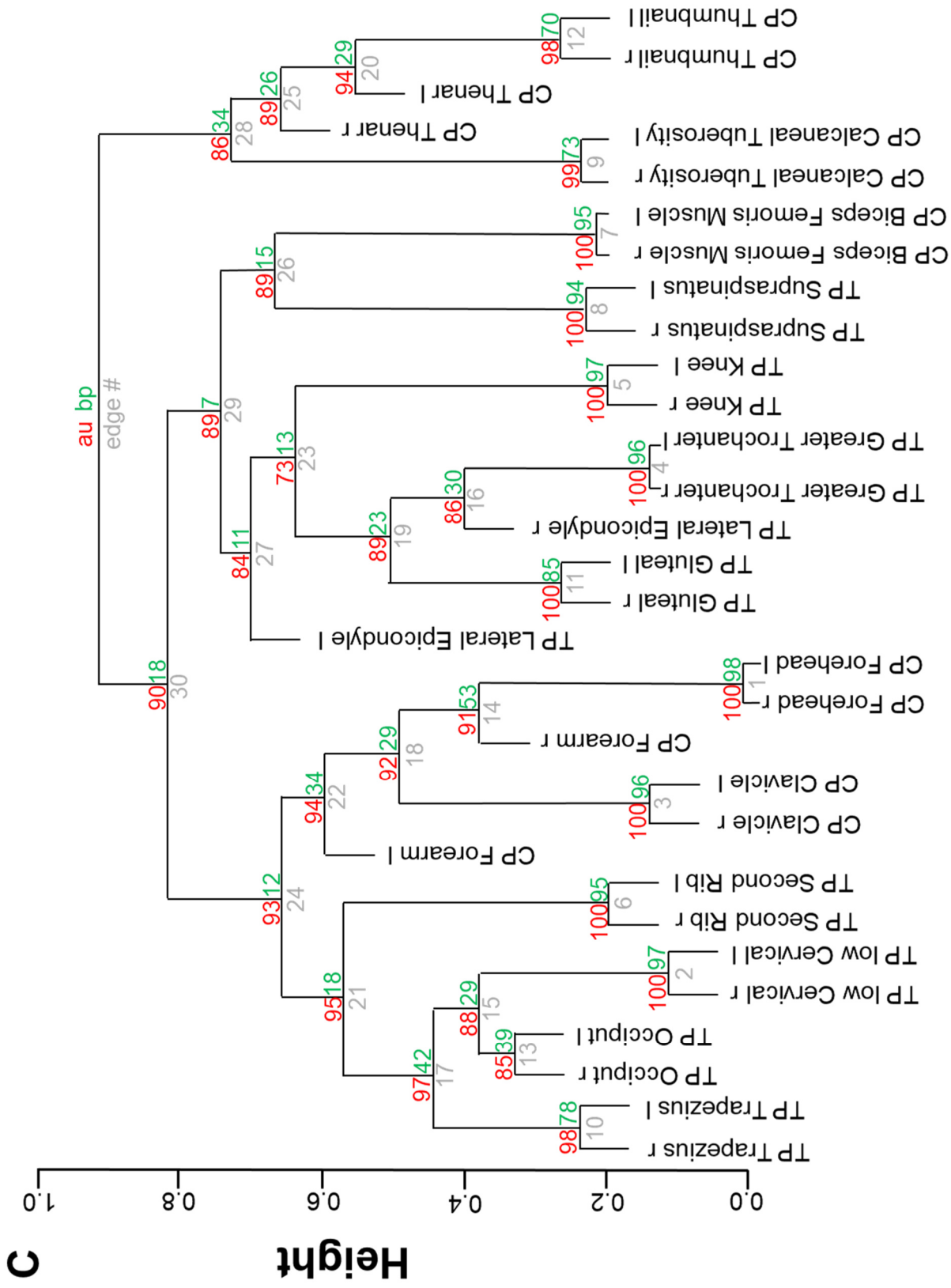
Knee
Thumb
Arms & hands
Head & upper front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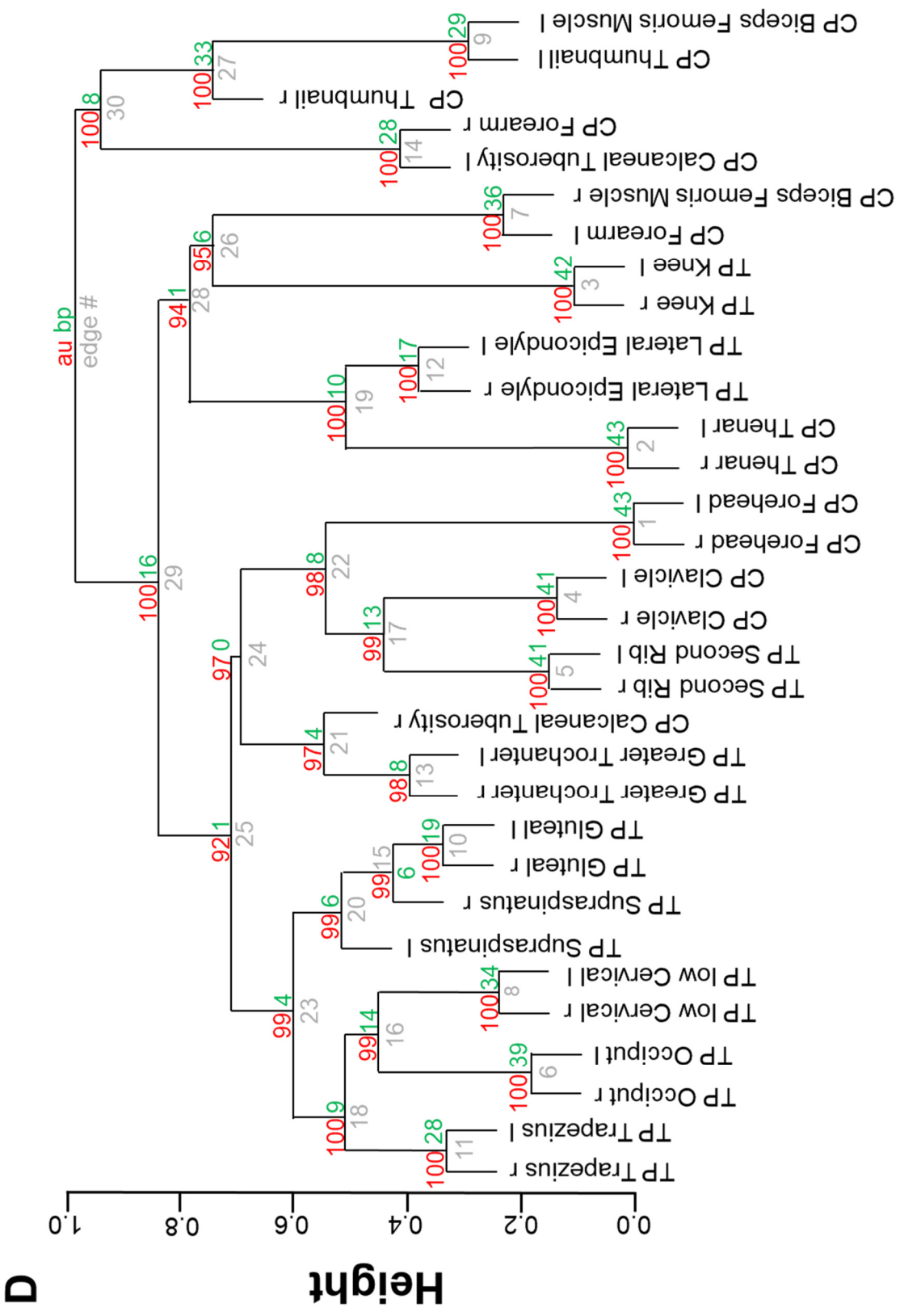
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CP Forehead r
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CP Thenar r
CP Thenar l
TP Lateral Epicondyle r
TP Lateral Epicondyle l
TP Knee r
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CP Forearm l
CP Biceps Femoris Muscle r
CP Calcaneal Tuberosity l
CP Forearm r
CP Thumbnail r
CP Thumbnail l
CP Biceps Femoris Muscle l

Figure 3: *Results of cluster analysis of individual pain intensity ratings at "tender" and "control point" sites; hierarchical latent class with multiscale bootstrap resampling (Suzuki & Shimodaira, 2015). (**A**, **B**): regional clusters of pain sensitivity to manual pressure probing on body map; sites of the same regional clusters on front and back marked by identical colors. (**C**, **D**): cluster dendrogram of sensitive body sites; nodes corresponding to regional clusters. Red and green numbers AU/BP (arbitrary unbiased/bootstrap probability) values of significant clusters (AU ≥ 95% significant). TP = ACR tender point, CP = control point, l = left, r = right; "height" scale on the left: distance from the center of gravity of the particular cluster, i.e., the dissimilarity relative to the other members of the cluster.*
*ACR tender points were clearly separated from control points in the dendrogram for FMS patients (**C**), but not in cUBP (**D**). In FMS patients, tender points on the upper back and cervical region formed a coherent region of pressure pain sensitivity (violet marks in **A**; left dendra in **C**) so did the tender points on the arms and legs including the gluteal and hip (orange and olive marks, medial dendra) and were clearly separated from the control points on the hands and feet (blue marks, right dendra). The control points on the clavicle and the forearm formed a cluster of their own (green marks, separate sub-dendron middle-left). In cUBP, in contrast, pressure pain sensitivity was clustered mainly according to macro-anatomical regions and distributed across ACR tender and control points (e.g., green marks on hands and epicondyle, olive marks on clavicle and second rib, in **B**).*

In FMS, latent class analysis separated pain intensities of the manual probes at tender and control points in functionally and regionally distinct clusters; in cUBP regional clusters were retained also but with tender and control sites in the same clusters. The separation of the regional and functional groupings of pressure pain sensitivities were reproduced by the LCA of the combined algometer and manual test at the exemplary tender and control points on the trapezius and the thenar in both groups (dendrograms in Figure S13 in Supplemental).

In FMS patients, in particular, the cluster of tender points on the back, shoulder, neck and occiput formed a coherent region (pink and purple sites in Figure 3 A) as did the tender points on the extremities (olive, orange) and one on the upper back (supraspinatus, dark orange). These regions of classical tender points separated from the corresponding pressure-sensitive control points (cf. cluster dendrogram in Figure 3 C). Notably, pressure pain sensitivity at control points were arranged in separate regional groups, too, on hands and feet (dark blue), on the clavicle and the forearm (green) and the forehead (turquoise) with the only exception of the CP on the biceps femoris (dark orange). Tender and control points at left and right body sides were consistently linked at the lowest dendrogram level in both FMS and cUBP patients.

The LCA of pressure sensitivities of cUBP patients resulted in a different but also well-structured cluster solution reflecting predominantly anatomical vicinity regardless of the "tender" or "control point" status of the stimulation site (Figure 3 B, D). In particular, tender and control points on the head, upper back and front and the hip were classified

together (olive, orange, red, purple) as were the test sites on the upper and lower extremities (blue and green).

The consistent spatial and functional organization of pressure sensitivities was confirmed by the separate combined LCAs using only the algometer and manual test indicators from the selected exemplary trapezius “tender” and the thenar “control” points at both sides of the body (dendrograms in Figure S13 in Supplemental). Again, tender and control point measures were separated into different sub-clusters in FMS for both algometer and manual tests while in cUBP patients the sub-clusters were classified according to the assessment method, one by the algometer measures, the other by the manual pressure measures irrespective of tender or control point status. This confirms the structural differences to FMS found in the preparatory PCA and argues for the inclusion of both algometer and manual probe measures in the final indicator set for the LCA profiling at the personal level.

3.2.3 Sensitivity to non-mechanoceptive pain: heat-pain

The comparison with heat pain sensitivity at the selected trapezius “tender” and thenar control sites showed that the enhanced pressure sensitivity of FMS patients was not paralleled by the non-mechanoceptive cutaneous pain modality. The characteristic spatial and/or functional differences of pressure pain sensitivity between the exemplary tender and control points were not reproduced and varied widely over different measures of near- and supra-threshold heat pain sensitivity. Phasic heat pain thresholds did not differ between FMS and cUBP at both sites (averages: 44.7 ± 3.0 °C vs. 46.1 ± 2.6 °C) while tonic heat pain thresholds at the thenar of FMS patients tended to be lower than in cUBP (43.3 ± 1.7 °C vs. 44.6 ± 1.6 °C; $p < 0.05$, uncorrected). Accordingly, phasic as well as tonic heat pain thresholds at the thenar of healthy controls were higher than in FMS patients (e.g., PT_{lim}: 46.2 ± 2.3 vs. 43.4 ± 2.9 °C; $p < 0.001$). Supra-threshold sensitivity to heat pain in terms of pain intensity as a function of stimulus temperature did not differ between groups (cf. summary of sensory assessments for heat pain in Table S14 in Supplemental).

These differential patterns of heat pain indicators across body sites and prior diagnostic groups were incorporated in the measurement model for the non-mechanoceptive modality. It consists of a minimal set of heat pain sensitivity parameters derived from the intercorrelations between specific measures of the extended initial assessment set (summary of correlation and principal component analysis of heat pain indicators in Table S15 & S16 in Supplemental). In particular,

phasic self-adjusted (PT_{adj}) and tonic heat pain thresholds (PT_{ton}) at the same site were highly correlated in both FMS (ρ, thenar: 0.923; trapezius: 0.956; $p < 0.001$) and cUBP patients (ρ, thenar: 0.915; trapezius: 0.863; $p < 0.001$). Threshold correlations between stimulation sites, however, were low or insignificant in FMS patients and only moderate in cUBP. This reproduces the intercorrelations of algometer thresholds in FMS vs. cUBP described earlier. Heat pain thresholds correlated weakly with supra-threshold pain intensities in FMS patients (0.217 - 0.653; $p < 0.05$) and moderately in cUBP (0.414 - 0.517; $p < 0.01$). Stimulation method mattered being highest between thresholds with similar stimulation and response mode, that is, for $PT_{adj} \times PT_{ton}$. Therefore, only one phasic threshold and one tonic threshold per site and supra-threshold pain intensity were included in the final set of heat pain sensitivity markers for the identification of pressure and heat pain phenotypes below. In addition, the behavioral measure (ΔT) of temporal summation after 30 s of tonic heat was retained as an indicator of short-term sensitization or “wind-up” in which FMS differed from healthy controls (t-test: $p = 0.032$) although not from cUBP. We assumed that the sensory heterogeneity of the prior diagnosis groups could have obscured relevant differences in sensitization propensities between subgroups with widespread and/or regional pain however apt to show different sensory profiles at final reclassification.

The suggested measurement model for heat pain sensitivity for the cross-modal comparison was verified stepwise by principal components analysis and latent class analysis. The former comprised several successive exploratory PCAs with partial heat pain vectors to maximize entry numbers for specific combinations. First, only heat pain thresholds at the two selected tender and control sites on the trapezius and thenar, were entered; second, supra-threshold intensity and, third, temporal summation were added (cf. PCA overview in Table S16 in Supplemental). The first threshold PCA yielded two distinct components for both FMS and cUBP explaining respectively 88.5 % and 81.3 % variance with different compositions: In FMS, the two components represented the “tender” (trapezius) and “control points” (thenar) with high loadings of phasic and tonic thresholds from left and right body sides. In cUBP, in contrast, the two principal components were not related to the functional difference between the trapezius and thenar but to method differences between phasic and tonic thresholds. This corresponds to the correlations above and reflects analogous group-specific relations in pressure sensitivity (section 3.2.1.). The second exploratory PCA with supra-threshold heat pain intensity at corresponding stimulation sites separated near-

threshold from supra-threshold sensitivity on two different components explaining 76.2 % and 79.3 % variance in FMS and cUBP, respectively. This underscores the difference between heat pain thresholds and supra-threshold sensitivity and the necessity to include both in sensory profiling. The third exploratory PCA including temporal summation yielded a separate third sensitization component in FMS patients (72.3 % variance). In cUBP thresholds formed also a separate component while temporal summation loaded together with supra-threshold intensity on the second of two components (62.8 % variance). These exploratory PCAs showed that (1) heat pain thresholds, (2) supra-threshold sensitivity and (3) temporal summation are independent aspects of thermo-nociceptive processing and at least one marker of each heat pain dimension would be necessary in a comprehensive sensory profile. Further, the non-mechanoceptive pain modality at “tender points” appeared to differ also from that in control points and should be represented in the sensory profile.

This was confirmed in the subsequent LCA of the full heat pain vector which resulted in simple 2-cluster structures reproducing the PCA components with important specifications (dendrograms in Figure S17 in Supplemental): In both FMS and cUBP patients, phasic heat pain thresholds, PT_{lim}, were well separated from tonic thresholds, PT_{ton} (AU/BP: FMS = 100/99; cUBP = 100/94). The LCAs with supra-threshold intensity and temporal summation confirmed the PCA in classifying thresholds, intensity ratings and temporal summation in different clusters. As behavioral and subjective measures of the latter (ΔT, ΔE) were equivalent, only ΔT was included as sensitization marker in the final thermo-nociceptive indicator set used for the cross-modal group comparison of pressure pain sensitivity with the non-mechanoceptive sensory modality.

3.2.4 Transmodal hyperalgesia

To identify transmodal factors and sensory classes of generally enhanced pain sensitivity common to pressure and heat pain sensitivity (hypothesis #6) relevant for comprehensive sensory phenotyping combined LCAs were run on a further minimal indicator set of both. Again, preparatory correlation and principal component analyses were necessary to minimize the entered indicator vectors to retain maximal eligible cases for sufficient power of the combined cluster analyses.

3.2.4.1 Correlations between pressure and heat pain sensitivity

Pressure and heat pain sensitivity indicators (thresholds, supra-threshold intensity) correlated weakly to moderately with each other in FMS and mostly insignificantly in

cUBP patients (overview in Table S18 in Supplemental). Sporadic correlations distributed across measures and body regions in both groups and were higher within homologous than across different body regions (FMS: algometer pain × phasic heat pain thresholds: ρ = 0.452, p < 0.05; cUBP: n. s.). Remarkably, the number of sensitive ACR “tender” and control points of FMS patients correlated also with the heat pain thresholds at the trapezius “tender” ($\rho = -0.430$, p > 0.01) and the thenar control point (– 0567, p < 0.05). In FMS, temporal summation to heat correlated also moderately with the algometer pressure pain threshold and intensity on both the trapezius and the thenar suggesting that temporal heat summation reflected a generalized tendency to sensitize in this group with widespread pain. However, sample size was much reduced for this parameter combination (26) and enough cUBP data were not available for comparison. The measure was retained nevertheless in the combination of pressure and heat pain indicators for the following PCA and LCA of FMS data.

3.2.4.2 Transmodal dimensions of pain sensitivity

Common trans-modal dimensions of pressure and heat pain sensitivity were extracted by exploratory PCAs of site-specific and regional averages of pressure pain sensitivity combined, first, with heat pain thresholds at corresponding sites and, second, with supra-threshold heat pain intensity and temporal summation added (overview in Table S19 & S20 in Supplemental).

The transmodal PCA of pressure and heat pain sensitivity of FMS patients (excluding summation) resulted in three principal components explaining 65 % of the variance: The first component (27.0 % variance) represented a combination of the spatial spread of pressure sensitivity (number of sensitive tender and control points) with heat pain thresholds at the thenar reference; the second component (22.1 %) combined the algometer measures of pressure sensitivity (thresholds, supra-threshold intensity) with the heat pain thresholds at the trapezius tender point. The independent third component (15.9 %) contained only pressure pain sensitivity at the trapezius “tender point”. Using regional averages of pressure and heat pain sensitivity resulted in corresponding components. The separate PCA including the behavioral temporal summation measure (ΔT) and the absolute intensity at the end of 30 s tonic heat of FMS patients yielded five components (74% variance) with a separate component for the sensitization indicator ΔT (mean and temperature gradient; 12.4 %, cf. Table S21 in Supplemental). The other factors reproduced the basic FMS structure described above with more or less similar cross-modal and modality-specific loadings.

The transmodal PCA of cUBP data (restricted to phasic heat pain thresholds) produced four components (80 % variance) repeating the method-specific loading pattern of the separate PCAs of pressure and heat pain sensitivity which differed characteristically from that of FMS. The first three components were composed exclusively of pressure pain indicators from the manual probe (first component, 29.5 %: number of sensitive tender and control points; pain intensity at the trapezius) and the algometer test (second component, 20.2 %: supra-threshold pain intensity at the trapezius and the thenar; third component: algometer pressure pain thresholds). Heat pain thresholds loaded on a separate fourth thermo-nociceptive component.

3.2.4.3 Transmodal clusters of pain sensitivity

The principal components of the combined set of pressure and heat pain sensitivity measures were used to select optimal indicator sets for two separate LCAs to identify cross-modal sensory phenotypes with maximum case numbers despite increased sample attrition after including heat pain measures. The first LCA included pressure and heat pain thresholds and supra-threshold intensities from corresponding sites at the right trapezius “tender” and the left thenar control point. The second LCA used average pain intensities of sites in the functional anatomy regions of the Heidelberg pain drawing mask (head-cervical, thoracic, lumbar, upper and lower limb region) instead of individual test sites to account for regional associations. Two main clusters of pressure and heat pain sensitivity measures at the trapezius and thenar were found with some composition differences between FMS and cUBP. The second LCA with regional averages reproduced the general two-cluster structure corresponding to anatomical regions (cf. Figure S22 in Supplemental).

In FMS patients, the main cluster 1 was pressure pain-specific composed of the semi-quantitative manual probe and the quantitative algometer test in method-specific sub-clusters. The manual probe sub-cluster comprised the number of hypersensitive body sites together with the pain intensity of the probe at the trapezius “tender” and the thenar control point. Tender and control point measures were well separated at the third and fourth level. The pain ratings of the quantitative algometer test at the trapezius tender point and the thenar control point classified appropriately in the algometer sub-cluster. Main cluster 2 collected the pain thresholds in both modalities at the selected tender and control sites on the trapezius and thenar with algometer pressure and thermode heat pain thresholds in modality-specific sub-clusters at the second dendron level. The trapezius tender point site at the back separated from the control site at the

thenar at the third dendron level in both modalities. Phasic and tonic heat pain thresholds on the left and right body side grouped together at the lowest level apparently measuring the same sensitivity aspect.

In cUBP, the main cluster 1 was pressure-specific as in FMS patients including the numbers of hypersensitive tender and control points with the pain intensity ratings of both the manual and the algometer test at the trapezius tender as well as the thenar control point (cf. Figure S22 b, left in Supplemental). Main cluster 2 contained all threshold measures of both modalities as in FMS; however, the site-specific and function-related grouping of heat pain thresholds at the trapezius tender point versus the thenar control point was not retained and substituted by method-specific sub-clusters within the heat pain modality (phasic vs. tonic heat pain thresholds). The second, region-related LCA revealed another striking deviation in classifying the pain intensity of the manual probes in the lumbar region with the heat pain thresholds. This deserves consideration with respect to the high prevalence of lower back pain in our sample of cUBP patients (63.6 %).

Additional exploratory site- and region-related cross-modal cluster analyses of pressure and heat pain indicators were run with supra-threshold sensitivity to tonic heat and temporal summation of heat as indicator of cross-modal short-term sensitization for which complete data were available only for FMS patients (cf. Figure S22 e,f in Supplemental). Here the previous modality specificity of pressure and heat pain measures was lost and the heat pain thresholds and supra-threshold heat pain intensity clustered together with number of sensitive tender and control points. Remarkably, temporal heat pain summation was linked to the algometer pressure threshold. This would argue for a common source of general pain sensitivity and the inclusion as classificator for the sensory phenotyping at the patient level.

3.3 Sensory and clinical phenotypes in patients with prior diagnoses of fibromyalgia and chronic unspecific back pain

The statistical and structural analysis of semi-quantitative and quantitative sensory characteristics defined the necessary and sufficient indicator set for the sensory phenotyping in relation to clinical pain characteristics of the FMS and cUBP patients. Accordingly, the optimal set of sensory parameters should include one representative of (1) the spatial distribution of hypersensitivity to percutaneous pressure; (2) quantitative sensory test measures of pressure pain sensitivity; and (3) quantitative

sensory test measures of cutaneous heat pain sensitivity from representative body areas.

However, combining the heat pain sensitivity with hypersensitivity to pressure stimulation and essential aspects of clinical pain resulted in small case numbers in the available database and low power. Further, preparatory correlational analysis showed that heat pain parameters correlated only scarcely with clinical pain in both FMS and cUBP patients (cf. overview in Table S23 in Supplemental). In contrast, pressure pain sensitivity correlated at least moderately with clinical pain, in particular, the number of sensitive “tender points” with the WPI (number of regions in pain; FMS: $\rho = 0.287$; $p = 0.003$, < 0.01, corrected; cUBP: n. s.). In addition, these correlations appear to be underestimated because both the WPI and the numbers of sensitive test points are scale-limited variables subject to ceiling effects in FMS and floor effects in cUBP (cf. lower and upper scale limits in Figures 1, 2 and Figure S24 in Supplemental).

Therefore, the final sensory profiling by LCA at the patient level concentrated on the necessary indicators of pressure sensitivity (categories 1 and 2) and sufficient clinical pain markers (WPI and current pain intensity). Heat pain sensitivity was compared only ex post between the sensory-clinical phenotypes identified by the LCA in relation to prior FMS and cUBP diagnoses (section 3.3.3.).

3.3.1 Profiles of pressure pain sensitivity and clinical widespread pain

Initial exploratory LCA runs with the combined set of pressure pain sensitivity and clinical pain characteristics derived above showed that no more than six classifiers should be entered to produce stable profile clusters given the number of FMS and cUBP patients with complete data sets remaining in the analysis (69 and 90). The best six classifiers (BIC and CAIC indices) included present pain intensity and number of pain regions as clinical characteristics with selected pressure sensitivity indicators from the manual probe and the algometer test, i.e., number of sensitive “tender” and “control points”, test pain intensity and the algometer pressure pain threshold at the right trapezius “tender point”. In the following, only this final LCA on the total sample of 159 patients with reliable and interpretable cluster solutions is reported (Figure 4; further information on LCAs methods, fit criteria, etc., in Table S25 and Table S26 in Supplemental).

The LC model with four clusters of patients with prior diagnoses of either FMS or cUBP fitted best (BIC, CAIC) with very similar profiles irrespective of whether the number of

pain sites was based on current or major pain or the WPI. Sensory-clinical profiles differentiated best when the WPI was used for the spread of pain regions as clinical marker (Figure 4). These characteristic sensory phenotypes were reproduced with female data only to control for the uneven gender distributions in the FMS and cUBP groups (cf. Table S27; Figure S28 in Supplemental).

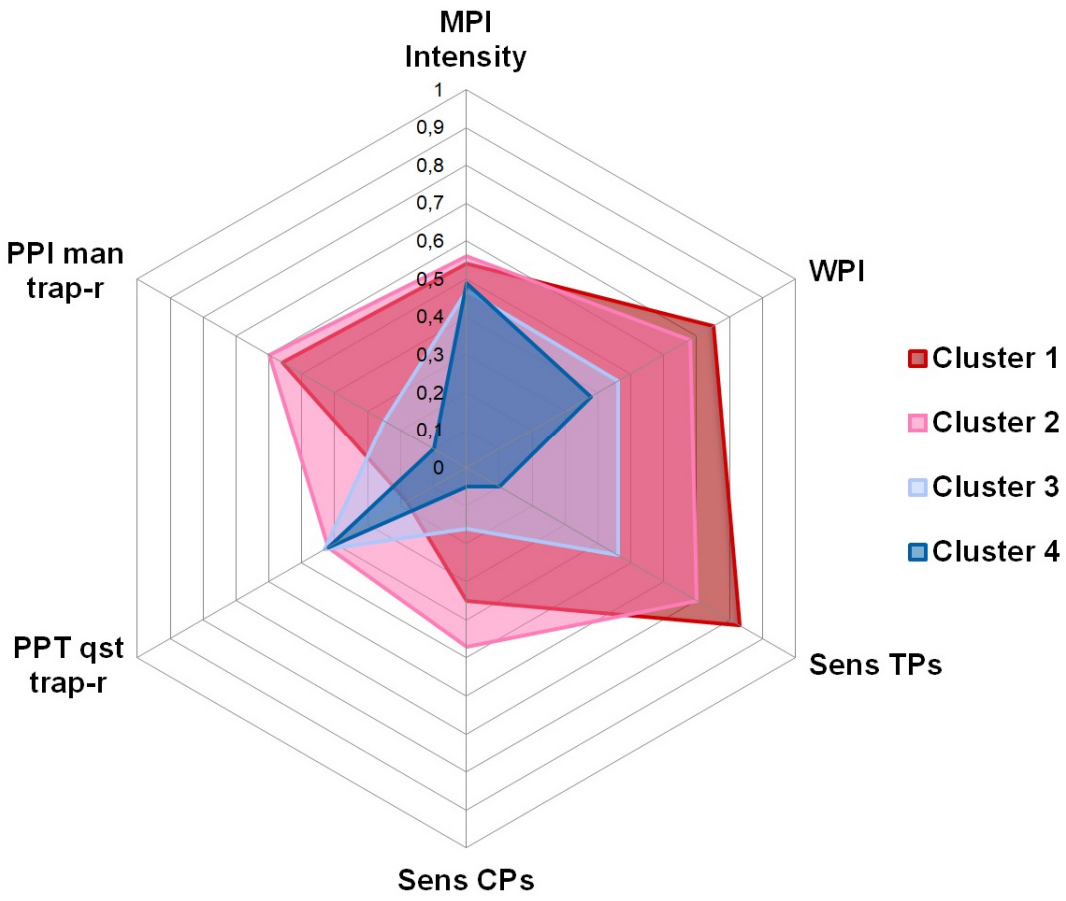

Figure 4: *Discriminator profiles of four phenotypes of pain and pressure sensitivity of patients with prior FMS and cUBP diagnoses. Polar chart of sensory-clinical profiles of the four main clusters of FMS and cUBP patients identified by the LCA with the best fit (BIC/CAIC indices) for the reduced indicator set. Polar axes: range-standardized means of indicators (0 – 1; cf. Vermunt & Magidson, 2015). MPI Intensity = present pain intensity (MPI-D, scale 1, item #1); WPI = Widespread Pain Index; Sens TPs = number of sensitive ACR "tender points"; Sens CPs = number of sensitive control points; PPT qst trap-r = pressure pain threshold at the right trapezius in quantitative algometer test; PPI man trap-r = pressure pain intensity at the right trapezius in semi-quantitative manual probe.*
Highly pressure-sensitive clusters 1 and 2 (dark red and pink) overlap considerably. They are primarily characterized by widespread pain (high WPI), many pressure-sensitive ACR "tender points" and a relatively high number of sensitive control points as well as distinct pain of the manual probe at the trapezius tender point. Cluster 1 was distinguished additionally by the very low pressure pain threshold in the algometer test. The low pressure-sensitive clusters 3 and 4 (light and dark blue) exhibited a low WPI and few sensitive "tender" and control points. Pain intensity of the manual probe at the right trapezius was also low.

All four clusters were characterized by medium intensity of current pain divided into two cluster pairs with high vs. moderate WPI and high vs. low pain intensity in the manual sensitivity test (cluster 1 & 2 vs. cluster 3 & 4 in Figure 4). The first cluster pair with widespread pain and high pressure sensitivity and the second cluster pair with narrow spread pain with low pressure pain sensitivity were further differentiated into four sensitivity categories from low to high by the numbers of sensitive tender and control points. In addition, cluster 1 was differentiated from all other clusters by the very low pressure pain threshold in the quantitative sensory algometer test. Note also that not only the number of sensitive ACR tender points but also of sensitive control points differentiated the widespread pain clusters 1 and 2 from the clusters 3 and 4 showing very few pressure-sensitive control points.

Table 4. Four clusters of clinical characteristics and sensory phenotypes in patients with FMS and cUBP

(A) Prior FMS and cUBP diagnoses

	Cluster				
Prior Diagnosis	**1**	**2**	**3**	**4**	**Σ**
FMS	44 [a] (94/64)	16 (76/23)	0 [b] (0/0)	9 (16/13)	69
cUBP	3 (6/3)	5 (24/6)	33 (100/37)	49 (84/54)	90
FS ≥ 12	40 (85/49)	17 (81/21)	5 (15/6)	19 (33/23)	81
< 12	7 (15/9)	4 (19/5)	28 (85/39)	39 (67/50)	78
Σ	47	21	33	58	159

Correlation clusters × prior FMS and cUBP diagnoses: $C_{corr,} = 0.881$, $p < 0.001$; clusters × FS ≥ 12: $C_{corr} = 0.713$, $p < 0.001$. Notes. Cluster numbering according to rank order of numbers of sensitive tender points; LCA maximum likelihood extraction sequence 4-1-3-2.

(B) Discriminator profiles

	Cluster				
Indicator	1	2	3	4	**Distance [g]**
1. Sensitive Tender Points [c]	16 ± 1.5 [89 ± 8]	13 ± 3.0 [72 ± 17]	0 + 2 [b] [0 + 14]	6.5 ± 3 [36 ± 17]	0.404
2.Pressure Pain intensity [d]	6.0 ± 2.0	6.0 ± 1.5	0.0 ± 0.0 [b]	2.0 ± 2.0	0.330
3.WPI [c]	13 ± 3.0 [68 ± 16]	11 ± 3.0 [68 ± 16]	4 ± 2.0 [b] [21 ± 11]	5 ± 1.6 [26 ± 09]	0.248
4.Sensitive Control Points [c]	3 ± 2.5 [21 ± 18]	6 ± 2.3 [43 ± 20]	0 ± 0 [b]	0 + 2 [0 + 14]	0.242
5.Pressure Pain Threshold [e]	1.8 ± 0.6	4.0 ± 0.0	4.0 ± 0.5 [b]	4.0 ± 1.5	0.130
6. Present Pain Intensity [f]	3.0 ± 0.5	4.0 ± 0.5	3.0 ± 1 [b]	3.00 ±1	0.060
Description	***widespread pain***; highly pressure-sensitive	***mixed pain***; moderately pressure-sensitive	***regional pain***; weakly pressure-sensitive	***mixed pain***; normally pressure-sensitive	

[a] *Absolute frequencies; in brackets: column/row %. Cluster 1 & 2: "FMS-like"; cluster 3 & 4: "cUBP-like".*
[b] *No prior FMS diagnoses in cluster 3.*
[c] *Absolute frequencies; in brackets: % of points tested (18 ACR tender points, 14 control points, 19 WPI body sites); medians ± 0.5 IQD.*
[d] *Pressure pain intensity of the manual test at the right trapezius, VAS rating 0 – 10; medians ± 0.5 IQD.*
[e] *Pressure pain threshold algometer test; means ± SD.*
[f] *Present pain intensity (MPI-D, item #1), NRS scale 0 – 6; medians ± IQD.*
[g] *Absolute cluster mean differences between all cluster pairs for the indicator (0 – 1 standardized means; cf. Vermunt & Madison, 2005). Notes. The non-parametric estimator does not regard oblique relations between profile vectors; it results in ordinal ranking of the LCA discriminators for parameter selection, but not for statistical testing. See also section on cross-validation of LCA sensory profiles and Table S26 in Supplemental, Standardized point distances per indicator.*

The best discriminating indicators according to absolute profile distances between the four clusters was the number of sensitive tender points followed by the pain intensity rating at the trapezius tender point in the manual test and the WPI of clinical pain (Table 4 A). The first two sensory discriminators differed significantly between all four clusters (Kruskal-Wallis & pairwise U-tests: number tender points: $p = 0.012$; pain intensity trapezius: $p < 0.001$, both corrected familywise; complete sensory statistics in Table S29 in Supplemental). The WPI differentiated only between the high and low sensitivity cluster pairs but not within them (cluster 1 & 2 vs. cluster 3 & 4: U-test, $p < 0.001$; corrected single contrasts, n. s.). The low pain threshold in the algometer test at the trapezius differentiated cluster 1 from the rest ($p < 0.001$, uncorrected) suggesting a unique phenotype within the widespread pain population.

The clinical and sensory profiles in Figure 4, however, are not accompanied by differences in clinical pain intensity despite the obvious differences in spatial spread as well as pressure pain sensitivity. Whether this relates to differences between subgroups of diagnostic syndromes is clarified by the reclassification of clinicians' prior diagnoses and the diagnoses according to the Fibromyalgia Symptom scale (FS ≥ 12) into the four posterior clusters according to LCA-derived sensory-clinical phenotypes (Table 4 A).

Prior FMS and cUBP diagnoses were distributed meaningfully and highly significantly different over the four clusters (Table 4 A; $p < 0.001$; corrected contingency, $C_{corr} = 0.881$, df = 3). Clusters 1 and 2 with high WPI and many sensitive tender points comprise most FMS patients (87 %) and cluster 1 collected two thirds of them. The latter was also differentiated from all other clusters by the lowest pressure pain threshold in the quantitative algometer test. In contrast, clusters 3 and 4 with low to moderate WPI contain 91 % cUBP patients showing also low pressure sensitivity in the manual and the algometer test. Cluster 3 with the least sensitive patients consists only of cUBP patients and no FMS patients at all. Cluster 4 with low to medium pressure sensitivity contains mainly cUBP patients (84.5 %) and only 9 (15.5 %) FMS patients. Table 4 B illustrates the close relations between the clinical profiles of widespread vs. regional pain and the phenotypes of high and low pressure sensitivity. However, it shows also that the prior diagnosis groups of FMS and cUBP were inhomogeneous and may be reclassified by sensory phenotypes into at least four subgroups with different clinical and pathogenetic profiles.

This becomes particularly clear by cross-tabulating clusters and screening diagnoses according to the Fibromyalgia Scale criterion of ≥ 12: The FS criterion misclassified not only 20 % of clinicians' prior diagnoses (FMS: 19 %; cUBP: 21 %) but the cross-classification with the pain-pressure sensitivity phenotypes of the four clusters was more variable and more patients belonging to clusters 1 or 2 vs. 3 or 4 were misclassified (FS ≥ 12: 30 %; FS < 12: 14 %). Moreover, it is apparent from the 3-way classification of the four pain-pressure sensitivity clusters with prior clinicians' diagnoses and FS screening diagnoses: Clusters largely correspond to clinical diagnosis, but the FS criterion led to misclassification especially in the cUBP patients in cluster 3 and 4 (FMS: 14%, cUBP: 24 %, C_{corr} = 0.310 and 0.331, df = 3, n. s., Table 4). These results are in line with the mismatch of prior diagnoses (FMS vs. cUBP) and the FS screening diagnoses (FS ≥ 12, cf. Table 2, section 3.1) and question the discriminative validity of the screening instrument.

3.3.2 Discriminant analysis of widespread vs. regional pain

The discriminative power of the selected indicator set characterizing the 4-cluster classification was cross-validated with stepwise discriminant function analysis with individual indicators entering in the order of their absolute distance scores (cf. Table S26 in Supplemental). Three canonical discriminant functions of the four sensory indicators alone sufficed to differentiate the four clusters (functions 1∗2: Wilks Λ = 0.093; 2∗3: Λ = 0.595; function 3: Λ = 0.881; p < 0.001; overview in Table S30 in Supplemental). Pain intensity and WPI added not substantially to cluster discrimination although contributing to cluster building by LCA. The first discriminant function explained 89.8 % of the variance (canonical R^2 = 0.84), the second 7.9 % (canonical R^2 = 0.32) and the third 2.2 % (canonical R^2 = 0.12). Importantly, clusters were systematically positioned in the discriminant function space where clusters 1 and 2 were well separable from 3 and 4 with less good discrimination within these pairs in accord with the cluster pair characterization above (Figure 5).

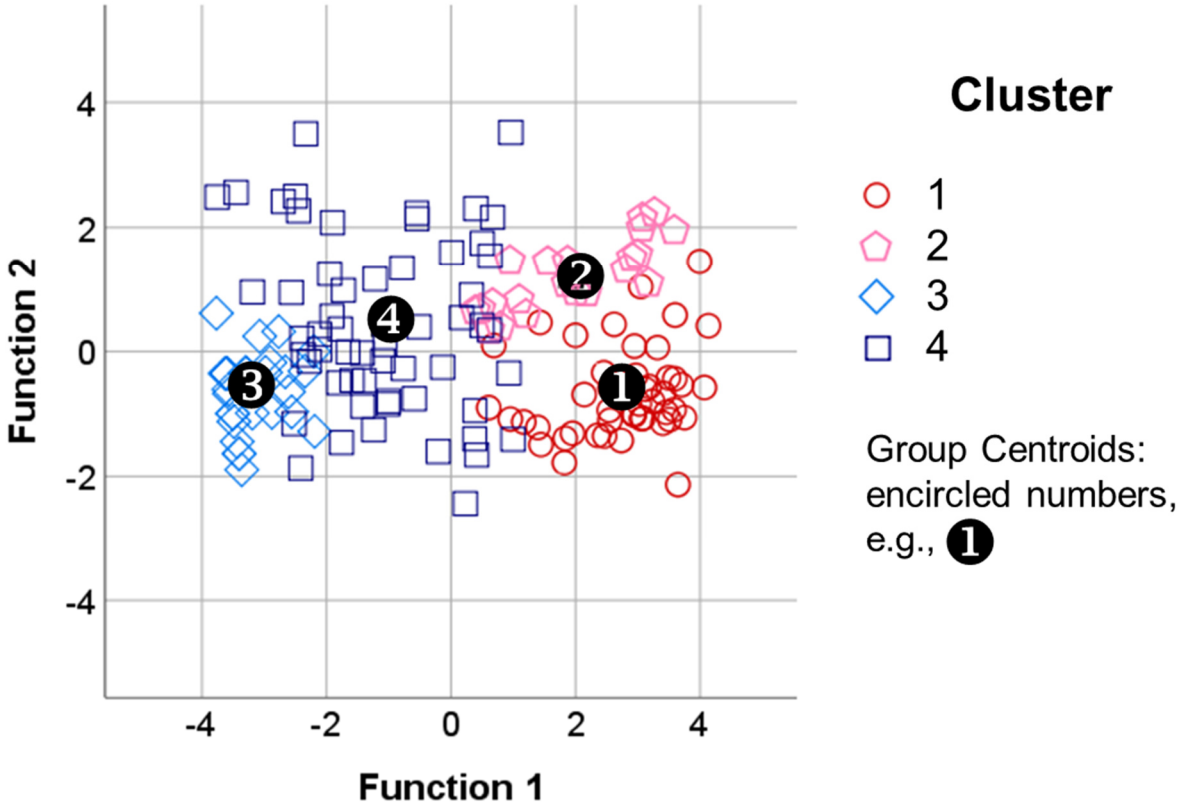

Figure 5: *Discriminant analysis validation of sensory-clinical phenotypes of widespread and regional pain. Result of the linear discriminant function analysis of sensory-clinical phenotypes based on the four clusters shown in Figure 4: Location of patients in the 2-dimensional projection of the 3D orthogonal discriminant function space. Abscissa: Function 1 (first step separation with highest weights for semi-quantitative manual test); ordinate: function 2 (second step separation with highest weight for quantitative algometer test); function 3 (least discriminating) omitted. Cluster centroids are shown as numbered filled black circles.*
Standardized canonical discriminant function coefficients: Function 1 = 0.868 × Sens TPs + 0.415 × PPI man trap-r – 0.035 × Sens CPs – 0.149 × PPT qst trap-r;
Function 2 = 0.024 × Sens TPs + 0.179 × PPI man trap-r + 0.367 × Sens CPs + 0.915 × PPT qst trap-r; Function 3 = – 0.547 × Sens TPs + 0.244 × PPI man trap-r + 0.921 × Sens CPs – 0.393 × PPT qst trap-r (parameter abbreviations as in Figure 4).
High-sensitive patients with widespread pain in cluster 1 and 2 (red circles and pentagons) are concentrated on the right according to their high positive values in the manual test. The singularly low-sensitive cUBP patients of cluster 3 concentrated in the lower left according to their negative values on function 1. Note the high concentration of cluster 1 patients in the lower right and of cluster 2 above them separated by the second discriminant function according to the quantitative algometer test values suggesting two more homogeneous subgroups to be identified by improved quantitative sensory testing. While these three clusters exhibit more or less homogenous subgroups, the moderately sensitive patients with mixed pain in cluster 4 vary considerably and distribute from the middle to the left overlapping partially with the other clusters. However, the second discriminant function separates a subgroup of this cluster on the upper left which might also be identified with more comprehensive quantitative sensory testing.
Technical note. A stepwise linear (orthogonal) discriminant function analysis was calculated with four a priori groups and Wilks' lambda for variable selection using SPSS version 25 (IBM, Armonk, NY, USA).

Number of sensitive ACR tender points had the highest weight on the first function followed by the pain intensity of the manual probe on the trapezius tender point. The algometer pressure pain threshold obtained the highest weight on the second discriminant function, whereas the number of sensitive control points contributed most to the third function. The three functions classified 82.4 % of the original LCA groupings correctly (N = 131). The control analysis with listwise inclusion of sensory and clinical indicators did not improve the correct classification rate (84.3 %; N =134).

False classifications of patients with respect to the original four sensory-clinical phenotypes occurred only between clusters 1 and 2 and between 3 and 4 by the discriminant functions leaving out intensity and spatial spread (WPI) of the clinical pain. Patients in cluster 3 having no sensitive tender point and, consequently, reporting no pain in the manual test at the trapezius tender point were 100 % correctly classified. This relates to the high frequency of cUBP patients in this cluster (33; 37 %) and the fewest critical WPI (FS ≥ 12) of all clusters (cf. Table 4). Cluster 2 classification was second best with 90.5 % correct. Cluster 1 (the highly pressure sensitive cluster with widespread pain) and cluster 4 (the low sensitivity cluster with several pain loci) were predicted less well with 80.9 % and 70.7 % correct, respectively. Overall classification into one of the two cluster pairs by the sensory profiles was much better and error rates dropped to 4.4 % (1 or 2) and 6.6 % (3 or 4).

3.3.3 Heat pain sensitivity and widespread pain

Exploring trans-modal associations of pain sensitivity with clinical pain characteristics was constrained by the small numbers of patients with complete data remaining in the analysis (33 FMS, 20 cUBP). Nevertheless, the robust LCA with the minimal sensory and clinical pain indicator set extracted by the pre-analyses (section 3.2.4) generated a stable, convergent 2-cluster solution with the WPI and present pain intensity as clinical markers, the number of sensitive tender points and algometer thresholds as indicators of pressure sensitivity and the tonic heat pain threshold at the thenar control point as cutaneous, non-mechanoceptive pain reference. These clusters related well to the two pairs of patient clusters found without heat pain: Cluster 1 was characterized by high WPIs and heightened pressure as well as heat pain sensitivity reflecting the first, high-sensitive cluster pair while cluster 2 contained the patients with low to moderate WPIs and lower sensitivity in both modalities related to the second, more insensitive cluster pair. Furthermore, patients with prior FMS and cUBP diagnoses

classified differentially also on the two cross-modal clusters (cluster 1: 79 % FMS, 5 % cUBP; cluster 2: 21 % FMS, 95 % cUBP; $p = 0.001$; $\chi^2 = 27.13$, $df = 1$).

This tentative cluster model was corroborated by direct ex-post comparisons with higher power including all patients for whom any heat pain measures data were available at all (69 FMS; 90 cUBP). This showed that only heat pain thresholds differed significantly between the four clusters (cluster 1 and 2 combined against cluster 3 and 4 combined: tonic heat pain threshold trapezius and thenar, $p < 0.001$; phasic heat pain thresholds at trapezius and thenar, $p = 0.049$ and 0.002); neither supra-threshold heat pain intensity nor temporal summation differed.

In summary, while there is evidence of cross-modal lowering of pain thresholds, in general, heat pain sensitivity does not add substantially to sensory phenotyping of the reclassified patient groups characterized by widespread pain and enhanced pressure pain sensitivity. Therefore, the following comparisons of coping with pain and secondary factors such as somato-psychic comorbidity and psychosocial factors will be based on the sensory and clinical phenotypes identified by the four clusters of widespread or regional pain with high or low pressure-pain sensitivity.

3.4 Comorbidity, coping and psychosocial factors in four clusters of clinical pain and pressure sensitivity

The subgroups of patients with prior diagnoses of FMS or cUBP identified by the four clusters of clinical and sensory phenotypes were further explored with respect to derived pain aspects not included in clustering, in particular, pain impact and coping, chronicity, functional level, comorbidity as well as psychosocial co-factors often associated with fibromyalgia and/or chronic unspecific back pain. Table 5 shows the results of corresponding group comparisons which differed from the general descriptive statistics of the prior diagnosis groups of section 3.1 (cf. Table 2).

Table 5. Pain characteristics, coping, comorbidity and psychosocial factors in four clusters of sensory-clinical phenotypes

(A) Pain characteristics of four clusters of sensory-clinical phenotypes

Cluster	**1**	**2**	**3**	**4**
Age [yrs.]	49.9 ± 8.9	48.4 ± 12.9	47.5 ± 13.7	50.2 ± 11.3
	[22 – 63]	[23 – 68]	[18 – 67]	[23 – 68]
Sex [f/m]	45 (95.7) /	19 (90.5) /	20 (60.6) /	39 (67.2) /
	2 (4.3)	2 (9.5)	13 (39.4)	19 (32.8)
Pain characteristics				
WPI [a]	13.0 ± 3.0	11.0 ± 2.0	4.0 ± 2.0	5.00 ± 1.63
	[3.0 - 19.0 / 47]	[5.0 – 19.0 / 21]	[0.0 – 14.0 / 33]	[2.0 - 15.0 / 58]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, U-test: p < 0.001***			
Pain intensity [b]	3.3 ± 1.24	3.4 ± 1.25	3.1 ± 1.46	2.9 ± 1.17
	[3.0 ± 0.5 / 47]	[4.0 ± 0.5 / 21]	[3.0 ± 1.0 / 33]	[3.0 ± 1.0 / 58]
	Kruskal Wallis: p = 0.072, n. s.; 1&2 vs. 3&4, U-test: p = 0.012*			
Pain severity [b]	3.8 ± 1.1	3.9 ± 1.1	3.6 ± 1.1	3.2 ± 1.1
	[1.3 – 6.0 / 47]	[2.0 – 5.3 / 19]	[1.0 – 6.0 / 32]	[1.0 – 5.7 / 57]
	Kruskal Wallis: p = 0.011*; 1&2 vs. 3&4, t-test: p = 0.005**			
Pain quality [c]				
Sensory scale SS10	22.9 ± 7.2	20.2 ± 6.1	17.4 ± 5.9	17.3 ± 6.1
	[10.0 – 39.0 / 47]	[14.0 – 34.0 / 21]	[10.0 – 33.0 / 31]	[10.0 – 37.0 / 54]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***			

[Table 5 A, continued:]

Cluster	**1**	**2**	**3**	**4**
Affective scale AS14	35.6 ± 10.3 [18.0 – 56.0 / 47]	33.5 ± 9.3 [20.0 – 52.0 / 21]	30.9 ± 10.1 [17.0 – 54.0 / 31]	29.5 ± 8.5 [14.0 – 48.0 / 55]
	Kruskal Wallis: p = 0.018*; 1&2 vs. 3&4, t-test: p = 0.001***			
Chronicity				
Chronic Pain Grade [d]	3.5 ± 1.0 / 38	3.0 ± 1.0 / 15	1.0 ± 1.5 / 23	2.0 ± 1.0 / 45
Grade I	7 (14.9)	3 (14.3)	12 (36.4)	20 (34.5)
Grade II	3 (6.4)	2 (9.5)	2 (6.1)	3 (5.2)
Grade III	9 (19.1)	5 (23.8)	2 (6.1)	16 (27.6)
Grade IV	16 (34.0)	5 (23.8)	7 (21.2)	6 (10.3)
	Kruskal Wallis Test: p = 0.004**; 1&2 vs. 3&4, U-test: p < 0.001***			

Statistical note. Significance levels familywise corrected (pain characteristics and chronicity: Bonferroni-Holm, k = 6). Cell entries mean ± SD or median ± ½ IQD for respective scale levels; [Range / N].

[a] *Widespread Pain Index (Range 0 – 19) according to the Fibromyalgia Survey Questionnaire (FSQ, Häuser et al., 2012), the survey version of the FS scale (Wolfe et al., 2016).*

[b] *MPI-D (Flor et al., 1990). Pain intensity = item #1; pain severity = scale value.*

[c] *Raw sum scores of the affective and sensory subscales (AS: 14 and SS: 10 items, respectively) of the German Pain Perception Scale (Schmerzempfindungs-Skala, SES, Geissner, 1996).*

[d] *CPG: chronic pain grade according to von Korff (1999). U-tests are of limited value cf. bimodality in cluster 4.*

(B) Pain impact, coping, comorbidity and psychosocial factors of clusters of sensory-clinical phenotypes and prior FMS and cUBP diagnoses

Cluster	1	2	3	4	FMS	cUBP
Pain impact						
FM impact [a]	56.6 ± 18.6	53.7 ± 14.3	39.9 ± 19.8	42.9 ± 14.8	53.8 ± 16.9	43.7 ± 18.0
	[19.6 – 90.0 / 24]	[24.1 – 71.7 / 1]	[14.8 – 76.9 / 18]	[7.2 – 69.5 / 50]	[19.6 – 90.0 / 46]	[7.2 – 77.8 / 54]
	Kruskal Wallis: p = 0.004**; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p = 0.005*	
Pain interference [b]	3.5 ± 1.4	3.3 ± 1.4	3.4 ± 1.4	2.4 ± 1.2	3.5 ± 1.3	2.8 ± 1.4
	[0.3 – 5.5 / 33]	[0.4 – 5.1 / 15]	[1.0 – 6.0 / 26]	[0.1 – 5.4 / 43]	[0.25 – 5.50 / 50]	[0.125 – 6.00 / 73]
	Kruskal Wallis: p = 0.001***; 1&2 vs. 3&4, t-test: p = 0.008*				t-test: p = 0.006*	
Functional capacity [c]	54.5 ± 16.9	57.5 ± 15.2	68.3 ± 20.0	74.6 ± 17.3	56.3 ± 17.2	71.6 ± 18.3
	[13.6 – 83.3 / 46]	[33.3 – 87.5 / 21]	[20.8 – 95.8 / 33]	[20.8 – 100.0 / 57]	[13.6 – 100.0 / 72]	[20.8 – 100.0 / 97]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	

[Table 5 B, continued]

Cluster	1	2	3	4	FMS	cUBP
Pain cognitions						
Catastrophizing [d]	2.6 ± 1.1	2.3 ± 0.6	1.7 ± 1.1	1.8 ± 0.9	2.4 ± 1.0	1.8 ± 1.0
	[0.0 – 5.0 / 27]	[1.0 – 3.0 / 13]	[0.0 – 5.0 / 18]	[0.0 – 4.0 / 34]	[0.0 – 5.0 / 45]	[0.0 – 5.0 / 52]
	Kruskal Wallis: p = 0.003**; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p = 0.006**	
Belief return work [e]	12.9 ± 9.8	9.6 ± 8.8	9.9 ± 8.0	6.9 ± 9.1	11.2 ± 9.0	7.5 ± 9.1
	[0.0 – 30.0 / 23]	[0.0 – 25.0 / 7]	[0.0 – 19.0 / 8]	[0.0 – 30.0 / 23]	[0.0 – 30.0 / 35]	[0.0 – 30.0 / 31]
	Kruskal-Wallis: p = 0.087, n. s.; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p = 0.107, n. s.	
Somatic comorbidity						
GBB sum [f]	46.9 ± 16.8	38.0 ± 10.3	24.6 ± 15.5	30.1 ± 14	43.8 ± 14.5	28.0 ± 15.1
	[9.0 – 82.0 / 45]	[14.0 – 54.0 / 21]	[5.0 – 61.0 / 33]	[11.0 – 69.0 / 55]	[15.0 – 82.0 / 71]	[5.0 – 69.0 / 95]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	
GBB – exhaustion [f]	14.6 ± 5.8	12.2 ± 4.6	7.8 ± 6.6	9.5 ± 5.8	14.0 ± 5.2	8.9 ± 6.1
	[0.0 – 24.0 / 45]	[4.0 – 20.0 / 21]	[0.0 – 23.0 / 33]	[0.0 – 23.0 / 56]	[0.0 – 24.0 / 71]	[0.0 – 23.0 / 96]
	Kruskal Wallis Test: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	

[Table 5 B, continued]

Cluster	1	2	3	4	FMS	cUBP
GBB gastrointestin. [f]	7.6 ± 5.6	5.0 ± 3.0	3.3 ± 4.0	4.1 ± 3.4	6.5 ± 4.9	3.9 ± 3.9
	[0.0 – 24.0 / 46]	[1.0 – 10.0 / 21]	[0.0 – 17.0 / 33]	[0.0 – 14.0 / 56]	[0.0 – 24.0 / 72]	[0.0 – 17.0 / 96]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	
GBB cardiovascul. [f]	7.0 ± 4.3	5.4 ± 3.5	2.7 ± 3.6	3.9 ± 3.6	6.3 ± 4.0	3.4 ± 3.6
	[0.0 – 17.0 / 46]	[0.0 – 13.0 / 21]	[0.0 – 16.0 / 33]	[0.0 – 13.0 / 55]	[0.0 – 17.0 / 72]	[0.0 – 16.0 / 95]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	
GBB musculoskel. [f]	17.3 ± 4.5	15.2 ± 4.1	10.8 ± 4.2	12.6 ± 4.4	16.8 ± 4.0	11.9 ± 4.4
	[5.0 – 24.0 / 46]	[6.0 – 24.0 / 21]	[5.0 – 20.0 / 33]	[6.0 – 23.0 / 55]	[8.0 – 24.0 / 72]	[5.0 – 23.0 / 95]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	
FGID [g] **N (%)**	18 (38.3)	9 (42.9)	1 (3.0)	12 (20.7)	32 (41.0)	9 (8.4)
	C_{corr} = 0.583, p = 0.001***				C_{corr} = 0.652, p < 0.001***	
SF-12 physical component [h]	29.6 ± 7.2	35.2 ± 9.9	35.6 ± 9.2	38.4 ± 9.0	31.2 ± 7.8	37.7 ± 9.3
	[18.4 – 48.9 / 44]	[20.9 – 54.4 / 19]	[19.4 – 54.3 / 31]	[22.2 – 60.2 / 51]	[18.0 – 54.0 / 66]	[19.0 – 60.0 / 90]
	Kruskal Wallis: p < 0.001***; 1&2 vs. 3&4, t-test: p < 0.001***				t-test: p < 0.001***	

[Table 5 B, continued]

Cluster	1	2	3	4	FMS	cUBP
PSQI sleep sum [i]	10.3 ± 4.3	11.7 ± 3.8	7.9 ± 4.8	9.0 ± 4.4	11.0 ± 4.4	8.8 ± 4.4
	[3.0 – 20.0 / 29]	[4.0 – 18.0 / 12]	[2.0 – 19.0 / 15]	[2.0 – 18.0 / 34]	[3.0 – 20.0 / 46]	[2.0 – 19.0 / 51]
	Kruskal Wallis: p = 0.075, n. s.; 1&2 vs. 3&4, t-test: p = 0.028*				t-test: p = 0.012*	
Psychic comorbidity						
General anxiety [j]	48.3 ± 12.5	50.7 ± 10.8	42.2 ± 11.2	43.7 ± 9.5	48.6 ± 11.8	43.2 ± 10.2
	[28.0 – 77.0 / 33]	[34.0 – 67.0 / 12]	[24.0 – 65.0 / 17]	[28.0 – 60.0 / 35]	[28.0 – 77.0 / 51]	[24.0 – 67.0 / 53]
	Kruskal Wallis: p = 0.110, n. s.; 1&2 vs. 3&4, t-test: p = 0.012*				t-test: p = 0.015*	
Psychosoc. factors						
Self-reported	34.2 ± 15.8	36.7 ± 13.5	25.7 ± 10.7	30.8 ± 12.9	35.0 ± 15.8	28.5 ± 12.1
stress [k]	[2.0 – 60.0 / 26]	[22.0 – 60.0 / 10]	[13.0 – 47.0 / 14]	[11.0 – 57.0 / 32]	[2.0 – 70.0 / 41]	[11.0 – 54.0 / 48]
	Kruskal Wallis: p = 0.152, n. s.; 1&2 vs. 3&4, t-test: p = 0.067, n. s.				t-test: p = 0.031*	
Social support [b]	3.6 ± 1.7	3.3 ± 1.8	3.2 ± 1.7	2.8 ± 1.7	3.3 ± 1.7	3.0 ± 1.7
	[0.0 – 6.0 / 40]	[0.0 – 6.0 / 20]	[0.0 – 6.0 / 28]	[0.0 – 5.7 / 51]	[0.0 – 6.0 / 65]	[0.0 – 6.0 / 86]
	Kruskal Wallis: p = 0.206, n. s.; 1&2 vs. 3&4, t-test: p = 0.076, n. s.				t-test: p = 0.213, n. s.	

[Table 5 B, continued]

Cluster	1	2	3	4	FMS	cUBP
Solicitous response [b]	3.2 ± 1.6	3.0 ± 1.6	2.7 ± 1.5	2.5 ± 1.4	3.1 ± 1.6	2.5 ± 1.5
	[0.2 – 6.0 / 43]	[0.0 – 5.4 / 19]	[0.4 – 6.0 / 28]	[0.0 – 5.0 / 50]	[0.2 – 6.0 / 68]	[0.0 – 6.0 / 84]
	Kruskal Wallis: p = 0.175, n. s.; 1&2 vs. 3&4, t-test: p = 0.030*				t-test: p = 0.024*	

*Statistical notes. Significance levels familywise Bonferroni-Holm corrected; k = 4 (pain impact), 7 (pain cognitions, coping), 12 (comorbidity) and 13 (psychosocial factors, stress). * p < 0.05; ** p < 0.01; *** p < 0.001 after correction. Variables with differences p > 0.10 not shown but included in familywise correction.*

[a] *Fibromyalgia Impact Questionnaire (German version: Offenbächer et al., 2000; original version: Burckhardt et al.,1991).*

[b] *MPI-D (Flor et al., 1990).*

[c] *Hanover Functional Ability Questionnaire (FFbH-R; Kohlmann & Raspe, 1996).*

[d] *German version of the Pain-Related Self Statements Scale (FSS; Flor et al., 1993).*

[e] *Fear-avoidance-beliefs questionnaire (FABQ; Pfingsten, et al., 1997).*

[f] *Giessen Subjective Complaints List (GBB-24; Brähler et al., 2008).*

[g] *Diagnoses according to self-report questionnaire for functional gastrointestinal disorders (Herschbach, 1996).*

[h] *Health-Related Quality of Life Questionnaire – Short Version (SF-12; Bullinger & Kirchberger, 1998).*

[i] *Pittsburg Sleeping Quality Index (PSQI; Buysse et al., 1989).*

[j] *State-Trait Anxiety Inventory (STAI-T; Laux et al., 1981).*

[k] *Short Questionnaire for Recognition of Stress-Factors (German " Kurzer Fragebogen zur Erfassung von Belastungen, KFB; Flor, 1991). Overall strain reported.*

The differences found could not have been due to age because its distributions were alike in all four clusters (Table 5). However, female patients were more prevalent in the widespread pain-like clusters 1 and 2 (95.7 % and 90.5 %) compared to the regional pain-like clusters 3 and 4 (60.6 % and 67.2 %) as in the groups with prior FMS and cUBP diagnoses (93.6 and 64.5 %). Clusters 1 and 2 also had significantly higher Chronic Pain Grades (CPG medians, cluster 1: 3.5; cluster 2: 3.0; cluster 3: 1.0; cluster 4: 2; Kruskal-Wallis, $p = 0.004$). Physical load at the work place or in the household (N = 92 valid cases) did not differ between clusters except minor differences on the subscale of musculoskeletal load on the shoulder (cf. Table S31 in Supplemental).

Comparing the complete array of sensory and clinical pain measures including those not used in the LCA profiles in relation to specific secondary chronicity and comorbidity factors qualifies the current evidence on their relative diagnostic significance in important ways (Table 5 B):

Closely pain-related indicators, in particular, pain severity (MPI-D, part I, subscale 1), sensory and affective pain quality (SES), interference (MPI-D, part I, subscale 2) and impact (Fibromyalgia Impact Questionnaire, FIQ) differed most between sensory phenotypes. Pain severity as well as present pain intensity was higher in patients of cluster 1 and 2 than in cluster 3 and 4 (t-test: $p = 0.005$; U-test: $p = 0.012$). Sensory and affective pain aspects (SES scales) scored higher in cluster 1 and 2 compared to cluster 3 and 4, while pain-related affective distress (MPI-D, part I, subscale 3) did not differ. In general, the differences reflected those between the prior diagnosis groups of FMS vs. cUBP.

Coping with pain showed a similar pattern at the cognitive level, with higher catastrophizing thoughts (FSS) in cluster 1 and 2 than in clusters 3 and 4 whereas active coping and the response to the question on having control over one's life (MPI-D, part I, subscales 5) did not differ. The subscales of the fear avoidance beliefs (FABQ) did also not differ between sensory-clinical clusters except "return to work prognosis" which was higher in clusters 1 and 2 compared to 3 and 4. There were no differences in FABQ scales between prior FMS and cUBP diagnosis groups.

Functional capacity (FFBH) of patients in clusters 1 and 2, however, was significantly lower than in clusters 3 and 4 ($p < 0.001$). The systematic increase from cluster 1 to cluster 4 related to pain severity and impact reflected an analogue difference between prior diagnosis groups.

Psychosocial factors, in particular, social support (MPI-D, part I, subscale 4) and responses by significant others (punishing, solicitous, distracting; MPI-D, part II, subscale 1-3) were not significantly different between the four clusters of clinical and sensory phenotypes. Perceived stress load (overall, work, psychosocial strain, KFB) did also not differ except for everyday strain which was higher in cluster 1 and 2 than in cluster 3 and 4. Cluster differences were also not found in the general activity level; only “outdoor activities” was somewhat lower in cluster 1 and 2 than in cluster 3 and 4. Most importantly and contrary to previous work on clinical FMS criteria, psychic comorbidity, i.e., depression and self-reported mental health (ADS, SF-12-mental) did not differ, neither between the four clusters of pain phenotypes nor prior diagnoses. Only trait anxiety (STAI-T) was somewhat higher in clusters 1 and 2 compared to clusters 3 and 4 ($p = 0.012$) as well as in FMS vs. cUBP ($p = 0.015$). Major depression diagnoses were below 5 % in all clusters as in the prior diagnosis groups. Subjective sleep quality (PSQI), a marker item for depression, was also not different between clusters despite a trend for worse sleep in cluster 1 and 2 ($p = 0.075$). This fits the fact that the decreased sleep quality reported previously could not be replicated in our patients with prior FMS diagnoses although the PSQI sum scores was slightly lower in FMS than in cUBP patients ($p = 0.012$; n. s., corrected).

In contrast, somatic comorbidity in terms of self-reported body complaints (GBB, total symptom burden) and somatic health (SF-12 physical component) differed strongly between the four clusters increasing progressively from cluster 3 and 4 to 2 and 1 (Kruskal-Wallis; $p < 0.001$). Clusters 1 and 2 were well separated from clusters 3 and 4 with respect to their somatic symptom burden (multiple t-tests; $p < 0.001$ corrected) similar to prior diagnostic groups. Patients in cluster 1 with widespread pain and high pressure pain sensitivity had the highest somatic symptom scores and the lowest physical well-being. Cluster 2 lay between cluster 1 and the low-symptomatic groups of cluster 3 and 4. This pattern was preserved when the pain-related GBB subscale “musculoskeletal complaints” was taken out. The GBB subscales of cardiovascular complaints, exhaustion, gastrointestinal complaints were also higher in cluster 1 and 2 than in cluster 3 and 4 indicating a higher somatic symptom burden in the first. The cluster differences in subjective somatic symptoms were not directly associated with prior medical diagnoses of gastrointestinal, endocrinological or urogenital disease according to anamnestic data (cf. Table S1 in Supplemental).

The higher gastrointestinal score in clusters 1 and 2 is underlined by the distribution of functional gastrointestinal disorders (irritable bowel syndrome, IBS, and/or non-ulcer dyspepsia, NUD) according to the FGID questionnaire across the four clusters and prior FMS and cUBP diagnoses (prevalence of subcategories in Table S32 in Supplemental). Again, functional gastrointestinal disorders were most frequent in cluster 1 and 2 (27 of 68; 39.7 %) and lowest in cluster 3 and 4 (13 of 91; 14.3 %); cluster 4 showed intermediate gastrointestinal disorders prevalence (12 of 58; 20.7 %). The frequencies were comparable to those in the prior diagnosis groups (FMS: 29 of 73; 39.7 %, cUBP: 8 of 69; 11.6 %). This general pattern of FGID distribution across clusters (1 ≈ 2 > 4 > 3) did not change when the FGID frequency was compared in females only.

4 Discussion

In this study, patients with prior diagnoses of Fibromyalgia Syndrome (FMS) and chronic unspecific back pain (cUBP) suffering from widespread and regional musculoskeletal pain of comparable severity were reclassified according to their sensory-clinical phenotypes of pressure and heat pain sensitivity combined with spatial spread and severity of the clinical pain. Sensory phenotypes were derived by stepwise data-reduction through descriptive statistical, correlational and structural analysis techniques identifying economic and coherent clusters of pathophysiologically and clinically meaningful indicators of pressure and heat pain sensitivity. The final optimized indicator set of four sensory and two clinical essential markers was apt to identify subgroups of patients with distinguishable sensory-clinical pain phenotypes independent of their prior diagnoses.

We hypothesized that the identified pain phenotypes would differentiate several subgroups of widespread and regional pain which differed in pain mechanisms, secondary responses to the pain and other, not directly pain-related aspects such as somato-psychic comorbidity and psychosocial co-factors. The general hypothesis 1 was clearly supported by the finding of four coherent clusters with distinct differences in pain sensitivity and degree of spatial spread of clinical pain across the body. The general hypothesis was qualified, however, with regard to the diagnostic significance of the classical ACR “tender points” and comorbid psychopathology and functional somatic symptoms.

Our hypothesis 2, that the total number of sensitive body sites indicates a more or less generalized pressure hypersensitivity and that a continuity from patients with more or less regionally confined pain (cUBP) to highly pressure sensitive patients with widespread pain (FMS) would exist, was also supported. This was reflected in the orderly sequence of numbers of pressure-sensitive body sites and pressure pain thresholds from cluster 4 to the most sensitive cluster 1 with informative exceptions of cluster 3 (see below).

However, the corollary assumption that classical ACR “tender points” did not qualitatively differ in this respect from control points at other muscle or soft tissue sites was rejected: FMS patients reported higher pain intensity when probed at tender points than at control points and provoked pain intensity increased linearly with numbers of sensitive ACR tender points but unsystematically with numbers of sensitive control points. Most, but not all cUBP patients reported less than 11 sensitive ACR tender points at re-examination and here pain intensity did not linearly increase with the number of sensitive tender or control points. These results support the older studies on enhanced pressure sensitivity of FMS patients in tender points which is less pronounced in control points (Granges & Littlejohn, 1993; Wolfe et al., 1990). Unspecific reduced pressure pain sensitivity at tender as well as control points has been interpreted as indication of a diffuse change in central pain modulation in FMS. Our results on the functional difference of tender points, however, emphasize the modality specificity and the clinical significance of ACR tender points which has been disputed previously (Wolfe et al., 2016).

Our hypothesis 3 suggested that two or more circumscribed subgroups could be differentiated within the continuum from localized, regional to widespread pain by the pattern of sensory data and clinical pain characteristics without recourse to secondary pain responses, not directly pain-related comorbidities and psychosocial co-factors. This was confirmed by the isolation of two intermediary subgroups of patients between those in cluster 1 with pronounced widespread pain, a high number of pressure-sensitive body sites and very low pressure pain thresholds and the patients in cluster 4 with regionally confined pain, low numbers of pressure-sensitive body sites and normal pressure pain thresholds. The intermediary clusters 2 and 3 resembled the respective neighboring (clusters 1 and 4) in certain aspects (large vs. small pain extent; high vs. low numbers of sensitive body sites) but differed characteristically in others representing two phenotypically discernible subgroups of different pathogenetic status:

Most patients in cluster 2 had prior FMS diagnosis and all but one patient had ≥ 11 “tender points” similar to the high-sensitive cluster 1 but showed less enhanced pressure sensitivity and still normal pressure pain thresholds at quantitative sensory testing. This sensory parameter was the only one differentiating the group from the high-sensitive cluster 1 arguing for an intermediary pain status with still developing pain enhancement. The few patients in the intermediary cluster 2 not meeting classical FMS criteria may be considered as having “widespread or FMS-like pain” and increased muscle and/or soft-tissue pain sensitivity, possibly on their way to aggravation. Cluster 4 predominated by cUBP patients with regional pain stands at the lower end of these three subgroups with progressively more widespread pain. It contained most of the cUBP patients characterized by several pain loci and a clandestine spread of muscle and soft-tissue hypersensitivity to manual probing but quantitative thresholds still normal. In contrast, patients in cluster 3 appear to be qualitatively different and not to fit into the continuum from regional to widespread pain. They showed regionally confined pain with a median WPI of 4 – 5 and low to normal pressure sensitivity similar to patients with regional pain in cluster 4. Cluster 3, however, consists exclusively of patients with prior cUBP diagnosis and the highest ratio of patients with an FS < 12 (85%). Their sensory characteristics deserve a closer look in a larger homogeneous group to improve differential diagnostic assessment of this group of “pure” back pain patients compared to those in cluster 4.

This demonstrates again the general problem of homogeneity and stability of the categorical diagnostic distinction of fibromyalgia based exclusively on standard clinical criteria as applied routinely in pain clinics and should be further pursued. Albeit prior diagnoses of FMS and cUBP had been applied by trained physicians in the collaborating pain clinics the differentiated sensory-clinical clusters contained varying mixtures of FMS and cUBP patients of whom 10% in the intermediary clusters no longer met extant tender point criteria at retesting (3 FMS < 11 TP; 12 cUBP ≥ 11). This fits with other studies in favor of a continuity of pressure-sensitive body sites arguing that more than 6 tender points qualified patients for a clinical FMS diagnosis by experienced physicians (e.g., Katz, Wolfe, & Michaud, 2006). Increasing numbers of hypersensitive body sites above that point could simply reflect a progressive spread with increasing pain severity rendering cut-off criteria more or less artificial. This is also shown in our results on the increasing pain intensity with increasing numbers of pressure-sensitive body sites specific to FMS. We expect that thorough qualitative and

quantitative sensory characterization of “tender” body regions would clarify the issue and allow better differentiation of subgroups at different stages and spread of pressure hypersensitivity which might follow also different history trajectories requiring specific treatments.

The number of body regions in pain recently put forward to differentiate widespread from regional syndromes of musculoskeletal pain (Wolfe et al., 2016) was corroborated as a distinct discriminator in this study, whereas present pain intensity and overall severity did not differentiate. This was independent of the pain type asked for (recent, current or major) and whether regions were defined according to the IASP Taxonomy or the 19 mostly non-articular pain sites specified by the WPI based on the Regional Pain Scale (Wolfe, 2003) as implemented in current FMS criteria (Wolfe et al., 2010; Wolfe et al., 2011; Wolfe et al., 2016). Number of pain regions, however, was not sufficient to identify the intermediary sensitivity clusters and sensory data were necessary in addition.

The corollary hypotheses 5 and 6, that quantitative sensory testing of heat pain sensitivity as non-mechanoceptive control modality would differentiate a separate phenotype of generalized hyperalgesia not limited to pressure stimulation could not be supported. We were not able to isolate a discernible phenotype of enhanced temporal summation related to impaired descending inhibitory control as found previously in FMS (Horn-Hofmann et al., 2018; Julien et al., 2005). Thus, the identified sensory phenotypes appear to be fairly specific to pressure pain and argue for its diagnostic significance in syndromes with widespread pain, in particular, for fibromyalgia. However, this interpretation of the heat pain part of the study is preliminary because of the reduced thermo-nociceptive assessments and the marked sample attrition after combining pressure and heat pain sensitivity indicators. The issue remains important, nevertheless, for deriving mechanism-based diagnostic categories and requires further transdiagnostic studies using thorough quantitative sensory testing beyond pressure sensitivity in conjunction with clinical assessment as already established for neuropathic pain conditions (Baron, Forster, & Binder, 2012). More sufficient comparative data on enhanced temporal summation, in particular, associated with the sensory-clinical phenotypes identified in our study are needed to elucidate the interaction of peripheral sensory and central pain mechanisms in widespread and regional pain syndromes. For instance, recent work has shown descending modulatory control of nociceptive signaling to be modality-specific especially for heat pain (Brietzke

et al., 2019; Horn-Hofmann et al., 2018) but the evidence on similar effects in pressure pain is still scarce and controversial (e.g., La Coba, Bruehl, Galvez-Sanchez, & Reyes Del Paso, 2018). Including sensory indicators of heat pain sensitivity and temporal summation as proxies for generalized hyperalgesia and impaired descending control in the sensory-clinical phenotyping of larger samples with musculoskeletal pain might reveal further subgroups with alterations in the central nervous system in the otherwise heterogeneous FMS construct (Sluka & Clauw, 2016).

The present study set out to differentiate sensory-clinical pain phenotypes within global chronic widespread and regional pain syndromes which could be related to different types of pain processing elucidating in this way the roles of secondary responses to pain, psychic and somatic comorbidities and psychosocial co-factors in the process of spreading pain becoming chronic (cf. hypothesis 4). This aim could only partially be achieved in so far as the directly pain-related indicators of severity, sensory and affective pain quality of patients' pain did not differ dramatically between phenotypes and to variable extent. Similarly, coping, interference by and impact of the pain symptoms including global chronicity (CPG) were not characteristic and cluster differences in single variables appeared to be population-dependent and related to prior diagnosis ratios. This suggests evermore that the phenotypic domains of primary sensory pain processing and the clinical picture should be distinguished carefully from the individual dealing with and the life consequences of the pain in construing nosological entities. This conclusion is emphasized by the fact that psychic comorbidity (in particular depression) and psychosocial co-factors (burden of stress) did not differ between the phenotypically defined subgroups. This argues clearly against including comorbid depression or depression-equivalents (e.g., sleep disturbance) into cardinal criteria of FMS (Häuser et al., 2009) and is in line with the current controversy about further FMS revisions (Arnold et al., 2019; Wolfe, 2019). Entering depression and anxiety markers together with the sensory characteristics in sufficiently powered studies would be needed to decide whether psychopathological subsyndromes could be isolated within the sensory-clinical chronic pain clusters identified in our analysis.

In contrast to the fairly even distribution of comorbid psychopathology, the burden of functional somatic symptoms other than pain differed clearly between phenotypical clusters. Self-reported body complaints and perceived somatic health assessed by established questionnaires scored highest in the highly sensitive clusters with widespread pain containing many patients with prior FMS diagnoses. Cardiovascular

complaints, exhaustion and gastrointestinal complaints measured by the respective GBB subscales were most prominent in these subgroups. The differences in the subjective symptom burden were not directly associated with prior medical diagnoses of gastrointestinal, endocrinological or urogenital disease according to anamnestic data. The enhanced medically unexplained somatic symptoms may reflect psychosomatic correlates of somatoform pain (Häuser & Henningsen, 2014) or indicate a general hypervigilance to somatic input with enhanced symptom perception not necessarily limited to FMS (Boeckle, Schrimpf, Liegl, & Pieh, 2016; Craig, 2011; Mier et al., 2017). Earlier work had already suggested that the high incidence of other somatic symptoms of patients with widespread pain and conventional FMS diagnoses was due to an underlying common functional somatic syndrome of which the extant diagnostic categories represented only different severities (Wessely, Nimnuan, & Sharpe, 1999). The systematic trend of increasing functional somatic symptoms from the low to the high sensitive clusters with increasing spatial spread of pain in our study would indeed argue for such a dimensional diagnostic view on other somatic symptoms comorbid to the primary chronic pain disorder instead of further subcategories (cf. Rief et al., 2019). Moreover, in our pain patients, somatic symptoms were not evenly distributed across organismic systems. In particular, the relative high incidence of gastrointestinal symptoms as well as circumscribed functional gastrointestinal disorders such as the irritable bowel syndrome concurs with the accumulating evidence of a discriminable subsyndrome of fibromyalgia with associated IBS and/or NUD (Becker et al., 2011; Costantini et al., 2017; Thieme et al., 2015). This and the reported comorbidity with pelvic pain (Johnson & Makai, 2018) would argue for gender-specific syndromes of enhanced sensitivity to noxious stimuli including visceral pain possibly explaining the dominance of females in both IBS and fibromyalgia (Sperber & Dekel, 2010; Tremolaterra et al., 2014). Similar arguments could be raised for comorbid chronic fatigue syndrome, sleep disorders and other somatic syndromes of the depressive spectrum (Iacob et al., 2016; Thieme, Turk, & Flor, 2004). The issue has to be clarified, however, by appropriate structural analyses including sensory phenotyping and quantitative somatic symptom assessment not relying on clinical categories alone.

Limitations

This retrospective, cross-sectional study is limited in two respects, first, by the non-random samples from which the sensory and clinical data at entrance were obtained, and, second, by the multiple structure-finding methods by which the indicator sets for the final sensory and clinical phenotyping were optimized to retain maximal case numbers for sufficient power. The statistical probabilities of this explorative definition phase are inflated but the final profile clustering is not nor are the comparisons between clusters with respect to a priori and external criteria not used in clustering (prior diagnoses, comorbidity, co-factors). The combined explorative-inferential strategy may also have lost relevant phenotypes marked by indicators abandoned because of sample attrition, gender differences in prevalence or unreliability of sensory assessments. The phenotypes as positively identified, however, should be valid and so is the core result on the phenotypical heterogeneity of fibromyalgia and regional pain categories and the necessity to re-install minimal sensory assessment into diagnostic evaluation of chronic musculoskeletal pain.

Conflict of interest

There is no conflict of interest with any party.

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3 GENERAL DISCUSSION

3.1 General characterization of the dissertation project

The dissertation explored the discriminability of subsyndromes of chronic musculoskeletal pain (MSP) on the basis of mechanism-related somatosensory and clinical phenotypes within the continuum from regionally confined to widespread pain. Two empirical studies were conducted:

The first study questioned the one-dimensionality and generality of the construct of chronicity given the multidimensionality of pain and the multifactorial causation of different syndromes. Two exemplary samples from model populations of chronic MSP patients and a nationwide sample of active workers at risk for chronic MSP were compared. The marker sets of the IASP Pain Taxonomy Axis IV (IASP Taxonomy Working Group, 2017), the Chronic Pain Grade (Korff et al., 1992) and the Mainz Pain Staging System (Pfingsten et al., 2000) were reanalyzed by correlations and frequency distributions of successive duration classes. Factor and latent class analyses were applied to assess the dimensional structure of pain and chronicity.

The second study based on a dimensional analysis of sensory and clinical characteristics within a circumscribed dataset of chronic MSP patients with prior clinical diagnoses of fibromyalgia syndrome (FMS) and chronic unspecific back pain (cUBP). The role of sensory and clinical characteristics and their discriminative power to differentiate widespread from regional pain was questioned against the background of the recent scientific debate on revisions of FMS classification (Arnold et al., 2019; Wolfe et al., 2016; Wolfe, 2019). Necessary and sufficient markers of sensory and clinical characteristics were to be identified. All markers of sensory and clinical characteristics were derived from a comprehensive set of semiquantitative and quantitative indicators of pressure and heat pain sensitivity combined with established indices of spatial spread and severity of the clinical pain. Finally, differences between the empirically derived sensory-clinical phenotypes in psychopathology such as depressive symptoms, other somatic complaints and psychosocial characteristics were evaluated.

3.2 Study 1: The chronicity construct

Results of the first study yielded a multidimensional structure of the chronicity construct, that differed between the diagnostic groups (patients vs. active workers). Duration and pain intensity related differently to each other and differed between the diagnostic groups. Patients reported lower pain intensities after longer durations (negative correlation), while employees recorded the lowest intensities at durations below six months moderately increasing in consecutive duration classes (positive correlation). The correlations of both intensities and durations with the CPG were also group-dependent: Pain duration correlated negatively with the CPG in patients (lower CPG the longer the pain duration) and the intensity distributions developed non-monotonically with increasing CPG from Grade II to IV. In employees, in contrast, duration did not correlate with the CPG, but intensity and CPG were positively correlated. By comparison, the MPSS did not correlate with duration in patients, while MPSS was positively correlated in employees. Pain intensity correlated positively with MPSS in both groups. The major finding derived by factor and hierarchical latent class analyses (LCA) revealed that chronicity refers to a composite construct. This construct is reflected differently in global indices depending on whether they emphasize either severity and duration or interference and disability facets.

Factor analyses did not reveal a general, common ‘chronicity’ factor. Instead, three factors were identified in the patient sample, while only two factors were found in the employee sample. The two factors in the employee sample comprised disability and pain characteristics loading on the first factor. Characteristics of the chronic development such as duration and health care utilization were loading on the second factor. The three factors in the patient sample were differently composed: The first factor comprised primarily disability, the second factor contained pain characteristics and the third resembled the chronic development. The LCA yielded two super-clusters in both samples, the first comprising the chronic development, while the second entailed disability and pain characteristics. Whereas the first cluster appeared relatively similar in both samples, the second differed in composition revealing sub-clusters composed of disability one the hand and pain characteristics on the other hand. In summary, the study revealed the construct of ‘chronicity’ of MSP is inherently multifactorial and different for the diagnostic group considered.

The study highlights the multifactorial composition of chronicity, which was not in focus in scientific research before. Previous studies used, in particular, duration as classifier

for a state of chronicity (> 12 weeks; Furlan et al., 2015) or simply base the chronic pain state on the diagnosis of the physician at study entry (Geneen et al., 2017). Those studies applying the CPG appreciate the consideration of severity and disability in only one compound code in order to practically assess both aspects at the same time together (Dunn, Jordan, & Croft, 2011; Rushton et al., 2018). Thereby neglecting the multidimensionality within this instrument and ignoring the fact that the highest CPG Grades III and IV solely base on disability scores. An assessment of different dimensions of chronicity with scores for each dimension is not available in the scientific literature. If the search for multidimensional assessment of chronicity was expanded and other dimensions apart from the state of chronicity, such as operant aspects and activities, were allowed, the West Haven-Yale Multidimensional Pain Inventory was the only instrument available that considered the multifactorial composition and did not derive any compound score (Flor et al., 1990; Kerns et al., 1985; Turk & Rudy, 1987b, 1988).

To conclude, the implementation of the results in form of a differential assessment of the multidimensional structure of chronicity adapted for the diagnostic group considered is highly desirable, but not yet realized. In future studies, comprehensive questionnaires for chronicity would comprise items assessing the primary clinical characteristics of the pain, the direct consequences of its current interference with activities and the related aspects of the patient history. A possibility for a translation of the results into practice would be a three-dimensional index of these components in the assessment of chronicity instead of the conventional one-dimensional approach by a global index such as the CPG. Applying a three-dimensional index would help to better stratify pain patients in scientific practice, but also help to derive a differential indication of specific treatment modules in pain therapy. The appropriate statistical model that manages a three-dimensional criterion of chronicity prediction is provided by the nonlinear canonical regression analysis of extant databases. This differential regression model is supposed to better identify psycho-social factors and somatic agents that lead to higher scores in one of the dimensions inherent in the multidimensional chronicity construct (pain characteristics, disability or duration).

In order to design an economic instrument assessing the multiple dimensions, it will be further necessary to identify items loading highest on one of these three dimensions. Moreover, subsequent analyses of the chronicity indices applied in the study (CPG, MPSS and intensity and duration) with other chronicity indices such as the Örebro

Musculoskeletal Pain Questionnaire (Linton & Halldén, 1998) or the Heidelberg Short Questionnaire (Neubauer, Junge, Pirron, Seemann, & Schiltenwolf, 2006) would be also recommended in order to validate the results. It is expected that the three dimensions derived in our study will be repeated, but maybe further expanded by dimensions comprising cognitive-evaluative or affective characteristics as implied by the content of the items of the latter two indices. Finally, it is obligatory that the results are further validated in comparable datasets of participants with MSP but also repeated in other exemplary groups from different pain populations for example neuropathic pain.

3.3 Study 2: Sensory and clinical pain phenotypes

The second study showed that patients with prior diagnoses of Fibromyalgia Syndrome (FMS) and chronic unspecific back pain (cUBP) could be reclassified into several sensory and clinical phenotypes by thorough sensory testing and comprehensive clinical pain characterization. Four clusters of differential sensory-clinical phenotypes were discovered that covered a spectrum from regional to widespread MSP. The final optimized indicator set of the clusters included four sensory markers (number of sensitive ACR tender and control points, test pain intensity and pressure pain threshold both at the trapezius tender point) and two clinical pain markers (WPI pain regions, present pain intensity). A consecutive discriminant analysis revealed that sensory markers sufficed to distinguish between the four clusters with a high correct rate. The sensory-clinical phenotypes differed substantially in somatic symptom burden, impairment and functionality. There were no differences in depression or psychosocial factors such as stress load.

The results are in contrast to the recent revisions of FMS diagnostics (Arnold et al., 2019; Wolfe et al., 2016) that rely only on a minimum number of clinical pain regions and symptoms of somatic and psychic comorbidity. The study showed that primary somatosensory characteristics suffice to differentiate within MSP groups. The most distinctive indicator was the tender point count.

This strongly supports to retain the ACR tender points as markers for chronic widespread pain in research and clinical assessment of FMS (Wolfe et al., 1990). Although the pathophysiology behind the pressure pain sensitivity at these specific points remains unknown (Eich et al., 2017), the tender point count is supposed to be a differential diagnostic marker. Previous research was not able to identify a specific

muscle pathology behind the sensitivity at these points (Simms, 1996). More recent research focused on the extraction of common etiological factors of sensitive myofascial trigger points and the sensitivity at tender points because of their frequently found association (Ge et al., 2009; Ge et al., 2010). The overlap with myofascial trigger points proposes a peripheral etiology primarily related to muscle overuse or direct trauma (Bron & Dommerholt, 2012), however, there are characteristic differences between tender and trigger points in terms of stimulation and origin (Mense, 2011). It is supposed that the sensory and clinical pain phenotypes derived in the present study could help to identify pathophysiologic mechanisms not limited to the ACR tender points. Neurobiological research suppose a peripheral etiology of FMS with the pain maintained by a combination of tonic impulses from deep tissues together with central sensitization (Price & Staud, 2005). The profiling of sensitive ACR tender points together with other sensory characteristics such as pain thresholds at selected sites in various modalities could be a mean to differentiate pathophysiologic mechanisms as successfully shown for peripheral neuropathic pain (Baron et al., 2017). Research in molecular neurobiology has revealed a diversity of nociceptive neurons (Dubin & Patapoutian, 2010) and it is likely that patterns of differential activation of neurons are associated with these sensory-clinical phenotypes.

Moreover, the sensory characteristics found in the present study are in line with other critical research searching for best discriminators that differentiate between patients with prior clinical FMS diagnosis and patients with chronic non-inflammatory rheumatic pain (Ghavidel-Parsa et al., 2019). These authors showed also sensory parameters as best discriminating, i.e., the algometer pressure pain threshold at the lateral epicondyle tender point. However, the results of the discriminative power of sensory characteristics is not limited to FMS patients, sensory nociceptive characteristics in three modalities (pressure, heat and cold) were also discovered to differentiate subgroups within chronic low back pain patients (Rabey, Slater, O'Sullivan, Beales, & Smith, 2015). This line of empirical evidence renders the exclusion of sensory characteristics in the differentiation of FMS from other regional unspecific MSP syndromes obsolete.

This empirical study is in contrast to previous studies as it focused on both sensory and clinical pain indicators combined to derive clusters within a spectrum from widespread to regional pain. Other studies were either limited to correlational analyses and a subsequent comparison of correct classification rates of those patients

diagnosed by the ACR 1990 criteria vs. the ACR 2010/11 criteria (e.g., Kim, Lee, & Kim, 2012; Wolfe, 2003; Wolfe et al., 2010) or based on consensus by experts (Arnold et al., 2019). This circularity of discrimination studies using the clinical diagnoses based on their own criteria as external reference for hit and miss may fail to identify the underlying indicator dimensions and/or domains causing the apparent correlations. There is only one study available that extracted dimensions from the combined item pool of the ACR 1990 and 2010/11 criteria in conjunction with the Fibromyalgia Impact Questionnaire, but no sensory markers. The latter two instruments comprise clinical pain characteristics, in particular the number of clinical pain regions and pain intensity, together with not directly pain-related symptoms of psychic comorbidity, fatigue and impairment (Ghavidel-Parsa et al., 2019). There is no study available that systematically starts extracting the primary dimensions of sensory and clinical characteristics (cf. Figure 1 in chapter 1.1.2: process model of core eliciting and sustaining mechanisms in MSP becoming chronic). As a potential consequence, the necessary evidence why a certain correspondence of FMS classification emerged is lacking and might, at the worst, be the result of certain confounding variables such as depressive mood. These confounding variables obscure the actual causal relationship and hamper research on underlying mechanisms.

The revised classification systems not only abandoned the tender point testing as cardinal criteria but also include characteristics of secondary comorbid somatic and psychiatric disorders: The ACTTION-American Pain Society Pain Taxonomy (AAPT) diagnostic criteria for FMS includes sleeping problems as cardinal criteria for FMS (Arnold et al., 2019). Apart from symptoms of fatigue and somatic complaints such as “pain or cramps in lower abdomen” the ACR 2010/2011 fibromyalgia diagnostic criteria incorporates non-somatosensory criteria such as depression (page 326; Wolfe et al., 2016). This inclusion of non-primary pain related characteristics adds to the high comorbidity of FMS with functional gastrointestinal disorders but also with depression as repeatedly reported (e.g., Buskila & Cohen, 2007; Whitehead, Palsson, & Jones, 2002). The high coincidence of functional gastrointestinal disorders and psychic comorbidity has face validity for the inclusion of such criteria. However, without systematic evidence showing clinical or non-somatosensory criteria corresponding to ACR tender points it is premature to exclude primary sensory indictors as cardinal criteria for FMS diagnosis.

Further empirical studies are strongly needed that include both sensory and clinical pain characteristics, isolate dimensions and derive a parsimonious set of indicators that differentiate within other MSP disorders with several to many pain locations. Replication studies, in addition, are necessary that support the sensory-clinical phenotypes derived in the present study. Such studies are recommended to apply at least the number of sensitive ACR tender points, the number of some control points, the WPI, a specific near-threshold intensity rating and a corresponding algometer pain threshold, the latter both measured at the trapezius ACR tender point. Depending on the sample size, it would be highly appreciable to include other sensory-clinical pain characteristics, such as supra-threshold sensitivity or sensitization to heat pain together with the temporal pattern of clinical pain. If other secondary indicators are subsequently integrated, e.g., indicators of fatigue or depression, resulting model fits could be compared.

3.4 Conclusions: Relevance for basic science and clinical settings

The dissertation project showed a systematic phenotypic approach to derive distinguishable dimensions within chronic MSP syndromes from primary sensory-clinical pain characteristics to distal psychosocial factors. The studies discovered a multidimensional structure of chronicity and identified necessary and sufficient sensory and clinical indicator domains able to differentiate between different MSP syndromes. The following paragraph discusses the implications for research and clinical practice.

3.4.1 Multidimensional assessment of the chronicity construct

Chronicity in MSP was discovered as inherently multidimensional construct. There was evidence for at least three core domains of chronicity in MSP, i.e., the primary clinical pain characteristics, the direct consequences of current interference with activities and aspects of the patient history (duration and health care utilization), which are only weakly coupled and varied across syndromes. The results underline that there is no single ‘chronicity’ entity, for all syndromes and all pain populations, over the whole range of severity and durations of the pain disorder. At present, evaluation of chronicity should be specific to the syndrome considered as well as the population and diagnostic context of the person investigated. Sticking to global indices leads to inherently inhomogeneous patient groups that obscure the relationships of predictive factors and, hence, hampers the necessary search for core mechanisms in chronic MSP.

As a desideratum it is recommended to use a 3- to 4-dimensional (multivariate) instead of global (scalar) indices in assessing chronicity, in particular, of musculoskeletal pain. The items should assess as a minimum requirement the primary clinical characteristics, the direct consequences of current interference with activities and aspects of the patient history. The study reminds researchers and medical practitioners to consider the inherently multidimensional structure behind the chronicity construct. The appropriate consideration of this multivariate clinical endpoint criterion establishes the basis for mechanism-oriented research on differential pathophysiology in chronic MSP syndromes.

3.4.2 Main indicator domains for chronic musculoskeletal pain

The second study showed that subsyndromes within the continuum from regionally confined to widespread chronic MSP were primarily discriminable by sensory pain characteristics (i.e., number of sensitive ACR tender and control points, test pain intensity and pressure pain threshold both at the trapezius tender point) which differentiated four meaningful phenotypes relating to different pain processing and symptom generation. The cluster of regionally confined pain comprising patients only weakly pressure sensitive was separated from the cluster of widespread pain, entailing patients with high pressure sensitivity. It is assumed that the former cluster of regional pain relates to peripheral sensitization whereas the latter cluster of widespread pain is more likely to be associated with central sensitization (Graven-Nielsen & Arendt-Nielsen, 2010; Roussel et al., 2013; Staud, 2002). The two intermediate clusters are supposed to be in a transition stage from regional to widespread pain and, hence, the relative importance of peripheral and central processes is supposed to be shifted accordingly. One of the intermediate clusters did not fit as well as the other cluster into the continuum from regional to widespread pain. It comprised exclusively cUBP patients and, hence, is suggestive for a distinctive pathogenetic determination related to back pain but deserves further research in order to substantiate a differential assessment of this group of patients in comparison to patients with multilocular or widespread pain.

Furthermore, there was evidence for a lowering of heat pain thresholds in the pressure sensitive, FMS-like, clusters 1 and 2. In particular, the tonic heat pain thresholds at the trapezius and thenar differed significantly between cluster 1 and 2 vs. cluster 3 and 4 underlining the assumed involvement of central sensitization in these first two clusters.

However, this result bases on ex-post comparisons and low power due to the reduced sample size in the dataset with pressure and heat pain indicators combined.
The best clinical indicator was the number of pain sites as measured with the WPI, but could be also replaced with other regional indices such as the number of pain regions according to the IASP Taxonomy of chronic pain. By comparison, the pain intensity did not proof as distinctive indicator. Moreover, secondary indicators for psychic comorbidity or psychosocial aspects did also not differ between the sensory-clinical phenotypes and, thus, were considered as not necessary to differentiate subsyndromes within MSP.
In summary, the results suggest that necessary and sufficient indicator sets to identify meaningful pain phenotypes within the spectrum from regional to widespread MSP required at least three sensory indicator domains: (1) the spatial distribution of hypersensitivity to percutaneous pressure, (2) pressure pain sensitivity as measured with quantitative sensory test measures and, although only weakly supported with the available data, (3) quantitative sensory test measures of non-mechanoceptive modalities such as cutaneous heat pain sensitivity.
As a desideratum it is recommended to apply a representative measure of each of the three sensory domains in diagnostic assessment of chronic MSP syndromes. For practical reasons the assessment could be in form of bedside testing and might include a reduced number of sensitive control points. The results remind researchers and physicians of the importance of sensory testing yielding different and even more differential diagnostic information than the clinical pain assessment.

3.4.3 Categorical vs. dimensional diagnostics

The dissertation aimed at setting the necessary prerequisites for a dimensional assessment of MSP with the identification of phenotypes that base on core domains related to pathophysiologic mechanisms in chronic MSP. Given the heterogeneity and the diversity of initializing and sustaining mechanisms of chronic MSP, the common diagnostic classification systems started by revising the coding of chronic unspecific MSP syndromes in order to eliminate the dichotomy of chronic pain with either somatic or psychosomatic origin (cf. 1.2.1 Diagnostic of medically unexplained pain in general introduction). However, aspects of depression or mental distress are still included as cardinal criteria for these unspecific MSP disorders (cf. DSM IV; American Psychiatric Association, 2013). The results of the PhD thesis contradict the inclusion of such secondary characteristics since the systematic phenotypic approach showed sensory

and clinical pain indicators as sufficient to discriminate within chronic unspecific MSP syndromes. Moreover, depressive symptomatology did not differ between the resulting phenotypes. A translation of these results into application within these classification systems would be highly appreciable and is supposed to result in the end of an inclusion of symptoms of spurious comorbidity diagnoses in the diagnostic of MSP pain syndromes.

The dissertation study applied a dimensional approach, which enabled data analyses of distinguishable core domains with high statistical power. This in contrast to the available diagnostic manuals which apply a categorical classification despite the inherent dimensional nature of continuous clinical phenomena (Chmura Kraemer, Noda, & O'Hara, 2004; Goldberg, 2000). Diagnostic categories are assigned for a certain number of symptoms, leaving the decision to what extent the symptom has to be present to fulfill a criterion to the clinician. Those patients that exhibit several symptoms qualifying for more than one diagnosis receive a comorbid diagnosis. This common practice contributes to potential variation within different patient diagnoses, as the actual contributing dimensions causing the symptomatology are obscured.

By comparison, dimensional diagnostic approaches quantify within a spectrum of multiple continuously or ordinally scaled dimensions across different diagnoses - as shown for mental disorders in the Research Domain Criteria project (RDoC) (Cuthbert, 2014). The dissertation project postulates that chronic MSP syndromes can be specified within the same spectrum of multiaxial dimensions that are related to proximal (close to the pain physiology) over intermediate (pain sustaining) to distal (secondary pain modulating) mechanisms. Further studies using a systematic phenotypic approach with more extended sensory and clinical indicator sets promise to detect additional dimensions at the next level of approximation to the multi-staged cascade of pain becoming chronic.

3.4.4 Empirically guided intervention assignment

A dimensional phenotypic classification could also improve the selection of necessary modules within multimodal pain therapy (Mathews, 2014). There is a high need to standardize the selection of modules specific to the pain symptomatology in order to avoid polypragmasia (Kaiser, Treede, & Sabatowski, 2017). Recent revisions of diagnostic classification systems (cf. DSM-V: somatic symptom and related disorders, American Psychiatric Association, 2013; ICD-11: chronic primary pain, Treede et al., 2015) do not provide individual treatment recommendations, leaving the decision to

physicians and therapists. Although the results of this dissertation do not cover such individual treatment decisions, they might serve as basis for group level decisions as exemplarily attempted in Figure 2 (Flowchart of empirically guided treatment components of multimodal pain therapy as derived from the dissertation results).

Patients suffering from chronic MSP with a prior diagnosis of FMS or cUPB would now be further distinguished by sensory and clinical characteristics (as derived from the pain and pressure sensitivity profiles in the second study; cf. Figure 4 and Table 4 B). Chronicity was identified as multidimensional construct composed of at least three dimensions (severity, impairment and duration) as one of the essential results of the first study. Empirical research would now be necessary that combines the different dimensions inherent in the chronicity construct with the sensory-clinical pain phenotypes. However, for this exemplary treatment derivation it is assumed that both patient groups present, on average, medium severity and impairment with relatively long duration >60 months (cf. Table 1B and Table 2 in second study). Treatments are selected corresponding to the indicator domains at the proximal level as previously derived from the process chart of mechanisms in pain becoming chronic (cf. Figure 1 in chapter 1.1.2); i.e., each sensory-clinical phenotype is associated with a specific sensory or perceptual pain therapy at the same level closely related to the pain pathophysiology.

Those patients qualifying for the cluster of widespread pain with high pressure sensitivity (cluster 1; cf. Figure 2, left) are supposed to benefit from a desensitization training that increases the pain tolerance at selected ACR tender point sites which had been shown to have limited success in complex regional pain syndrome (Harden et al., 2013). The pathophysiology behind the pressure pain sensitivity at ACR tender points is still unknown (Eich et al., 2017), however, as the sensitivity at the ACR tender points was shown as most distinctive indicator in the second study, it is supposed that the pain therapy should also directly target this sensory phenomenon. As the pressure pain sensitivity at the right trapezius quantitatively assessed by the algometer was only reduced in this cluster 1 and corresponding pain intensity of the manual probe high, the pain tolerance training is recommended to start at this specific ACR tender point (cf. for more details on sequence of loci to be trained in caption of Figure 2). The pressure at each specific site shall be increased gradually starting below the individual pain threshold in the initial examination.

The desensitization training is effective if the patient reports a decreased number of sensitive ACR tender points. This sensory generalization may also lead to a reduction of clinical pain sites and, thus, a reduced WPI. Under the condition that sensory generalization was successful the supposed general hypervigilance to somatic or visceral afferent signaling underlying gastrointestinal or heart complaints could be checked by assessing elevated scores in somatic comorbidity (cf. caption of Figure 2 and discussion section in the second study). If the scores of somatic symptom complaints are very high, it is supposed that patients might benefit from a direct perceptual training that aims to shift the attention away from the clinical pain symptomology and overall somatic input (Kleinstäuber, Thomas, Witthöft, & Hiller, 2018). The differential selection of treatment modules could be supplemented by a training to increase physical functioning by physiotherapy (Kaiser et al., 2017), since the overall functional capacity was evaluated as relatively low in cluster 1 and 2.

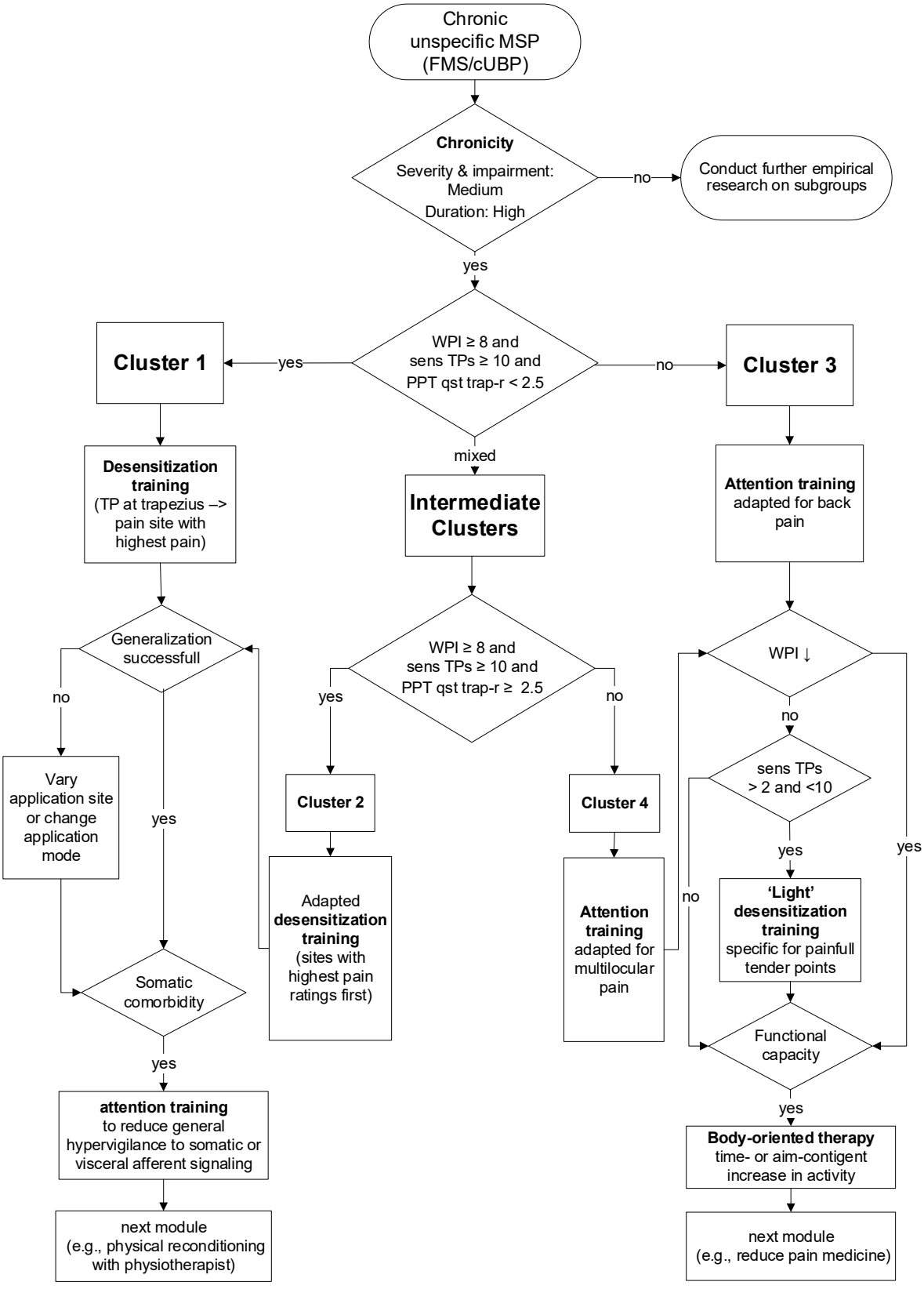

Figure 2: *Flowchart of empirically guided treatment components of multimodal pain therapy as derived from the dissertation results. Exemplary treatment indication schema for the four clusters identified in the second study for the application of selective modules (abbreviations as in Figure 4 in the second study). It is assumed that both patient groups with a priori diagnosis of FMS or cUBP report pain since a long duration and, on average, medium values in severity and impairment (empirical research would be necessary for patients with other values on these dimensions inherent in the chronicity construct). A Widespread Pain Index (WPI) of ≥ 8,*

sensitive ACR tender points (sens TPs) ≥ 10 and a reduced pressure pain threshold at the right trapezius (PPT qst trap-r) of <2.5 kp in the algometer testing differentiated best between cluster 1 vs. cluster 3 (cf. Table 4 B and Figure 5 in the second study).
Those patients qualifying for cluster 1 (left) are recommended to receive a desensitization training with an algometer. The study's results suggest to start generalizing the pain tolerance at the right ACR trapezius tender point, since the pain intensity at this particular tender point differentiated the sensory-clinical profile clusters best after the overall ACR tender point count. If the pain threshold and the corresponding pain intensity rating can be increased, the left trapezius followed by the tender point with the next highest pain intensity in manual probe is recommended to be trained bilaterally. It is supposed that a generalization of the training to other loci has started If the pain thresholds have increased at all four sites selected. Under the condition that there is no generalization, it is suggested to expand the training to other more distal sites, e.g., the tender point at the knee, or to vary the application mode, e.g., with pinprick. The sensory generalization is also supposed to result in a decreased number of clinical pain sites (WPI). The therapy could be continued with the treatment of the general hypervigilance to input of somatic or visceral afferent signaling assessed by somatic symptom complaints (cf. Table 5: Giessen Symptom Questionnaire, GBB-24; Brähler, Hinz, & Scheer, 1995). If the GBB-24 scores are high, it is supposed that patients might benefit from an expanded attention training to reduce the possible hypervigilance to overall somatic input such as gastrointestinal or heart complaints. The differential allocation of modules could be continued with physical reconditioning (cf. Table 5: functional capacity decreased in cluster 1, assessed by Hanover Functional Ability Questionnaire FFbH-R; Kohlmann & Raspe, 1996).
For those patients qualifying for cluster 3 (right) with regional pain an attention training adapted for chronic back pain is recommended. If this attention training is ineffective and patients have also a limited number of sensitive tender points, a reduced version of the desensitization training could be applied. This 'light' version would target the particular sensitive tender points, starting with the respective point with the highest pain intensity and continue with the second highest pain intensity rating and so forth. Both trainings, the desensitization and the attention training, could be supplemented with a body-oriented therapy. This body-oriented therapy is recommended to implement a time- or aim contingent increase in activity, since the functional capacity in cluster 3 remained high. The next module could focus on a decrease of pain medication.
The intermediate cluster 2 (middle left) might also benefit from an adapted desensitization training. This training is recommended to start at the specific tender point with the highest pain rating in manual probe and would then be continued with the second highest and so forth. In contrast to cluster 1, the application will not necessarily start at the trapezius ACR tender point, since patients in this cluster do not report a reduced pressure pain threshold in the algometer test. A generalization occurs if pain thresholds have increased at the four sites with the respective highest pain rating. If no generalization occurs, the decision tree corresponds to cluster 1 which suggests to vary the application site or to vary the application mode.
The intermediate cluster 4 (middle right) is considered to benefit from an attention training adapted for multilocular pain followed by the 'light' version of the desensitization training.

By comparison, for those patients qualifying for the cluster of regional pain (cluster 3; cf. Figure 2, right) an attention training adapted for chronic back pain is recommended that aims to shift attention away from the back pain (cf. Kleinstäuber et al., 2018). The patients in this cluster were shown to be weakly pressure sensitive but reported clinical pain at the back, hence, the training was supposed to target the clinical pain perception. Therapy effectiveness should be assessed by the clinical endpoint of a decreased WPI with special emphasis on back or spine locations. Another option,

under the condition of missing therapy success, might be the application of a body-oriented therapy that indirectly aims to shift the attention away from the pain utilizing the remaining functional capacity of those patients in cluster 3 and cluster 4. This body-oriented therapy is recommended to apply the time- or aim-contingent increase of activity irrespective of the pain symptomatology (Flor & Turk, 2011b; Geneen et al., 2017; Marley et al., 2017). The next following module could comprise the medical assistance to decrease the use of pain medication as a modulating variable (for a possible implementation: cf. Flor & Turk, 2011b).

For the intermediate clusters (cluster 2 and 4; cf. Figure 2, middle) not meeting all of the specific criteria (i.e., high scores in WPI and tender point count, but reduced pressure sensitivity) the previous treatment suggestions have to be adapted. It is suggested that those patients in cluster 2 (cf. Figure 2, middle left) with high WPI and high tender point count also receive a desensitization training, since the number of sensitive tender points remains still high in this group. However, as the algometer pressure pain threshold at the trapezius is not reduced in this group, the desensitization training would start at the specific tender point with the highest pain intensity in manual probe and follow a generalization plan that continues with the next highest pain reported (cf. caption of Figure 2 for details). Those patients in cluster 4 (cf. Figure 2, middle right) reporting multilocular pain in the WPI and some sensitive ACR tender points (cf. Figure 2, right: sens TP > 2 and <10) are recommended to receive an adapted attention training for multilocular pain not specifically related to back pain (cf. Kleinstäuber et al., 2018). Patients in this cluster might be in a transition stage from localized to widespread pain, hence, this attention training is supposed to highlight the perceptual processes that are involved in the generalization of pain to other body parts. The training effectiveness is again measured by a reduced WPI. Under the condition that this adapted attention training for multilocular pain is not effective, a ‘light’ desensitization training is suggested that only treats the limited number of sensitive ACR tender points (cf. caption of Figure 2 for details).

This example for an empirical deduction of treatment modules is reduced to primary sensory and perceptual treatment options, but would be expanded accordingly if other domains were considered in empirical phenotyping of chronic MSP.

3.5 Open questions and outlook

Both studies contributed to the understanding of the multifactorial structure of chronicity and the particular relevance of sensory characteristics in the assessment of MSP syndromes, but also raised further questions.

The two studies provide a way to empirically assess necessary and sufficient characteristics referring to marker domains in chronic MSP syndromes and highlight the advantages to consequently follow a phenotypic approach in order to derive a dimensional diagnostic. Future studies could continue this work and combine the necessary components of chronicity (duration, severity and impairment) and the sensory and clinical pain phenotypes in sample selection. A possible realization might be starting with selected samples that share the same sensory and clinical pain characteristics of one out of the four empirically derived clusters in the second study. These samples would be subsequently assessed for the inherent chronicity components preferably analyzed by linear and probabilistic structure finding procedures (e.g., with principal components and latent class analyses). It is expected that the sensory-clinical phenotypes will be split up in further subsamples depending on their relative loading on the chronicity components. Patients with a longer pain history might, for example, reveal moderate values in pain intensity. The selection of further possible indicator variables supposed to better inform the existing phenotypes would then also start at proximal domains closely related to the pain pathophysiology and end at distal marker domains comprising comorbidity and psychosocial aspects (cf. Figure 1 in chapter 1.1.2 and Table 1 in chapter 1.1.3). In the example of patients reporting a relatively long pain duration with moderate values of pain intensity, the proximal to distal selection strategy for the next indicators would include markers of affective pain perception. Marker variables would, thus, be selected out of the affective-motivational domain. The next following level would be a selection of marker variables out of the cognitive-evaluative domain and so forth. In this regard, it could be also likely that there emerge certain dimensions involving aspects of more than one domain, e.g., suffering comprising the affective but also cognitive load caused by the pain symptomatology (Bustan et al., 2015). The clusters would, finally, be checked for possible differences in psychosocial factors. Of course, this systematic phenotypic approach needs to be assessed in large samples comprising diverse musculoskeletal patient clients with heterogeneous characteristics.

Another interesting field of research is the identification of neuronal and neurochemical differences in the emerging sub-clusters. It is likely, that the phenotypes identified by this thorough mechanism-oriented deduction also share the same structural and endocrinological characteristics.

The phenotypic characterization presented here serves as an example for a dimensional assessment of musculoskeletal pain syndromes. The results help to identify necessary and sufficient marker variables necessary to identify subgroups within musculoskeletal pain syndromes differing in pain processing and maintaining factors. A dimensional assessment closely related to involved pathogenetic mechanisms contributes to the adequate and economic selection of modules within multimodal pain therapy. This opens another interesting field of research that evaluates therapy success by comparing a focused sequential pain therapy by one of the conventionally applied multimodal pain therapy in selected pain centers.

4 SUMMARY

The dissertation investigated the differentiation of subsyndromes in a spectrum from regional to widespread chronic musculoskeletal pain on the basis of mechanism-related somatosensory and clinical phenotypes within the framework of the multidimensional model of chronic pain. The first study analyzed the dimensional structure of the chronicity construct and its necessary and sufficient components. The second study identified discriminable pain-related phenotypes in two exemplary syndromes of chronic musculoskeletal pain by a stepwise cluster-analytic approach and related these to secondary comorbidity and psychosocial factors.

In the first study, diagnostic entrance data of 185 patients with chronic regional vs. widespread musculoskeletal pain (unspecific back pain, fibromyalgia syndrome) from regional pain clinics and of 170 active employees in a nationwide prevention program were included in a retrospective cross-sectional analysis to reanalyze the construct of chronicity. The marker sets of three established chronicity indices (IASP Pain Taxonomy Axis IV, Chronic Pain Grade, Mainz Pain Staging System) were reanalyzed by correlations and frequency distributions of successive duration classes. Factor and latent class analyses were applied to assess the dimensional structure of pain and chronicity. Pain intensity distributions showed inhomogeneous courses from short to long durations differing between groups. Both dimensions, pain intensity and duration, related unsystematically to CPG and MPSS. Different dimensions and clusters of chronicity markers were discovered, that differed between the groups (three dimensions and clusters in patients, two dimensions and clusters in employees). In fact, there was evidence for at least three weakly coupled core domains of chronicity, i.e., the primary clinical pain characteristics, the direct consequences of current interference with activities and aspects of the patient history (duration and health care utilization).

In the second study, the sensory and clinical characteristics of the patient sample were reanalyzed to identify necessary and sufficient markers differentiating subsyndromes with different sensory-clinical phenotypes along the continuum from regionally confined to extensively widespread pain. For this purpose, 107 chronic unspecific back pain patients and 78 patients with fibromyalgia syndrome were taken as exemplary instantiations with circumscribed diagnoses. Four clusters of differential sensory-clinical phenotypes covering a spectrum from regional to widespread pain were

discovered on the basis of four pressure pain sensitivity markers (number of sensitive ACR tender and control points, test pain intensity and pressure pain threshold) and two clinical pain markers (number of pain regions, present pain intensity). A consecutive discriminant analysis showed that the pressure sensitivity markers alone sufficed already to discriminate between the clusters with a high correct rate. The sensory-clinical phenotypes differed also in other somatic symptoms and impairment but not in psychopathology nor in psychosocial co-factors.

The project showed that differential diagnostics of chronic musculoskeletal pain requires at least a multifactorial determination of its chronicity with respect to the necessary components of duration, severity and impairment and the identification of the individual pain phenotype by comprehensive sensory and clinical assessment. This is considered as the prerequisite of differential indication of specific modules in multimodal pain therapy to avoid unselective polypragmasia.

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