Chronic Pain with Neuropathic Characteristic

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Maryam Shaygan

aus Shiraz (Iran)

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Betreuungsausschuss:

Prof. Dr. Birgit Kröner-Herwig, Abteilung für Klinische Psychologie und Psychotherapie, Georg-Elias-Müller-Institut für Psychologie

Prof. Dr. Uta Lass, Abteilung für experimentelle Psychologie, Georg-Elias-Müller-Institut für Psychologie

Mitglieder der Prüfungskommission:

Referentin: Prof. Dr. Birgit Kröner-Herwig

Korreferentin: Prof. Dr. Uta Lass

Weitere Mitglieder der Prüfungskommission:

Prof. Dr. Margarete Boos, Abteilung Sozial- und Kommunikationspsychologie, Georg-Elias-Müller-Institut für Psychologie

Prof. Dr. Andreas Glöckner, Abteilung Psychologische Diagnostik, Urteilen und Entscheiden, Georg-Elias-Müller-Institut für Psychologie

Prof. Dr. York Hagmayer, Abteilung Kognitionswissenschaften und Entscheidungspsychologie, Georg-Elias-Müller-Institut für Psychologie

Prof. Dr. Nivedita Mani, Free Floater Nachwuchsgruppe Spracherwerb, Georg-Elias-Müller-Institut für Psychologie

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Dedicated to

My Beloved Husband

&

My Little Princess, Helma

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PREFACE

The present work is a publication-based dissertation based on two original manuscripts. Article 1 is published in the "European Journal of Pain" (Shaygan, Böger, Kröner-Herwig, 2013). The second article is accepted for publication in the journal of "Neuropsychiatric Disease and Treatment".

Article 1

Shaygan, M., Böger, A., Kröner-Herwig, B. (2013). Clinical features of chronic pain with neuropathic characteristics: A symptom-based assessment using the Pain DETECT Questionnaire. *Eur J Pain*, 17 (10), 1529-38.

Article 2

Shaygan, M., Böger, A., Kröner-Herwig, B. (accepted). Neuropathic sensory symptoms: Association with pain and psychological factors. *Neuropsychiatric Disease and Treatment.*

Both studies—using independent samples—were carried out in cooperation with Clinic for Pain Management at the Red Cross Hospital in Kassel. The studies were supervised regarding design, statistical analysis and publication by Professor Dr. B. Kröner-Herwig. The author of this dissertation played the dominant role regarding (a) the idea and development of study design, (b) the collection of data, (c) the statistical analysis and interpretation of data, and (d) the preparation for publication of manuscripts. In order to integrate the articles into a larger context, the following text provides common theoretical background and the objectives of the individual studies. Methods, main results and conclusions of each study will be summarized, followed by a joint discussion of both studies. In the second part of the dissertation, the two original articles are provided.

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Abstract

Chronic pain conditions are often categorised into two major groups, namely nociceptive (caused by tissue damage) or neuropathic (caused by nerve damage) pain. In the past few years, this dichotomous approach (*either* neuropathic *or* nociceptive) has been questioned and it has been suggested that not only "typical" neuropathic pain syndromes but also otherwise chronic pain (e.g. back pain) may have neuropathic components of pain. This dimensional perspective is consistent with basic scientific opinion regarding chronic pain mechanisms; however, further studies are needed to examine it empirically. Neuropathic symptoms (e.g. burning and prickling sensations) have a central role in the clinical diagnosis of the neuropathic components of pain. The main aim of the first study was to assess the severity of self-reported neuropathic symptoms in different syndromes of chronic pain (e.g. headache, musculoskeletal pain, postsurgical pain).

Using validated screening tools for neuropathic symptoms, a number of recent *population-based* studies reported higher levels of pain intensity, as well as anxiety and depressive symptoms, in respondents who scored high on neuropathic symptoms, compared to those who scored low. Consequently, many authors have suggested the assumption of the uniqueness of neuropathic pain quality in its intensity and distressing characteristic. We aimed to further examine the association of the severity of neuropathic symptoms with pain-related (e.g. pain intensity and chronicity) and psychological factors (e.g. depression) in clinical samples of patients: one sample of patients with diverse types of chronic pain (study 1), and 4 samples of patients with typical neuropathic pain, radiculopathy, fibromyalgia or nociceptive back pain (study 2). In study 2, we also compared different *patterns* of neuropathic symptoms regarding pain and psychological factors.

Seven hundred and six (study 1: n=400; study 2: n=306) patients suffering from a chronic pain condition enrolled for multidisciplinary pain treatment were considered for inclusion in the research project. The criteria for inclusion were: an age of over 18 years and having chronic pain

according to ICD-10 criteria (F45.41 or R52.1-2). In study 2 only patients with typical neuropathic pain, back pain with (*radiculopathy*) or without (*nociceptive back pain*) clinical signs of nerve involvement, and fibromyalgia were included. The pain DETECT questionnaire was used to assess the severity of neuropathic symptoms in patients.

A high severity of neuropathic symptoms was found not only in "typical neuropathic pain" but also in fibromyalgia and postsurgical pain (study 1).

At first sight, our findings in a sample of patients with diverse types of chronic pain (study 1) suggested that neuropathic symptoms are associated with a high level of pain intensity, pain chronicity, functional disability and depression. However, in study 2 considering patients who had been diagnosed with typical neuropathic pain, radiculopathy or fibromyalgia, neither severity nor different patterns of neuropathic symptoms were correlated with the pain-related and psychological variables. A subgroup of nociceptive back pain patients who scored high on self-reported neuropathic symptoms reported high levels of pain intensity, depression, catastrophising and non-acceptance of pain suggesting a general response tendency (response bias) in this subgroup of nociceptive back pain patients.

In summary, the results corroborate and support a dimensional perspective of neuropathic pain. Our findings lend *no support* to the assumption of many authors that a high severity of neuropathic symptoms principally results in high levels of pain intensity and psychological distress as it is not the case in patients with an underlying pathology of neuropathic symptoms. The results highlight the influence of cognitive-emotional factors on the experience and report of pain. The implications of these findings for research and clinical practice are discussed.

I. Synopsis of publications

1. Introduction

Chronic pain is a widespread disabling health problem. In an epidemiological study by Breivik, Collett, Vittorio, Cohen and Gallacher (2006), the prevalence of chronic pain, defined as pain lasting more than 6 months, occurring several times during the last week, with an intensity of 5 or more on a numeric rating scale (0–10) for the last episode of experienced pain, was 19% in adult Europeans. Chronic pain is frequently associated with reduced capacity to work (Breivik et al., 2006) and it has a dramatic impact on the lives of affected individuals and a substantial economic impact on society.

Chronic pain conditions are often categorised into two major groups, namely, nociceptive and neuropathic pain (Woolf et al., 1998). Nociceptive pain has been defined as '*Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors*' (International Association for the Study of Pain, 2011). Nociceptive pain is commonly described as deep, dull, throbbing, cramping and aching in its **quality** (Victor, Jensen, Gammaitoni, Gould, White, & Galer, 2008).

1.1 Neuropathic pain: definition, classification, aetiology and epidemiology

Neuropathic pain, often called **"typical neuropathic pain"**, has been recently redefined as *'pain caused by a lesion or disease affecting the somatosensory system'* (Treede et al., 2008). This definition replaced the old definition of neuropathic pain (Merskey & Bogduk, 1994), which defined it as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system'. The term "somatosensory system" replaces the previous term "nervous system" to distinguish neuropathic pain from pain caused by lesions in other parts of the nervous system, such as the central motor pathways, e.g., pain associated with spasticity and rigidity (Jensen et al., 2011). Moreover, the term "disease" replaces the previous term "dysfunction", which may erroneously be interpreted as the normal plasticity of the nociceptive system. This means that dysfunction without evidence of injury is no longer regarded as meeting the criteria for

neuropathic pain (Bennett, 2010). Thus, dysfunctional pain conditions without any identifiable nerve lesion, such as **fibromyalgia**, should not be categorised as neuropathic pain (Treede et al., 2008). Fibromyalgia is a chronic painful syndrome that is characterised by abnormal pain sensitivity (e.g., hyperalgesia) and widespread pain (Staud, 2011). Although in the majority of fibromyalgia patients, no nerve lesions can be demonstrated, sensory dysfunctions in these patients can be explained in terms of other pathogenic mechanisms, such as a dysfunction of the endogenous systems modulating afferent activity (Bradley et al., 2002; Kosek et al., 1996; Uceyler et al., 2013).

Depending upon the location of a nerve injury, neuropathic pain is commonly classified as central (originating from damage to the brain or spinal cord, e.g., multiple sclerosis, post-stroke pain) or peripheral (originating from damage to the peripheral nerve, plexus, dorsal root ganglion, or root, e.g., diabetic polyneuropathy and post-herpetic neuralgia; Haanpää & Treede, 2010).

Many common diseases, injuries, and interventions may cause neuropathic pain by producing lesions in the somatosensory pathways in the peripheral or central nervous system. The most common causes of neural damage and subsequent pain are metabolic disease (e.g., diabetes), infection (e.g., herpes zoster), trauma (e.g., spinal cord injury), ischemia (e.g., post-stroke pain), surgery and tumor infiltration (Dworkin, 2002). Because of the large number of underlying causes of neuropathic pain and the lack of standardised measurement methods for identifying the neural damage, the overall prevalence of neuropathic pain syndromes in the general population is difficult to quantify (Freynhagen & Bennett, 2009; Haanpää & Treede, 2010).

However, a number of studies have examined the epidemiology of the important specific causes of neuropathic pain. For example, one prospective study of the first five years following spinal cord injury indicated that, after a spinal cord injury, 41% of individuals had neuropathic pain at the level of the injury (Siddall, McClelland, Rutkowski, & Cousins, 2003). The incidence

of postherpetic neuralgia (PHN) ranges from between 25% and 50% of patients affected by herpes zoster at three months after rash onset (Schmader, 2002). The point prevalence of diabetic peripheral neuropathy (DPN) was found to be 26.4% among patients with type 2 diabetes (Davies, Brophy, Williams, & Taylor, 2006).

1.2 Clinical presentations of neuropathic pain: a different pain quality from nociceptive pain

Clinically, neuropathic pain is characterised by a complex pattern of **abnormal sensory symptoms**, including positive and negative sensory symptoms. Positive sensory symptoms reflect an abnormally high level of excitability or disinhibition in the somatosensory system and include spontaneous pain and stimulus-dependent pain. Spontaneous pain occurs in the absence of any stimulation and is commonly described by patients as burning, shooting or "electric-like" in quality. Stimulus-dependent pain includes allodynia (i.e., pain in response to a non-painful stimulus) and hyperalgesia (i.e., increased pain sensitivity to a painful stimulus) (Baron, Binder, & Wasner, 2010).

Negative sensory symptoms in neuropathic pain may result from a partial or complete loss of impulse conduction in the neural tissues and include hypoesthesia (decreased sensitivity to stimulation), hypoalgesia (diminished pain in response to a normally painful stimulus) and analgesia (absence of pain in response to stimulation that would normally be painful) (Gilron, Watson, Cahill, & Moulin, 2006).

1.3 A dimensional perspective on neuropathic pain

In the past few years, the dichotomous approach classification of chronic pain (*either* neuropathic *or* nociceptive) has been questioned and it has been suggested that chronic pain may be better conceptualised as a *spectrum*, in which pain may have more or less neuropathic components (Bennett, Smith, Torrance, & Lee, 2006; Bennett, 2010). Consequently, one other

category of chronic pain, i.e., "mixed pain", which is defined as a syndrome with both nociceptive and neuropathic components of pain, has been considered (Freynhagen & Baron, 2009). The combination of nociceptive and neuropathic pathological mechanisms of pain is particularly supposed in radicular back pain (radiculopathy) (e.g., Freynhagen & Baron, 2009) and postsurgical pain (e.g., Shaladi, Saltari, Crestani, & Piva, 2009). **Radiculopathy** is thought to be caused by lesions of nociceptive sprouts or mechanical compression of nerve roots within the degenerated disc (Baron & Binder, 2004). Also, long-term **postsurgical pain** probably results from surgical injury to peripheral nerves (Schaladi et al., 2009). While "typical neuropathic pain" conditions (e.g., diabetic polyneuropathy and post-herpetic neuralgia) generally do not provide serious diagnostic difficulties, it is more difficult to detect a neuropathic component in "mixed pain" conditions like radicular back pain (Attal & Bouhassira, 2004). Nevertheless, differentiation between nociceptive and neuropathic components of pain is clinically important and has a direct impact on therapeutic decisions about pain: Anticonvulsants and antidepressants are predominantly pharmacological treatment options for neuropathic pain, whereas nociceptive pain is sensitive to non-steroidal anti-inflammatory drugs (NSAIDS) (Freynhagen & Bennett, 2009; Haanpää & Treede, 2010).

1.4 Screening tools for neuropathic symptoms

The definition of neuropathic pain (Treede et al., 2008) seems to be easily applicable, but in fact, it describes a mechanism-based diagnosis of pain, which can hardly be verified. Pain patients typically present a complex pattern of **self-report symptoms** rather than recognisable neurological lesions or definable mechanisms (Bennett, Attal, Backonja, Baron, Bouhassira, Freynhagen et al., 2007). Hence, the lack of objective markers, as well as the lack of a gold standard for the detection of neuropathic pain makes the identification of neuropathic components of pain a continuing challenge for clinicians (Haanpää et al., 2011; Torrance, Smith, Watson, & Bennett, 2007). Nevertheless, the separation of the neuropathic components of pain from those that are non-neuropathic has direct implications for treatment strategies. Hence, it is

of the high importance for the clinician to identify the presence of different pain components (i.e., nociceptive, neuropathic or both) to select adequate treatments in each individual patient (Freynhagen & Bennett, 2009; Haanpää & Treede, 2010). Techniques such as quantitative sensory testing, functional imaging and skin biopsies are tools that provide valuable information about the neurobiology of pain. However, these investigations are expensive and require a level of technical expertise that is only obtainable at a few highly specialised centres (Scholz et al., 2009). Additionally, many clinicians in both primary and secondary care do not have the adequate skill or time for a thorough neurological examination (Bennett et al., 2007). Therefore, the examination of symptoms assessed by self-report has became a major focus in the assessment of neuropathic pain.

The results of the study by Boureau, Doubrere and Luu (1990) provided evidence that six sensory symptoms, i.e., burning, coldness, tingling, prickling, itching and "electric-like" sensations, are more frequently chosen by patients with "typical neuropathic pain" syndromes. Moreover, although still under discussion, some recent studies suggest that the pattern of neuropathic symptoms provides a guide to the underlying mechanisms of pain that optimises the treatment of pain (Baron et al., 2010; Baron, Tölle, Gockel, Brosz, & Freynhagen, 2009; Baron, 2006; Dworkin, 2002). Hence, efforts have been recently undertaken to develop symptom-based screening tools to help to assess "pain with neuropathic characteristics", i.e., pain with distinct neuropathic symptomatology (e.g., Freyhagen, Baron, Gockel, & Tölle, 2006). One feature that is common to all of these tools is a reliance on verbal descriptors of **pain quality**. Although screening tools can be a guide to identify patients with neuropathic pain, they seem to fail to identify about 10-20% of patients with clinically diagnosed neuropathic types of pain and thus do not replace clinical judgement (Bennett et al., 2007).

Pain DETECT Questionnaire:

One of the five validated screening tools, the so-called **Pain DETECT Questionnaire** (PDQ, Freynhagen, Baron, Gockel, & Tölle, 2006a), was developed to detect neuropathic pain components in chronic low back pain and in "typical neuropathic pain" syndromes. The PDQ is a self-report questionnaire consisting of nine items that ask about the intensity and quality of pain with a total score ranging from -1 to 38. The questions address the presence of seven sensory symptoms rated on a 0–5 rating scale (never to very strong):

1. burning pain,
2. paresthesias,
3. mechanical allodynia,
4. spontaneous pain attacks,
5. thermal hyperalgesia,
6. numbness,
7. pressure hyperalgesia.

The PDQ also comprises two questions regarding the course of pain and the radiation of pain:

1. Please select the picture that best describes the course of your pain.
    - Persistent pain with slight fluctuations
    - Persistent pain with pain attacks
    - Pain attacks without pain between them
    - Pain attacks with pain between them
2. Does your pain radiate to other regions of your body? Yes/No

It was validated in a sample of patients with either neuropathic pain, including post-herpetic neuralgia, polyneuropathy, nerve trauma and low back pain (LBP in which the source of pain is

in the lumbar vertebrae, sacrum and/or coccyx) or nociceptive pain, including visceral pain, osteoarthritis, inflammatory arthropathies and non-neuropathic LBP. The instrument categorises the patients into three groups: **Neuropathic**, **non-Neuropathic**, **Unclear**. The questionnaire demonstrated good internal consistency (Cronbach's alpha= 0.83; Freynhagen et al., 2006a).

1.5 The association of neuropathic symptoms with pain-related parameters and psychological distress

Consistent with the general literature on chronic pain, there is strong evidence of the negative impact of neuropathic pain on patients and society. Neuropathic pain can result in psychological distress (*defined as a state of emotional suffering characterised by symptoms of depression and anxiety*; Mirowsky & Ross, 2002), physical disability, reduced quality of life, and increased health care costs (Dworkin, 2002; Freynhagen & Bennett, 2009; Haanpää et al., 2011; Haanpää & Treede, 2010).

After the development of standardized screening tools for neuropathic symptoms, a number of *population-based studies* (postal questionnaire surveys) in non-clinical samples reported a higher level of pain intensity as well as anxiety and depressive symptoms in respondents who scored high on neuropathic symptoms, compared to those who scored low (e.g., Attal, Lanteri-Minet, Laurent, Fermanian, & Bouhassira, 2011; Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008; Freynhagen et al., 2006a; Smith, Torrance, Bennett, & Lee, 2007; Torrance, Smith, Bennett, Lee, 2006). Despite the fact that the diagnosis of chronic neuropathic pain was not clinically evaluated in participants in these population-based studies, many authors generalised these findings to chronic clinical neuropathic pain. They concluded that the neuropathic quality of pain is of higher intensity and unpleasant than the nociceptive pain and that it results in more psychological distress in patients. Similar results were documented in a survey by Attal and colleagues (2011), who found a lower level of quality of life and a greater use of health care facilities in subjects who scored high on neuropathic symptoms. They suggested that *"it is the particular features, the strange and unpleasant signs and symptoms of*

this type of pain, and the distressing and unpleasant nature of the neuropathic symptoms themselves that impact on quality of life".

The assumption, that the neuropathic pain is more intense and distressing than the nociceptive pain, has been repeatedly iterated in a large number of literature available in this field (e.g., Förster et al., 2013; Freynhagen & Bennett, 2009; Haanpää et al., 2009). However, there is not enough convincing evidence that supports this assumption.

Studies concerning differences in the pain-related features and psychological characteristics of *medically* diagnosed neuropathic and nociceptive pain are rare. Daniel, Narewska, Serpell, Hoggart, Johnson, and Rice (2008) found that patients with postherpetic neuropathic pain and nociceptive back pain did not differ in their reports of depressive/anxiety symptoms, dysfunctional cognition (e.g., fearful appraisals of pain) and physical function. Also, some previous *clinical* studies, found no differences in pain intensity between typical neuropathic and nociceptive pain (e.g., Bennett, 2001; Dworkin, Jensen, Gammaitoni, Olaleye, & Galer, 2007; Scholz et al., 2009). Thus, studies on "comparison of patients with medically diagnosed neuropathic vs. nociceptive pain" and "comparison of population samples reporting pain with high vs. low level of severity of neuropathic symptoms" produced obviously inconsistent results on differences regarding pain features like general intensity and psychological distress. However, none of the above mentioned clinical studies examined the severity of neuropathic symptoms and its direct association with pain and psychological distress.

1.6 Pain experience: the biopsychosocial perspective of chronic pain

The earliest theories of pain focused primarily on the biological or pathophysiological components of pain. In 1968, Melzack and Casey described pain in terms of three dimensions, the "sensory-discriminative" (e.g., intensity and quality of the pain), the "affective-motivational" (e.g., pain unpleasantness), and the "cognitive-evaluative" (e.g., pain appraisals). They emphasised that pain experience is a function of the interaction of these dimensions and cannot be ascribed exclusively to any one of them. In consequence, in order to fully understand a

person's experience of pain, the interrelationships between biological, psychological, and sociocultural factors need to be considered. On the basis of this biopsychosocial approach, pain intensity and unpleasantness are not simply determined by the magnitude of the tissue damage or physical factors; rather, psychological factors (emotions and cognitions) also can modulate perceived pain intensity and unpleasantness in patients (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Turk, Meichenbaum, & Genest, 1983).

1.7 The effect of psychological factors on symptom report

Pain is a **subjective** experience. Accumulated research has demonstrated that the **report** of subjective symptoms is influenced by several psychological factors, including negative affectivity and cognitive self-appraisal (Diest, Peuter, Eertmans, Bogaerts, Victoir, & Bergh, 2005; Haythornthwaite, Sieber, & Kerns, 1991; Watson & Pennebaker, 1989; Watson & Clark, 1984). Negative affectivity has been generally described as a tendency to experience and report a wide range of negative feelings, such as anxiety, hostility, depression and fear, and has been shown to be a rather reliable and valid psychometric construct (Clark, Watson, & Mineka, 1994; Diener & Emmons, 1985; Keogh & Reidy, 2000; Watson & Clark, 1984). It has repeatedly been found that individuals who score high on self-report questionnaires of negative affectivity also report high levels of many somatic symptoms as well (e.g., Costa & McCrae, 1980, 1985; Pennebaker, 1982).

There are several possible explanations for this association of emotional and somatic conditions, including a true co-occurrence of psychological and medical illness in the same individual. Another possible explanation is that some individuals may have a greater tendency to perceive and respond to both negative psychological and physical experiences, i.e., to amplify all forms of distress. This **general negative response tendency (response bias)** is revealed by a dominance of responses at the negative pole of a rating scale (e.g., Deary, Chalder, & Sharpe, 2007; Kolk, Hanewald, Schagen, & Gijsbersvan Wijk, 2002; Stea, Lee, & Sears, 2013; Watson & Pennebaker, 1989; Watson & Clark, 1984). However, a growing number of studies has

suggested that there is considerable variation in how strongly reports of different symptoms are influenced by this response bias. For example, response bias has been suggested to be *more* influential in report of symptoms in patients *without any previous experience or knowledge* about them (Petersen, van den Berg, Janssens, & van den Berg, 2011), and with symptoms *without any identified pathology* than those that can be verified by clinical examination or medical tests (e.g., Cohen, William, Ronald, Cuneyt, & David, 2003; Deary et al., 2007; De Gucht, Fischler, & Heiser, 2004; Feldman, Cohen, Doyle, Skoner, & Gwaltney, 1999; Kisely, Goldberg, & Simon, 1997; Kolket al., 2002). This clinical phenomenon has attracted a number of names, including the term "somatosensory amplification", which refers to a predisposition to focus on certain weak and infrequent bodily sensations, as well as a tendency to appraise them as pathological and symptomatic of disease, rather than to normalise them. In this context, attentional and interpretational processes seem to play an important role in the mechanisms of the response bias phenomenon (Barsky, Goodson, Lane, & Cleary, 1988; Deary et al., 2007; Kolk et al., 2002).

In conclusion, it is argued that not only does the character of experienced pain associated with somatosensory and neurologic mechanisms determine the symptom report, but also an individual tendency to select specific response categories, in this case, preferring the endpoints of a response scale independently of the item content. The negative response tendency has been suggested to inflate the association of somatic complaints and psychological factors (e.g. Watson & Pennebaker, 1989; Lahey, Hakes, Hariri, Appelgate, Zald, Rathouz, 2012).

2. Aims of the thesis

The dimensional perspective of neuropathic pain is compatible with basic scientific opinion regarding chronic pain mechanisms (Backonja, 2003; Bennett et al., 2007; Freynhagen & Baron, 2009). Further studies, however, are needed to empirically examine this perspective (Bennett, 2010). The main directive of the first study was to further examine the dimensional perspective by quantitative assessment of the severity of self-reported neuropathic symptoms in diverse types of chronic pain (study 1). The severity of neuropathic symptoms has a central role in the clinical diagnosis of neuropathic components of pain, as it was depicted before. Previous research had generally been focused on a global dichotomous categorisation of different types of pain, i.e. neuropathic or nociceptive, when assessing the severity of neuropathic symptoms. So far, no study has explicitly analysed the severity of neuropathic symptoms in diverse types of pain, although this might provide a better understanding of the dimensionality of neuropathic pain, and help to improve the diagnosis of neuropathic pain components. The valid diagnosis of neuropathic pain may, in turn, provide an opportunity for adequate pain treatment.

We further aimed to examine the association of the severity of neuropathic symptoms with pain-related features and psychological factors, as there has been a controversy within the existing literature. In the first study, we examined this association in a sample of patients with different types of chronic pain (study 1), as the dimensional perspective of neuropathic pain suggests the likelihood of a differential extent of neuropathic components in different types of pain. The patients were categorised on the basis of the self-reported severity of neuropathic symptoms and were compared regarding pain intensity, pain chronicity, pain-related disability, length of hospital stay and depressive symptoms. Also, the predictive strength of the mentioned variables regarding the neuropathic score was analysed.

The main aim of the second study was to analyse this association within samples of patients particularly diagnosed as having an *underlying pathology* of neuropathic symptoms. We wanted to find out whether patients with typical neuropathic pain, radiculopathy or fibromyalgia who report different levels of the severity of neuropathic symptoms also differ in pain intensity, pain chronicity, depressive symptoms, pain catastrophising and acceptance. In study 2, we also compared different *patterns* of neuropathic symptoms regarding the above mentioned variables. By including patients with a "certain" neuropathic component of pain and/or neurological dysfunction assessed by neurological examinations in study 2, we increased the reliability of findings regarding the association of neuropathic symptoms with pain and psychological factors.

As described before, response bias has been suggested to be more influential in report of symptoms in patients without any previous experience or knowledge about the questioned symptoms. Hence, we were interested in the examination of this association in a sample of patients clinically diagnosed with a nociceptive type of pain i.e. nociceptive back pain. This might provide a better insight into the observed association of neuropathic symptoms with other indicators of health status assessed in population, or non-selected sample of pain patients including both neuropathic and nociceptive pain patients (study 1), which might explain some of the inconsistencies in the literature.

3. Summary of the original studies

Within the research project, two studies—using independent samples—were carried out in cooperation with the Pain Management unit at the Red Cross Hospital in Kassel. In the following sections, the samples and the main results of these studies are summarised. Both studies were approved by the ethics committee of the Georg-Elias-Müller-Institute of Psychology.

3.1 Summary of study 1: Clinical features of chronic pain with neuropathic characteristics: a symptom-based assessment using the Pain DETECT Questionnaire

This study aimed to assess the severity of self-reported neuropathic symptoms in different syndromes of chronic pain and to group the syndromes according to the severity of their neuropathic symptoms. These groups were compared regarding pain variables like intensity and chronicity, as well as pain-related disability, length of hospital stay, pain history and depressive symptoms. The predictive strength of the above mentioned variables regarding the severity of neuropathic symptoms was to be analysed.

Four hundred patients enrolled for multidisciplinary pain treatment were considered for inclusion in the study. The criteria for inclusion were: an age over 18 years and a diagnosis of chronic pain according to ICD-10 criteria (F45.41 or R52.1-2, International Statistical Classification of Diseases and Related Health Problems, 2012). The classification of pain syndromes was based on IASP Taxonomy (Turk & Rudy, 1987), using the well validated "Multiaxial Pain Classification System- Somatic Dimension" (MASK-S, Hildebrandt, Pfingsten, Maier, & Klinger, 1992; Klinger, Hasenbring, Pfingsten, Hürter, Maier, & Hildebrandt, 2000). A total of five primary diagnoses (i.e., headache, spinal column pain (mainly including back pain), musculoskeletal pain, typical neuropathic pain, postsurgical pain) were assigned. Because of the low numbers of patients with facial pain, ischemic pain, visceral pain and somatic unclassifiable pain, these diagnostic groups were collapsed into a single category, i.e., other pain.

The severity of neuropathic symptoms in each diagnostic group was assessed by the pain DETECT questionnaire (PDQ, Freynhagen et al., 2006a). One-way analyses of variance (ANOVAs) and post-hoc Tukey's tests were conducted to explore differences between the diagnostic groups regarding the severity of neuropathic symptoms (PDQ score).

According to Freynhagen et al. (2006a), the above mentioned diagnostic groups were recategorised on the basis of the severity of their neuropathic symptoms: **Neuropathic** (NP), **non-Neuropathic** (no-NP) and **Unclear** (UC) groups. ANOVAs and post-hoc Turkey's tests were performed in order to test the differences between the three groups (NP, no-NP, UC) regarding pain intensity, pain chronicity, disability, length of hospital stay, pain history and depressive symptoms. Univariate logistic regressions were applied to determine the association of these variables with the severity of neuropathic symptoms. The variables with a significant association to the severity of neuropathic symptoms were fed into a hierarchical multiple regression analysis.

Our findings demonstrated the presence of distinct self-reported neuropathic symptoms in 37% of all patients included. The validity of the PDQ score was supported by the fact that patients who had been clinically diagnosed with “typical neuropathic pain” scored highest on the PDQ ($M=17.79$, $SD=6.38$; $F(5, 394)=2.26$; $p=0.04$), being significantly higher than in three of the other groups, i.e., the “spinal column pain”, “headache” and “other pain” groups, with the exception of “musculoskeletal pain” and “postsurgical pain”.

A high PDQ score in the musculoskeletal pain category in the present study may result from a high percentage of *fibromyalgia* patients (60%, $PDQ\ score_{fibromyalgia} = 17.70$) in this group in our sample. As mentioned earlier, similarities in neuropathic symptoms between fibromyalgia and “typical neuropathic pain” may be explained by pathogenic mechanisms such as impaired small fibre function and a dysfunction of the endogenous systems modulating afferent activity in fibromyalgia (Bradley et al., 2002; Kosek et al., 1996; Uceyler et al., 2013). Although there is no

evidence of nerve injury in the majority of fibromyalgia patients and thus not fulfilling the criteria for typical neuropathic pain, the PDQ cannot distinguish fibromyalgia from neuropathic pain disorders on the basis of the neuropathic symptom score. This failing differentiation is a clear disadvantage for the choice of adequate treatment strategies. Furthermore, since some previous studies (e.g., Gormsen, Rosenberg, Bach, & Jensen, 2010; Koroschetz et al., 2011) have documented higher levels of pain intensity, depression and anxiety in fibromyalgia patients compared to neuropathic pain patients, this finding should be considered when interpreting the association of the severity of neuropathic symptoms with the intensity of pain and psychological distress in samples of chronic pain patients while not considering the proportion of fibromyalgia patients in the sample.

We also found a high severity of neuropathic symptoms in "*postsurgical pain"* not significantly differing from "typical neuropathic pain". This finding provides some support for the assertion that a large component of persistent pain after surgery is defined by somatosensory symptoms defining as neuropathic pain (e.g., Kehlet, Jensen, & Woolf, 2006; Shaladi et al., 2009; Shipton, 2008).

Contrasting this result, a significantly lower severity of neuropathic symptoms was found in "spinal column pain" compared to "typical neuropathic pain". According to Freynhagen et al. (2006b), only one-third of chronic back pain patients reported three or more neuropathic pain symptoms. This indicates that, although in a minor proportion of patients with back pain (e.g. radiculopathy) neuropathic mechanisms play a distinct role regarding their pain (Mahn et al., 2011), this is not the case in the majority of these patients and also clearly less neuropathic symptoms are reported.

Altogether, these results obviously demonstrate a spectrum of expression of neuropathic symptoms in different syndromes of chronic pain that challenges the dichotomous classification of chronic pain as nociceptive or neuropathic pain. Moreover, our findings lend support to the notion that, although diverse types of pain are distinct in their aetiology, they share some

similarities in the underlying pathophysiological mechanisms of pain generation (Costigan, Scholz, & Woolf, 2009).

Our findings, based on a clinical sample of patients with different types of chronic pain, demonstrated a higher level of pain intensity and depressive symptoms in the NP and UC groups compared with the no-NP group. ANOVAs and post-hoc tests demonstrated also significant differences between each of the analysed groups (NP, UC, no-NP) regarding pain chronicity and disability. The length of hospital stay in the NP group was significantly higher than in the no-NP group (see original article, Table 2). No group differences were found regarding pain history.

The results are consistent with findings in population-based studies (e.g., Attal et al., 2011; Freynhagen et al., 2006) but in contrast to Daniel et al. (2008), who did not find any differences regarding pain intensity, depressive/anxiety symptoms and physical function between patients with postherpetic neuropathic pain and nociceptive back pain. The following possible reasons for this discrepancy should be taken into account. First, the clinical characteristics of diverse types of chronic pain might influence the observed association. While in our study a high percentage of fibromyalgia patients (61%) was in the NP group, this was not the case in described clinical studies comparing typical neuropathic pain and nociceptive pain syndromes. Past research has documented the highest level of pain intensity, disability, depression and anxiety among fibromyalgia patients compared to other chronic pain patients, even those with neuropathic pain (e.g., Gormsen et al., 2010; Koroschetz et al., 2011), whatever the cause for this phenomenon might be. Thus, it is necessary to examine the association of neuropathic symptoms with the pain and psychological factors in specific diagnostic groups like fibromyalgia, separately.

Second, the possibility of response bias should be considered. As noted before, not only does the character of experienced pain associated with biological mechanisms determine the symptom *report*, but also cognitive, emotional and behavioural factors. The contribution of the psychological factors to the symptom *report* is more likely when patients do not have any identified pathology (Deary et al., 2007) or previous experience or knowledge about the

questioned symptoms. Based on clinical experience, the questioned symptoms in Pain DETECT Questionnaire like *"is cold or heat (bath water) in this area occasionally painful?*" or *"do you have sudden pain attacks in the area of your pain, like electric shocks"* were unfamiliar for many patients who had no previous experience about them. It is possible that some of these patients having a high level of negative affectivity (e.g. depression) and negative cognitive appraisals (e.g. pain catastrophizing) (mis)interpret and (mis)attribute rather inconspicuous sensations in the manner of the questioned neuropathic symptoms, inflating correlations among neuropathic symptoms and cognitive-emotional factors (e.g. depression). To gain a more precise insight regarding the association of neuropathic symptoms with pain and psychological factors, it should be analysed in a sample of patients who have been medically diagnosed with neuropathic components of pain (e.g. typical neuropathic pain syndromes).

In summary, the results of study 1 support the questioning of the dichotomous classification of chronic pain since a high severity of neuropathic symptoms was found in other diagnoses, particularly, in fibromyalgia (as a dysfunctional pain condition) and postsurgical pain (as a mixed pain syndrome). Chronic pain patients who scored high on self-reported neuropathic symptoms also reported high levels of pain intensity, pain chronicity, depression and functional disability. These findings provide some support for the common assumption that the neuropathic quality of pain is experienced and reported to be more intense and distressing than the pain without this specific quality. Whether this phenomenon is mainly based on the biological mechanisms of pain (neuropathic/nociceptive) or on other factors of pain processing so far remain obscure.

3.2 Summary of study 2: Neuropathic sensory symptoms: Association with pain and psychological factors

Our findings from study 1 provided some preliminary evidence for the common assumption that the neuropathic quality of pain is associated with more intense pain and distress in patients.

However, neither prior studies nor our first study medically evaluated specially regarding the presence of neuropathic components of pain in (all) patients who scored high on neuropathic symptoms.

The main aim of the second study was to examine the association of neuropathic symptoms with pain-related features and psychological factors in patients who had been diagnosed as having an underlying pathology of neuropathic symptoms.

In doing so, we first assessed self-reported neuropathic symptoms by the PDQ in patients with a clinical diagnosis of **"typical neuropathic pain"** (TNP), **"radiculopathy"** (RAD), **"fibromyalgia"** (FM) or **"nociceptive back pain"** (nBP). Cluster analysis was used to classify patients of each diagnostic group according to the self-reported *severity* of neuropathic symptoms (clustering 1). The association of the *severity* of neuropathic symptoms with pain-related parameters like pain intensity and chronicity, as well as psychological factors (depression, catastrophising, pain acceptance) in *each* of the four aforementioned diagnostic groups (i.e., TNP, RAD, FM and nBP) was determined.

In order to control for the response bias, a second clustering approach (clustering 2) was performed based on adjusted scores of neuropathic symptoms; relating actual responses to the individual mean responses. This means that the patient's rating of each item was subtracted from his/her individual mean of all seven items. This procedure is assumed to eliminate the response bias of patients (Baron et al., 2009; Elliott, Haviland, Kanouse, Hambarsoomian, & Hays, 2009). The adjusted scores, also, enabled us to categorise the patients of the different diagnostic groups in regard to their distinct *patterns* of neuropathic symptoms. The different *patterns* of neuropathic symptoms were compared regarding the above mentioned pain and psychological variables.

Three hundred and six patients (an independent sample from study 1) suffering from a chronic pain condition who were enrolled for multidisciplinary pain treatment were considered

for inclusion in the study. The criteria for inclusion were: an age over 18 years and having chronic pain according to ICD-10 criteria (F45.41 or R52.1-2, International Statistical Classification of Diseases and Related Health Problems, 2012). Chronic pain conditions included TNP syndromes (including peripheral and central neuropathic pain), RAD, FM or nBP that had been diagnosed by pain specialists based on history, clinical examination and further medical tests. Neuropathic sensory symptoms were again assessed by the Pain DETECT Questionnaire (PDQ, Freynhagen et al., 2006a).

As noted, to distinguish subgroups of patients with different levels of severity of self-reported neuropathic symptoms, a hierarchical cluster analysis including the seven scores of symptoms taken from the PDQ was performed (clustering 1). Multinominal regression analysis was used to examine the identified clusters as predictors of diagnostic groups (criterion). To investigate differences between these clusters regarding pain-related and psychological variables, ANOVAs were calculated (separately for each diagnostic group).

A further hierarchical cluster analysis (clustering 2) was conducted on the basis of adjusted scores. To explore the frequency of different diagnostic groups in each cluster, Chi-square tests were performed. ANOVAs assessed the differences between the identified clusters regarding the pain and psychological variables.

Clustering 1 identified three distinct clusters characterised by either a low, moderate or high level of severity of self-reported neuropathic symptoms that differed significantly from one another. The 3 clusters distinguished TNP from nBP, but not from RAD and FM. Radiculopathy is considered as back pain with both neuropathic and nociceptive components of pain (e.g., Freynhagen & Baron, 2009). As described, the presence of a high level of neuropathic symptoms in fibromyalgia is considered as a result of altered sensory processing that can be detected by functional imaging (Staud, Craggs, Perlstein, Robinson, Price, 2008). The identified severity-clusters (low, moderate or high) did not differ regarding pain intensity and chronicity, depression, pain acceptance and catastrophising in TNP, RAD and FM (see original article,

Table 3) but only in nBP. Thus, in patients who had been *medically* diagnosed with typical neuropathic pain, radiculopathy or fibromyalgia, an association of severity of neuropathic symptoms with the intensity of pain and psychological distress could not be supported. This indicates that the severity of neuropathic symptoms alone is not sufficient to produce a high level of pain intensity and psychological distress in patients.

There was a subgroup of nociceptive back pain patients who scored high on neuropathic symptoms. Significant differences between the 3 severity-clusters were found regarding nearly all variables with the exception of pain chronicity (see original article, Table 3). This finding suggests a general response tendency in those nociceptive back pain patients who scored high on neuropathic symptoms. As noted, past research has documented a close relation between negative affectivity and a higher level of reports of somatic symptoms, in particular, those symptoms whose respondents did not have any previous experience with or knowledge about them (Kolk et al., 2002; Watson & Clark, 1984; Watson & Pennebaker, 1989). Watson and Pennebaker, (1989) particularly pointed out that the negative response tendency inflates the association of somatic complaints and psychological factors. These findings underline the importance of considering a comprehensive assessment of pain qualities experienced by *both* groups of patients (i.e., neuropathic and nociceptive) when investigating the association of neuropathic symptoms with other indicators of health status.

The cluster analysis based on the adjusted neuropathic scores led to a four-cluster solution with distinct patterns of symptoms (see original article, Figure 1). This approach offered a good opportunity to illustrate the different qualities of pain. For example, whereas one cluster (cluster 1) was characterised by a high severity of prickling sensations, numbness and pain attacks, the other one (cluster 4) was identified by a severe burning pain, thermal hyperalgesia and also pain attacks. None of the symptom patterns was exclusively seen in any of the 4 diagnostic groups. Nevertheless, the distribution of the patterns differed largely between diagnostic groups. For

instance, symptom pattern 4 occurred only in 2% of the patients with nociceptive back pain but in nearly 20 % of typical neuropathic pain patients. Half of the nociceptive back pain patients demonstrated the symptom pattern characterised by a high level of pain attacks and pressure hyperalgesia (cluster 2). ANOVAs showed no significant differences regarding the pain and psychological variables when comparing the symptom patterns. This means that neither the symptom patterns frequently occurring in neuropathic pain nor the symptom patterns frequently occurring in nociceptive back pain were associated with a higher level of pain and psychological distress. This finding adds evidence to question a genuine association of neuropathic quality of pain with high levels of pain and psychological processes. At the same time, it highlights the adequacy of our strategy (adjusted scores) for analysis.

In sum, contrary to the suggestions of some authors, neither the severity of the neuropathic symptoms nor any pattern of these symptoms exclusively influences the intensity of pain and psychological distress in patients. As Melzack and Casey (1968) asserted, to consider the sensory features of pain as the only influential factor of perceived pain is to look at only part of the problem, and not even the most important part, at that. Our findings further suggest that individuals' psychological and behavioural responses to pain (e.g. utilization of the health care system and drug taking behaviour (assessed by MPSS), depression, pain catastrophizing, pain acceptance) can be quite uniform, regardless of whether patients suffer from pain with high or low neuropathic characteristics.

4. Discussion

Pain is an important public health problem that causes suffering and disability for many patients. The identification of neuropathic components of pain is of particular importance because this should have a direct impact on therapeutic decisions about pain (Haanpää et al., 2011; Sykes & Beydoun, 2014). In the last decade, the dichotomous approach classification of chronic pain has been questioned and a dimensional perspective has been proposed. According to this new perspective, chronic pain is a spectrum of neuropathic expression in which the pain quality may reflect the relative dominance of neuropathic mechanisms in the overall pain experience (Bennett et al., 2006). Recently, the uniqueness of the neuropathic quality of pain, in its intensity, unpleasantness and psychological burden, has been suggested by many authors based on the results of recent population-based studies (e.g., Attal et al., 2011; Bouhassira et al., 2008; Förster et al., 2013; Freynhagen & Bennett, 2009; Freynhagen et al., 2006a; Haanpää et al., 2009; Smith et al., 2007; Torrance, Smith, Bennett, & Lee, 2006).

Our studies addressed some important gaps regarding the state of knowledge. We assessed the severity of self-reported neuropathic symptoms in diverse types of chronic pain, while most studies focused on the dichotomous categorisation of chronic pain syndromes (neuropathic vs. nociceptive). Hence, the present study provided a better empirical understanding of the dimensionality of neuropathic pain. Most importantly, we examined the prevailing assumption of the uniqueness of the neuropathic quality of pain in different clinical samples of patients, i.e., in a sample of patients with diverse types of chronic pain (study 1), as well as within *each* sample of patients medically diagnosed with “typical neuropathic pain”, “radiculopathy”, “fibromyalgia” or “nociceptive back pain”, separately (study 2). Furthermore, not only different levels in the severity of neuropathic symptoms, but also, distinct patterns in these symptoms were compared regarding their association with various pain features and psychological factors.

Contrary to the dichotomous approach classification of chronic pain, a high severity of neuropathic symptoms was found not only in typical neuropathic pain but also in diagnoses like

fibromyalgia (as a dysfunctional pain condition), radiculopathy and postsurgical pain (as mixed pain syndromes). Some researchers have argued that, although these syndromes are not allocated to "typical neuropathic pain", they share some pathological mechanisms (e.g., Costigan et al., 2009; Koroschetz et al., 2011; Mahn et al., 2010). It must be stressed that the classification of fibromyalgia as a variant of neuropathic pain is a subject of controversy among researchers. Whereas Treede et al., (2008) suggested that pain conditions without any identifiable nerve lesion, such as fibromyalgia, should not be categorised as neuropathic pain, Uceyler et al., (2013) assessing the small fibers function in fibromyalgia suggested a neuropathic nature of pain in fibromyalgia syndrome. Altogether, the results lend support to the questioning of the dichotomous approach of the classification of chronic pain as either neuropathic or nociceptive pain.

At first sight, our findings in a sample of patients with diverse types of chronic pain (study 1) seem to support the results of population-based studies suggesting that the higher the severity of neuropathic symptoms, the higher the level of overall pain intensity and psychological distress will be. However, these results are in contrast to the results found in samples of patients particularly diagnosed as having an underlying pathology of neuropathic symptoms (study 2). Patients with typical neuropathic pain, radiculopathy or fibromyalgia who suffer from different levels of severity of neuropathic symptoms did not differ in the extent of pain intensity, pain chronicity, depression, catastrophising and pain acceptance. These findings provide compelling evidence that the severity of neuropathic symptoms does not principally result in a high intensity of pain related characteristics and psychological dysfunctional features. This can be explained by the fact that the experience of pain is a multidimensional phenomenon that consists of sensory, affective, cognitive and behavioural components, and not one of them exclusively (Turk et al., 1983, 1998).

A subgroup of nociceptive back pain patients who scored high on self-reported neuropathic symptoms also reported high levels of pain intensity, depression, catastrophising and less

acceptance of pain suggesting a general response tendency in this subgroup of nociceptive back pain patients. According to Social Comparison Theory (Festinger, 1954) and Temporal Comparison Theory (Albert, 1977; Zell & Alicke, 2009), individuals need comparison standards to evaluate their opinions, skills, social status, or physical state. Petersen et al., (2011) proposed the comparison standards as a predictor of symptom presentations and contended that, in evaluating a bodily state, individuals must use reference standards, such as their personal experience of symptoms in the past or their beliefs about the perceptions of sensations by relevant others, such as patients or healthy individuals. Having no previous personal experience of neuropathic symptoms and a lack of knowledge about the origin and meaning of these symptoms among patients with nociceptive back pain may explain the biased response tendency regarding these symptoms, *particularly* among those with negative affectivity (e.g. depression) and cognitive self-appraisals (e.g. pain catastrophising). The finding that different levels in the severity of neuropathic symptoms in nBP did not differentiate pain chronicity that was not obtained by self-report (contrary to all other questionnaires in the second study) may provide additional evidence for the argument above.

To eliminate the individual response bias regarding the neuropathic symptoms a second clustering approach was conducted that was based on the adjusted scores of neuropathic symptoms. This procedure provided a detailed insight into the different patterns of neuropathic symptoms. Symptom patterns that frequently occurred in typical neuropathic pain, radiculopathy or fibromyalgia did not show a higher level of pain and psychological distress, compared to those that predominantly occurred in nociceptive back pain. These findings clearly suggest that the assumption of the uniqueness of neuropathic pain quality in its intensity and distressing nature should be questioned.

Patients who were classified in the 4 clusters were characterised by different patterns of pain quality. They did, however, not differ in pain intensity and chronicity, depression and dysfunctional cognitions. This result invalidates the assertion of some authors that “the disease

burden of chronic pain depends on the nature of the pain, independently of its intensity and duration" (e.g., Attal et al., 2011; Freynhagen & Bennett, 2009). The finding can be explained by the fact that pain quality is only one of the factors that accounts for the pain experienced by chronic pain patients and it is not necessarily the most important. The results of the present study can be integrated well into earlier research suggesting that the psychological and behavioural responses to chronic pain are common to diverse samples of chronic pain patients, despite differences in their physical status and medical diagnosis (Turk & Rudy, 1990; Turk, Sist, Okifuji, Miner, Florio, Harrison et al., 1998).

There are some limitations in regard to our findings. The current findings are based on samples of pain patients who sought treatment in a tertiary care center and may not be representative of those who attend primary care. Furthermore, our samples of patients were recruited from a single clinic and this selection might have affected the results. A further problem is that, a number of chronic pain patients suffered from two or more pain syndromes, but only the dominant pain complaint, as evaluated by anaesthesiologists/neurologists, was considered. An additional limitation relates to the main assessment instrument: the use of the PDQ has not been validated in fibromyalgia and headache.

In sum, our findings seem to highlight the existence of neuropathic features in various diagnosed pain syndromes, which underlines the scepticism regarding a dichotomous approach in the classification of chronic pain. The results further suggest that the magnitude and quality of neuropathic symptoms alone are not sufficient to lead to a high level of pain and psychological distress in patients. It should be noted that these results in no way deny the contribution of the biological components of pain in the overall pain experienced by patients. There is little doubt that physical factors affect pain in patients and that treatment should include effective pharmacological, medical and surgical strategies. However, neglecting the importance of patients' conceptualisations and evaluations of their pain may hinder the successful treatment of pain.

Our findings also have several implications for studies on neuropathic pain. Particular attention should be paid to select syndrome specific samples of patients when investigating the association of neuropathic symptoms with other indicators of health status. In addition, further research, particularly population-based studies, should use measures that assess the pain qualities experienced by both neuropathic (e.g. burning pain, paresthesias, numbness) and nociceptive (e.g. deep, dull, throbbing) pain patients. The results also highlight the importance of using adjusted scores in self-report questionnaires to eliminate a potential response bias when investigating different self-reported symptoms. The findings further suggest that pain management strategies should not be based solely on the physical aspects of pain (e.g., intensity and quality of pain) because patients' evaluations moderate their pain experience and adaptation.

II. Original articles

1. Original article 1

Shaygan, M., Böger, A., Kröner-Herwig, B. (2013). Clinical features of chronic pain with neuropathic characteristics: A symptom-based assessment using the Pain DETECT Questionnaire. *Eur J Pain*, 17 (10), 1529-38.

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ORIGINAL ARTICLE

Clinical features of chronic pain with neuropathic characteristics: A symptom-based assessment using the Pain DETECT Questionnaire

M. Shaygan[1], A. Böger[2], B. Kröner-Herwig[1]

1 Georg-Elias-Müller-Institute of Psychology, University of Göttingen, Germany
2 Pain Management Clinic at the Red Cross Hospital, Kassel, Germany

Correspondence
Maryam Shaygan
E-mail:
maryam.shaygan@stud.uni-goettingen.de

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Abstract

Background: In general, chronic pain is categorized into two mechanism-based groups: nociceptive and neuropathic pain. This dichotomous approach is questioned and a dimensional perspective is suggested. The present study investigated neuropathic characteristics in different syndromes of chronic pain. We also examined the association of neuropathic characteristics with various pain related and psychological variables.
Methods: From April 2010 to January 2012, 400 patients suffering from a chronic pain condition enrolled for multidisciplinary pain treatment were considered for inclusion in the study. Criteria for inclusion were age over 18 years and having chronic pain according to ICD-10 (F45.41) criteria. The pain DETECT questionnaire was used to assess neuropathic characteristics of pain.
Results: Thirty-seven percent of patients with different pain diagnoses demonstrated distinct neuropathic characteristics. The diagnostic groups for neuropathic pain, musculoskeletal pain and post traumatic or surgical pain showed the most neuropathic features. The level of depression, pain chronicity and intensity, disability and length of hospital stay were significantly higher in patients suffering from neuropathic symptoms. A high level of depression and pain chronicity as well as high intensity of pain explained most of the variance in the neuropathic scores. Disability and length of hospital stay significantly predicted neuropathic characteristics only when examined separately, but not if included in a common regression model.
Conclusions: Any type of chronic pain may have more or less neuropathic characteristics. The pain-related parameters of high intensity and chronicity as well as negative affectivity and functional disability strongly correlate with neuropathic characteristics of pain.

1. Introduction

Chronic pain is a major health care problem in Europe (Breivik et al., 2006). In an epidemiological study, the point prevalence of chronic pain, defined by pain lasting more than 6 months, occurring several times during the last week, and last experienced pain having an intensity of 5 or more on a numeric rating scale (0–10), was 19% in adult Europeans. Sixty-one percent of patients were less able or unable to work outside the home and 19% had lost their job (Breivik et al., 2006). Thus, chronic pain has a dramatic impact on the lives of affected individuals and a substantial economic impact on society.

Chronic pain conditions are often categorized into two major groups, namely nociceptive and neuropathic pain (Woolf et al., 1998). Clinically, neuropathic pain is characterized by a complex

What's already known about this topic?
- Screening instruments are easy to use and reliable in discriminating between patients with predominantly neuropathic versus predominantly nociceptive pain.
- In general, researches have focused on phenomenological categorization when dealing with neuropathic pain.

What does this study add?
- This study adds evidence to the characterization of neuropathic features in otherwise diagnosed pain.
- The neuropathic dimension of pain is characterized by high levels of intensity and chronicity, negative affectivity and functional disability.

pattern of positive (e.g., burning pain, paresthesia, hypersensitivity) and negative (e.g., hypoesthesia, hypoalgesia) sensory abnormalities. However, there are still no consensual diagnostic criteria for neuropathic pain (Haanpää et al., 2011). In contrast to nociceptive pain, which is caused by actual tissue damage, neuropathic pain is defined as 'pain caused by a lesion or disease affecting the somatosensory system' (Jensen et al., 2011). This definition seems to be easily applicable, but in fact describes a mechanism-based diagnosis of pain, which can hardly be verified as validated. Moreover, pain patients typically present a complex pattern of symptoms rather than recognizable neurological lesions particularly in secondary or tertiary care chronic pain populations (Bennett et al., 2007). Hence, the lack of objective markers as well as a gold standard for detection of neuropathic pain (Torrance et al., 2007) makes the identification of neuropathic pain by clinicians a continuing challenge. Recently, efforts were undertaken to develop symptom-based, easy-to-use screening tools to help to assess pain with distinct neuropathic symptomatology (e.g., Bennett, 2001; Freynhagen et al., 2006a). Also, in the past few years, the dichotomous approach classification of chronic pain has been questioned and it has been suggested that neuropathic pain may be better conceptualized as a spectrum, in which pain may have 'more or less neuropathic components' (Attal and Bouhassira, 2004; Bennett et al., 2006).

The main aim of the present study was to assess the neuropathic characteristics of different syndromes of chronic pain based on patient self-reporting of pain characteristics, and to group the syndromes according to the level of neuropathic characteristics. These groups were assessed regarding various variables like intensity and chronicity of pain, pain-related disability, depressive symptoms and length of hospital stay, with the expectation of a higher level of severity of the mentioned variables in patients with distinct neuropathic characteristics. As a final step in the analysis, we examined which variables were predictive of neuropathic characteristics by regression analyses. It was expected that psychological factors, besides direct and indirect indicators of pain severity (e.g., intensity), contribute to the prediction of neuropathic characteristics, and the inclusion of a psychological variable (depression) in a multiple regression analysis would increase the total amount of variance explained by pain variables.

2. Methods

This cross-sectional study was conducted in a multidisciplinary tertiary care centre, comprising specialists in pain medicine, psychology and neighbouring professions. In-patients presenting with chronic pain as diagnosed by anaesthesiologists/neurologists were requested to complete the questionnaires presented by a hand-held computer (personal digital assistant), after having signed informed consent regarding their participation in the study. This method of data acquisition was validated in a study by Junker et al. (2008). Ethical approval was obtained from the Ethics Committee of the Georg-Elias-Mueller Institute for psychology.

2.1 Sample selection

From April 2010 to January 2012, 500 patients suffering from a chronic pain condition were referred to the pain treatment centre. Of the 500 patients, 400 were consecutively considered for inclusion in the study. Criteria for inclusion were age above 18 years and having chronic pain according to ICD-10 (F45.41, International Statistical Classification of Disease and Related Health Problems, 2012) criteria. The following exclusion criteria were set having a pain history less than 6 months, presence of malignant disease.

The main pain syndrome (defined as worst pain and reported as the main reason for seeking treatment) was assessed according to International Association for the Study of Pain Taxonomy (Turk and Rudy, 1987) using the widely used and well-validated Multiaxial Pain Classification System-Somatic Dimension (Hildebrandt et al., 1992; Klinger et al., 2000). A total of nine primary diagnoses (i.e., headache, facial pain, ischemic pain, spinal column pain, musculoskeletal pain, neuropathic pain, visceral pain, post traumatic or surgical pain, somatic unclassifiable pain, see Supporting Information Appendix S1) based on body region and aetiology were assigned. (Because of the low numbers of patients with facial pain, ischaemic pain, visceral pain and

somatic unclassifiable pain, these diagnostic groups were collapsed into a single category, i.e., other pain).

2.2 Assessment of pain characteristics and psychosocial variables

In addition to the standard socio-demographic assessment (age, gender, sickness history, education and employment status), the following variables were measured:

2.2.1 Neuropathic pain characteristics

The presence of neuropathic pain characteristics of the main pain syndrome was assessed by the pain DETECT questionnaire (PDQ; Freynhagen et al., 2006a). The PDQ is a patient-based (self-report) questionnaire to discriminate between neuropathic and nociceptive pain components. The questionnaire consists of nine items and the total score ranges from −1 to 38. It comprises questions regarding the subjective experience of a radiating quality of pain (yes/no), temporal characteristics of the individual pain pattern (selection between four pain course patterns) and the presence of seven sensory symptoms of neuropathic pain rated on a 0–5 rating scale (never to very strongly) like spontaneous burning sensation, prickling sensations, numbness etc. The PDQ was validated in a study by Freynhagen et al. (2006a) on 392 patients with either neuropathic pain ($n = 167$), including post-herpetic neuralgia, polyneuropathy, nerve trauma and low back pain (source of pain is in lumbar vertebrae, sacrum and/or coccyx) or nociceptive pain ($n = 225$), including visceral pain, osteoarthritis, inflammatory arthropathies and mechanical low back pain. The instrument indicated a sensitivity of 84% and a specificity and probability of correct assignment of 84% in identifying patients with distinct neuropathic characteristics of pain. As recommended by Freynhagen et al. (2006a), the following cut-off points were adopted as the most appropriate for screening purposes: score ≤ 12 (< 15% chance a neuropathic pain component is present; no-NP group); score ≥ 19 (> 90% chance a neuropathic pain component is likely; NP group). A score of 13–18 indicates uncertainty regarding neuropathy (UC group). The seven items concerning the presence of sensory symptoms of neuropathic pain demonstrated adequate internal consistency (Cronbach's alpha = 0.83).

2.2.2 Pain intensity

The average intensity of pain was assessed on a numeric rating scale (NRS). The NRS is an 11-point Likert scale ranging from 0 (no pain) to 10 (worst imaginable pain). It is an often-used reliable scale to assess intensity of pain (Dworkin et al., 2005).

2.2.3 Chronicity of pain

Pain chronicity was estimated employing the Mainz Pain Staging System (MPSS, Gerbershagen et al., 2002). The MPSS assesses three stages of pain chronicity based on 10 self-administered questions (in terms of four axes). Patients were requested to describe the occurrence of pain (e.g., several times per day), pain history (e.g., lasting up to several hours) and changes in pain intensity (e.g., frequently) *(temporal dimension, axis 1)*; pain distribution (e.g., multiple sites) *(spatial dimension, axis 2)*; drug use (e.g., at most two non-opioid analgesics) and number of previous drug withdrawal treatments (e.g., more than one withdrawal) *(drug taking behaviour, axis 3)*; change of personal physician (e.g., no change), pain-related hospitalizations (e.g., up to 1), pain-related operations (e.g., up to 1) and pain-related rehabilitation (e.g., one) *(utilization of the health care system, axis 4)*. The sum of the four axes reflects an additive value in the range of 4–12. This value determines the final stage of pain chronicity. Stage 1 is coded when the total score ranges from 4 to 6, stage 2 is based on a range from 7 to 8 and stage 3 is assigned when the total score is 9–12. The instrument was validated in a study by Pfingsten et al. (2000) with 542 patients with different diagnoses.

2.2.4 Disability

Pain-related disability was measured by the Pain Disability Index (PDI, Pollard, 1984). The PDI assesses subjective disability in seven areas: home/family responsibilities, recreation, social activities, occupation, sexual behaviour, self-care and life support activities using an 11-point scale from '0' (no disability) to '10' (total disability). Thus, the range of possible scores is 0–70. High scores reflect a high degree of disability. In a study by Dillmann et al. (1994), the reliability (Cronbach's alpha = 0.88) and validity of the German version of the instrument were confirmed. They found a significant correlation between the PDI score and the Oswestry Low Back Pain Disability Questionnaire (OBQ, Fairbank et al., 1980) (r = 0.76).

2.2.5 Depression

Depressive symptoms were assessed by the Patient Health Questionnaire for depression (PHQ-9, Spitzer et al., 1999). Each item of the questionnaire evaluates the presence of one of the nine DSM-IV (American Psychiatric Association, 1994) criteria for major depression. The nine items are answered on a 4-point rating scale ranging from 'not at all = 0' to 'nearly every day = 3'. The PHQ-9 score can range from 0 to 27. The instrument demonstrated high internal consistency (Cronbach's alpha = 0.89; Rief et al., 2004). In a study by Martin et al. (2006), the construct validity of the PHQ-9 was assessed by correlating its total score with a shortened version of the Beck Depression Inventory (Schmitt and Maes, 2000) (r = 0.73) and the General Health Questionnaire (Goldberg and Williams, 1988) (r = 0.59). The German version also showed a high sensitivity (98%) and specificity (80%) regarding the diagnosis of a depressive disorder (Löwe et al., 2002).

2.3 Statistical analysis

After calculation of individual means, patients were grouped into three categories (no-NP group: score ≤ 12; UC group: score 13–18; NP group: score ≥ 19, see Freynhagen et al., 2006a). One-way analysis of variance (ANOVA) and *post hoc* Turkey's test were performed in order to test the differences between the three defined groups regarding pain intensity, pain chronicity, depression, disability, pain history and length of hospital stay. Analysis of the categorical data was obtained by use of the chi-square test. The method of univariate logistic regression assessed the association of every potential predictor (independent variable) individually with neuropathic characteristics. Independent variables in the single models included age, sex, education level, depression, pain intensity, pain chronicity, disability, pain history and length of hospital stay. After conducting univariate analyses, the variables with a significant association to neuropathic characteristics were fed into hierarchical multiple regression analyses (method: Enter). First, pain intensity and pain chronicity were assessed regarding their association with neuropathic characteristics, as some studies have indicated these factors are correlated with neuropathic pain (Margot-Duclot et al., 2009; Gerbershagen et al., 2010). In a second step in the regression analyses, disability and length of hospital stay were entered into the model, as it has been shown that patients with neuropathic symptoms report lower functionally and a greater use of health care facilities (Freynhagen et al., 2006a; Gerbershagen et al., 2010). Finally, a psychological variable (depression) was entered into the model, as we wanted to investigate whether the inclusion of a psychological variable increased the total amount of explained variance in the dependent variable (neuropathic characteristics) after controlling for the previously entered pain-related variables. This statistical strategy allows determination of the increase in explained variance by each block of variables entered. Variance inflation factors (VIFs) were calculated for the independent variables in order to test the assumption of collinearity (Myers, 1990). All of the data were analysed by Statistical Package for the Social Sciences software, version 19. The significance level was set at $p < 0.05$.

3. Results

3.1 Study sample

Of the 500 patients, 100 patients had to be excluded from the study: 15 patients because they had pain history less than 6 months, 27 patients in whom tumour was diagnosed and 58 patients who refused to answer the questionnaires. Out of all 400 participants, 148 patients (37%) had a PDQ score ≥ 19 and were considered to have chronic pain with predominantly neuropathic characteristics (NP group). About 27% of patients ($n = 111$) were assigned to the 'unclear' group (UC; PDQ score: 13–18), and 141 patients (35.2%) had a PDQ score ≤ 12 and thus were considered to have chronic pain without any reliable neuropathic characteristics (no–NP group).

The mean age of the patients was 57.8 years old [standard deviation (SD) = 14.4], and the highest percentage of patients (28%) belonged to the age group between 51 and 60 years old (Table 1). The majority of patients were female (62.5%) and about 46% had primary education (Table 1).

There was no significant difference between the groups regarding mean age ($F\ (2,\ 397) = 1.15$; $p = 0.31$, Table 1). Also, no significant differences were found regarding age group ($X^2 = 14.3$, d.f. = 12, $p = 0.27$), sex ($X^2 = 1.24$, d.f. = 2, $p = 0.53$) or employment status ($X^2 = 1.53$, d.f. = 2, $p = 0.46$). However, our data demonstrated significant differences between groups regarding retirement due to normal age or disability ($X^2 = 14.43$, d.f. = 2, $p = 0.000$, Table 1).

3.2 Comparison of diagnostic groups

Fig. 1 shows the number of patients as well the PDQ scores in each of the diagnostic groups. The different diagnostic groups were examined regarding their PDQ scores by ANOVA and *post hoc* tests. The patients diagnosed with 'neuropathic pain' showed the highest PDQ scores ($M = 17.79$, $SD = 6.38$; $F\ (5,\ 394) = 2.26$; $p = 0.04$, Fig. 1). The PDQ score of the 'neuropathic pain' group was significantly different from 'spinal column pain' ($p = 0.01$), 'headache' ($p = 0.03$) and 'other pain' ($p = 0.03$) groups. However, the PDQ score of the 'neuropathic pain' group did not significantly differ from that of the 'musculoskeletal pain' or 'postsurgical pain' groups (Fig. 1).

3.3 Comparison of pain DETECT-groups (NP, UC, no-NP groups)

Results of ANOVA showed significant differences between the groups regarding pain intensity ($M_{NP} = 6.9$, $SD = 1.6$; $M_{UC} = 6.4$, $SD = 1.7$; $M_{no\text{-}NP} = 5.9$, $SD = 1.7$; $F\ (2{,}385) = 13.3$, $p = 0.000$) and depression ($M_{NP} = 14.2$, $SD = 5.3$; $M_{UC} = 12.5$, $SD = 7.3$, $M_{no\text{-}NP} = 9.1$, $SD = 4.8$, $F\ (2{,}307) = 22.68$, $p = 0.000$). *Post hoc* tests also revealed significant differences between NP versus no-NP and UC versus no-NP groups for pain intensity and depression (Table 2). In addition, there were significant differences between groups in pain chronicity score ($M_{NP} = 9.02$, $SD = 1.2$; $M_{UC} = 8.6$, $SD = 1.2$; $M_{no\text{-}NP} = 8.2$, $SD = 1.2$, $F\ (2{,}396) = 14.04$, $p = 0.000$) and disability ($M_{NP} = 43.2$, $SD = 13.8$; $M_{UC} = 38.2$, $SD = 14.3$, $M_{no\text{-}NP} = 33.2$, $SD = 13.9$, F

Table 1 Patient description and analysis of group differences (chi-square, *t*-tests).

Variable	NP $n = 148$	UC $n = 111$	no-NP $n = 141$	Total $n = 400$	F(df) / X^2 (df)
Age (Mean ± standard deviation)	57.5 ± 14.6	56.4 ± 12.1	59.2 ± 15.8	57.8 ± 14.4	F (2/ 397) = 1.15[a]
Age groups, *n* (%)					
<20	3 (2.0%)	0	4 (2.8%)	7 (1.8%)	
21–30	3 (2.0%)	1 (0.9%)	3 (2.1%)	7 (1.8%)	
31–40	9 (6.1%)	5 (4.5%)	8 (5.7%)	22 (5.5%)	
41–50	33 (22.3%)	31 (27.9%)	25 (17.7%)	89 (22.3%)	X^2 (12) = 14.3[a]
51–60	41 (27.7%)	38 (34.2%)	33 (23.4%)	112 (28%)	
61–70	27 (18.2%)	17 (15.3%)	26 (18.4%)	70 (17.5%)	
>70	32 (21.6%)	19 (17.1%)	42 (29.8%)	93 (23.3%)	
Sex, *n* (%)					
Female	96 (64.9%)	71 (64%)	83 (58.9%)	250 (62.5%)	X^2 (2) = 1.24[a]
Education level, *n* (%)					
None	1 (0.7%)	2 (1.8%)	3 (2.1%)	6 (1.5%)	
Primary education	67 (45.6%)	56 (51.4%)	60 (42.9%)	183 (46.2%)	
Secondary school	52 (35.4%)	26 (23.9%)	46 (32.9%)	124 (31.3%)	X^2 (8) = 7.11[a]
High school certificate	4 (2.7%)	7 (6.4%)	8 (5.7%)	19 (4.8%)	
College or university degree	23 (15.6%)	18 (16.5%)	23 (16.4%)	64 (16.2%)	
Employment status, (%)					
Employed / unemployed	30.3% / 9%	20.8% / 6.2%	28.7% / 5.1%	79.8% / 20.3%	X^2 (2) = 1.53[a]
Retired due to: (normal age / disability)	21.5% / 15.3%	12.9% / 12.3%	31.9% / 6.1%	66.3% / 33.7%	X^2 (2) = 14.43***

NP, chronic pain with neuropathic characteristics (PDQ score ≥ 19); UC, uncertainty regarding neuropathy (PDQ score 13–18); no-NP, chronic pain without any reliable neuropathic characteristics (PDQ score ≤ 12).

*** $p < 0.001$.

[a]Not significant.

(2,349) = 14.91, $p = 0.000$). Accordingly, *post hoc* tests demonstrated significant differences between each of the analysed groups regarding pain chronicity and disability (Table 2). The length of hospital stay in the NP group was also significantly different from the no-NP group ($M_{NP} = 15.1$, SD = 4.9; $M_{no\text{-}NP} = 13.6$, SD = 4.3; F (2,385) = 3.1, $p = 0.03$, Table 2). No significant differences were found when comparing the NP and UC ($p = 0.45$) or the UC and no-NP groups ($p = 0.49$). No group differences were found regarding pain history ($M_{NP} = 10.7$, SD = 9.1; $M_{UC} = 10.6$, SD = 10.2, $M_{no\text{-}NP} = 10$, SD = 9.4, $p = 0.8$, Table 2).

3.4 Univariate logistic regression models

Univariate multinominal logistic regression with no-NP as a reference group revealed that neither age ($p = 0.3$), sex ($p = 0.5$), education level ($p = 0.8$) nor pain history ($p = 0.8$) were significantly correlated with neuropathic characteristics when analysed as single predictors (Table 3). The variables pain chronicity (8.3% of explained variance), pain intensity (8% of explained variance), disability (9.6% of explained variance) and length of hospital stay (2.8% of explained variance) were significantly associated with neuropathic characteristics. The depression scores (PHQ score) were also significantly associated with neuropathic characteristics and achieved the best model fit, explaining 15 % of the variance (Table 3).

3.5 Multiple regression analyses

The collinearity statistics showed that tolerance levels were between 0.7 and 0.9 and VIFs for all variables were between 1.05 and 1.34, indicating that multicollinearity was not present. Hierarchical multiple regression analyses were conducted in order to examine the contributions of variable blocks entered simultaneously to the prediction of neuropathic characteristics. In the first step of the hierarchical regression analyses, pain chronicity and intensity were assessed regarding their association with neuropathic characteristics. These variables made significant contributions to the explanation of variance in 'neuropathic characteristics', explaining 13% of the variance. In the second step, disability and length of hospital stay were included in the model. Disability turned out to be a significant predictor in this model ($\beta = 0.17$, $p = 0.005$), but length of hospital stay did not. This model achieved a variance explanation of 2% more than the previous model ($R^2 = 15\%$) [$\Delta R^2 = 0.02$, ΔF (2, 286) = 4.4, $p = 0.01$, Table 4].

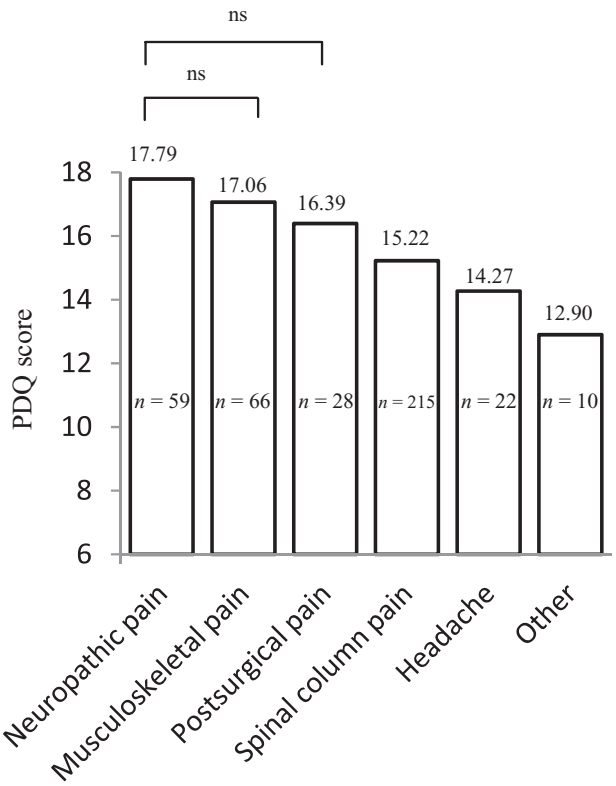

Figure 1 Number of patients as well as PDQ scores regarding pain diagnoses.
Note. PDQ score on pain DETECT questionnaire; other pain group includes: facial pain ($n = 1$), ischaemic pain ($n = 1$), visceral pain ($n = 2$) and somatic unclassifiable pain ($n = 6$); ns, not significant.

Finally, depression was entered into the model. Depression also contributed to the prediction of neuropathic characteristics in this model ($\beta = 0.23$, $p = 0.000$). The inclusion of a psychological variable led to a 5% increase in explained variance, for a total explanation of variance of 20% [$\Delta R^2 = 0.04$, ΔF (1, 285) = 15.3, $p = 0.000$, Table 4]. Pain chronicity ($\beta = 0.16$, $p = 0.004$) and pain intensity ($\beta = 0.12$, $p = 0.04$) also remained as predictive factors in this model, but the variable 'disability' did not maintain its status as a predictive variable ($p = 0.13$) [F (7, 285) = 10.21, $p = 0.000$].

4. Discussion

The main objective of the study was to investigate neuropathic characteristics of different pain diagnoses using the PDQ to scale the level of neuropathic symptoms.

Our findings demonstrated the presence of distinct neuropathic characteristics (PDQ score ≥ 19) in 37% of patients with different types of chronic pain, who belonged to pain syndrome groups not only clinically diagnosed as 'neuropathic pain', but also otherwise diagnosed pain. This finding is in accordance with some previous studies. Freynhagen et al. (2006b) reported that 33.5% of chronic back pain patients suffer from distinct neuropathic characteristics. Additionally, some previous studies on migraine (e.g., David and Biondi, 2006) and fibromyalgia (e.g., Koroschetz et al., 2011) indicated that neuropathic features are also present in those pain diagnoses. The validity of the PDQ score is supported by the fact that the clinical group with diagnosed 'neuropathic pain' scored the highest on the PDQ on average. However, it has to be pointed out that the clinical group diagnosed as 'neuropathic pain' demonstrated an average PDQ score less than 19 (the cut-off point for 'distinct' neuropathic characteristics). Moreover, no significant differences were found regarding the PDQ scores for the 'neuropathic pain', 'musculoskeletal pain' and 'post traumatic or surgical pain' groups.

This could be due to the fact that, although the PDQ was developed and validated on a sample of chronic pain patients with various neuropathic or nociceptive pain syndromes, it specifically targeted chronic low back pain. Thus, it seems that this screening tool could not be used to differentiate typical neuropathic entities

Table 2 Results of one-way analysis of variance (ANOVA) and *post hoc* Tukey's test.

Variable	NP ($n = 148$)	UC ($n = 111$)	no-NP ($n = 141$)	F (d.f.)	Tukey test ($p < 0.05$)
Mean pain intensity (NRS)	6.9 ± 1.6	6.4 ± 1.7	5.9 ± 1.7	13.3 (2 / 385)***	(NP, UC) > no-NP
Pain Chronicity (MPSS score)	9.02 ± 1.2	8.6 ± 1.2	8.2 ± 1.2	14.04 (2 / 396)***	NP > UC > no-NP
Disability (PDI)	43.2 ± 13.8	38.2 ± 14.3	33.2 ± 13.9	14.91 (2 / 349)***	NP > UC > no-NP
Depression (PHQ)	14.2 ± 5.3	12.5 ± 7.3	9.1 ± 4.8	22.68 (2 / 307)***	(NP, UC) > no-NP
Length of hospital days	15.1 ± 4.9	14.3 ± 4.4	13.6 ± 4.3	3.11 (2 / 385)*	NP > no-NP
Pain history (years)	10.7 ± 9.1	10.6 ± 10.2	10 ± 9.4	2.6 (2 / 327)[a]	–

NP, chronic pain with neuropathic characteristics (PDQ score ≥ 19); UC, uncertainty regarding neuropathy (PDQ score: 13–18); no-NP, chronic pain without any reliable neuropathic characteristics (PDQ score ≤ 12); NRS, Numeric Rating Scale; MPSS, Mainz Pain Staging System; PHQ, Patient Health Questionnaire; PDI, Pain Disability Index; *** $p < 0.001$; * $p < 0.05$; [a]Not significant.

Table 3 Single variable models: odds ratio, 95% confidence intervals, significance and nagelkerke.

Variables	UC	NP	Nagelkerke
Single variable models			
Age (years)	0.98 (0.97–1.00)[a]	0.99 (0.97–1.00)[a]	0.007
Sex	0.80 (0.48–1.34)[a]	0.77 (0.48–1.24)[a]	0.003
Education level			0.011
None	0.85 (0.12–5.6)[a]	0.35 (0.03–3.44)[a]	
Primary or secondary education	0.98 (0.50–1.95)[a]	1.12 (0.59–2.11)[a]	
High school certificate	1.11 (0.34–3.66)[a]	0.50 (0.13–1.89)[a]	
Depression (PHQ score)	1.13 (1.07–1.20)***	1.19 (1.12–1.26)***	0.15
Pain chronicity (MPSS score)	1.29 (1.05–1.59)*	1.67 (1.36–2.04)***	0.083
Pain intensity (NRS score)	1.19 (1.03–1.39)*	1.43 (1.24–1.67)***	0.080
Disability (PDI score)	1.02 (1.00–1.04)*	1.04 (1.03–1.06)***	0.096
length of hospital days	1.03 (0.97–1.09)*	1.06 (1.01–1.12)*	0.028
Pain history	1.00 (0.97–1.03)[a]	1.00 (0.98–1.03)[a]	0.001

Reference group in regression analysis: no-NP group, non-neuropathic pain group; UC, uncertainty regarding neuropathy; NP, neuropathic pain group; Sex (coding: 0 = male 1 = female); Education level: (coding: none = 0, Primary or secondary education = 1, High school certificate = 2, College or university degree = reference category); PHQ, Patient Health Questionnaire; MPSS, Mainz Pain Staging System; NRS, Numeric Rating Scale; PDI, Pain Disability Index.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.
[a]Not significant.

(e.g., Postherpetic neuralgia, Polyneuropathy) from some other types of chronic pain with distinct neuropathic characteristics (e.g., fibromyalgia).

A further possible limitation regarding our interpretation also has to be taken into account. A high percentage of fibromyalgia patients (60%, PDQ $score_{fibromyalgia} = 17.70$) in the musculoskeletal pain category in our sample may be responsible for the high PDQ score in the musculoskeletal pain category. Maletic and Raison (2009) suggested that neuropathic pain and fibromyalgia have similar phenomenological manifestations and may be variations of the same condition. Koroschetz et al. (2011) also reported that fibromyalgia and diabetic neuropathy patients experience very similar sensory phenomena. Moreover, prior studies have emphasized that surgery can be an important cause of neuropathic pain (Kehlet et al., 2006; Shaladi et al., 2009) and it has been assumed that the

Table 4 Neuropathic pain score: hierarchical regression analyses with depression and various pain-related variables as predictors.

Regression model						
Criterion	Predictors	R^2	B	SEB	β	P
	Model 1	0.131				
	Pain chronicity (MPSS)		1.25	0.31	0.22	0.000***
	Pain intensity (NRS)		0.83	0.22	0.20	0.000***
	Model 2					
	Pain chronicity (MPSS)	0.158	1.12	0.31	0.20	0.000***
	Pain intensity (NRS)		0.56	0.24	0.13	0.02*
	Disability (PDI)		0.08	0.02	0.17	0.005**
	Length of hospital stay		0.05	0.08	0.03	0.49[a]
	Model 3	0.201				
	Pain chronicity (MPSS)		0.90	0.31	0.16	0.004**
	Pain intensity (NRS)		0.48	0.23	0.12	0.04*
	Disability (PDI)		0.04	0.03	0.09	0.13[a]
	Length of hospital stay		–0.01	0.08	–0.007	0.89[a]
	Depression (PHQ)		0.29	0.07	0.23	0.000***

Variables in the equation: Depression on Patient Health Questionnaire (PHQ), pain chronicity on Mainz Pain Staging System (MPSS), pain intensity on 11-point Numeric Rating Scale (NRS) and disability on Pain Disability Index (PDI) were measured. Higher ratings on all of these variables correspond to a higher level of severity.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.
[a]Not significant.

frequency of neuropathic pain following surgical procedures amounts to approximately 20% of admitted patients (Shaladi et al., 2009). These findings seem to suggest similarities in symptomatology of 'neuropathic pain', 'musculoskeletal pain' and 'post traumatic or surgical pain', which would be reflected in parallel responses on symptom-based questionnaires. However, further research is necessary in this field.

In sum, our findings lend support to the notion that any type of chronic pain may have neuropathic characteristics. However, it seems that this screening tool could not separate typical neuropathic entities from some other pain syndromes with distinct neuropathic features.

In contrast to Daniel et al. (2008), who found that patients with neuropathic pain and patients with non-neuropathic low back pain were similar in their reports of pain intensity, dysfunctional cognition and physical function, the present study found significant differences between the NP, UC and no-NP groups in various pain-related variables.

Our findings demonstrated a higher level of pain intensity, pain-related disability and depressive symptoms in the NP group, consistent with some earlier studies (e.g., Freynhagen et al., 2006a; Attal et al., 2011; Beith et al., 2011). To explain these findings, Hansson et al. (2001) suggested that patients with neuropathic pain, in addition to the pain itself, experience various types of aversive or unfamiliar feelings like paresthesias and burning sensations. These different qualities of sensory experiences integrate into a global feeling of intense discomfort and painfulness. It can be assumed that these particular features of neuropathic pain have a negative impact on the general quality of life.

Additionally, although patients in the NP group did not report a significantly longer history of pain, a higher level of pain chronicity based on MPSS was found in this group. This finding replicates previous research by Gerbershagen et al. (2010). Consequently, the greater use of health care facilities and drugs among patients in the NP group (MPSS, axes 3, 4; Mehra et al., 2012), in line with a higher severity of pain and potentially inappropriate treatment of neuropathic pain may be responsible for a high level of chronicity in these patients, including long hospital stays and high levels of functional and affective disability.

The method of regression chosen to analyse the data allowed deeper insight into the structure of the data and validates the integrity of the reported results.

In line with the results of ANOVA and *post hoc* tests that characterized the neuropathic dimension of pain by high levels of pain intensity, pain chronicity and depression, regression analyses also reflected the same results (Margot-Duclot et al., 2009; Gerbershagen et al., 2010; Boogaard et al., 2011). As expected, the inclusion of a psychological variable (depression) in a multiple regression analysis significantly increased the total amount of variance explained by pain variables. Maletic and Raison (2009) proposed that major depression disorder (MDD) and neuropathic pain are associated, as they both have a common feature, i.e., neuroplastic change. They further argued that the recurrent and progressive nature of MDD is often ascribed to 'kindling', which reflects neuroplastic changes like central sensitization.

Also, the separate analyses of disability and length of hospital stay confirmed their power to predict neuropathic characteristics. However, these variables lost their predictive power in a common model, indicating that these variables shared some information regarding the prediction of neuropathic characteristics with other variables. Still, it does not seem justified to regard the multiple regression analysis as the final word regarding the associations of different variables to the criterion, and thus further research is necessary.

Altogether, on the basis of our results, chronic pain with neuropathic characteristics is characterized by a high level of pain intensity and chronicity as well negative affectivity and functional disability. This should have implications for the symptom-based therapeutic management of pain with distinct neuropathic features.

5. Limitations

Some limitations regarding our general conclusion might relate to the applied instrument. Although the PDQ was validated on chronic pain patients with typical neuropathic or nociceptive entities and it has been applied in several previous studies on different types of chronic pain (e.g., Gerbershagen et al., 2010; Koroschetz et al., 2011), this questionnaire specifically targets low back pain. Nevertheless, our data assessing different pain syndromes are consistent with recent studies using other screening tools (e.g., Attal et al., 2011). However, the questionnaire so far has not been validated regarding headache. Furthermore, comparing patients based only on the self-report questionnaire and not on clinical examination might endanger our findings. Despite this limitation, our findings are consistent with previous research on typical neuropathic pain (e.g., Gustorff et al., 2008; Huge et al., 2011).

Another limitation of the study is that we included a sample of patients from a single clinic for our study and this selection bias may affect the results of the study.

6. Conclusion

By using the pain DETECT assessment tool, the present study finds some evidence to question the categorical separation of so-called nociceptive and neuropathic pain on the basis of their pathological mechanisms. Although our findings are based on a symptom-oriented screening tool and not on clinical diagnostic data, it instigates further research examining therapeutic strategies depending on the syndrome quality, not on the supposed cause of pain. It can further be discussed whether treatment should especially target important symptoms determining the syndrome, like negative affectivity and disability, as well as the severity of pain. This would mean that pain characterized by a high neuropathic score should be aimed primary at reduction in pain severity, but also at improvements in the daily functions of the patient and an induction of positive affect by a multidisciplinary treatment. However, these conclusions can only be speculative at the moment.

Author contributions

M.S. contributed to study design, statistical analysis, data interpretation and paper writing.

A.B. contributed to study design, patient selection, investigation of subjects and patients and paper commenting.

B.K-H. contributed to study design, data interpretation, paper commenting and revision of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Subclassification of main pain syndrome of sample according to the Multiaxial Pain Classification System- Somatic Dimension (MASK-S, Hildebrandt et al., 1992; Klinger et al., 2000; Frettlöh et al., 2009).

Appendix S1. Sub-classification of main pain syndrome of sample according to the Multiaxial Pain Classification System- Somatic Dimension (MASK-S, Hildebrandt et al., 1992; Klinger et al., 2000; Frettlöh et al., 2009**)**

1. Headache

- Migraine
- Tension-type headache
- Cluster headache syndrome
- Drug-induced headache
- Headache attributed to disorders of facial or cranial structures
- Headache attributed to cranial or cervical vascular disorders
- Other specified headache syndromes

2. Non-neuropathic facial pain

- Atypical facial pain
- Facial pain attributed to other disorders (e.g., disorder of sinuses, teeth, etc)

3. Ischemic or vascular pain

- Pain attributed to arterial Insufficiency in the limbs
- Pain attributed to vasodilating functional disease of the limbs
- Other vascular disorders of the upper and lower limbs

4. spinal column pain

- Cervical spinal or radicular pain syndromes
- Thoracic spinal or radicular pain syndromes
- Lumbar spinal or radicular pain syndromes
- Sacral spinal or radicular pain syndromes
- Coccygeal pain syndromes
- Diffuse spinal pain

5. Musculoskeletal pain

- Arthropathies (e.g., inflammatory polyarthropathies, arthrosis and other joint disorders)
- Myalgia
- Disorders of muscles, synovium, tendon and other soft tissue disorders
- Fibromyalgia
- Chondropathies
- Osteopathies
- Other disorders of the musculoskeletal system and connective tissue

6. Neuropathic pain – Neuralgies (e.g., trigeminal neuralgia, postherpetic neuralgia, other specified neuralgies) – Polyneuropathies (diabetic polyneuropathy, inflammatory polyneuropathy, Polyneuropathy due to toxic agents, other specified polyneuropathies) – Mononeuropathies (carpal tunnel syndrome, diabetic mononeuropathy, other specified mononeuropathies) – Complex regional pain syndrome (CRPS) – Phantom and stump pain – Central nervous system disease (e.g., multiple sclerosis, thalamus infarction, other specified central nervous system disease)
7. Visceral pain – Chest pain – Abdominal pain – Chronic pelvic pain syndromes – Diseases of the bladder, uterus, ovaries, testis, and prostate – Pain perceived in the rectum, perineum, and external genitalia
8. Post traumatic or surgical pain
9. Pain disorders related to psychological factors

2. Original article 2

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ORIGINAL RESEARCH

Short running header [Neuropathic sensory symptoms]

Neuropathic sensory symptoms: Association with pain and psychological factors

Maryam Shaygan[1]

Andreas Böger[2]

Birgit Kröner-Herwig[1]

[1]Georg-Elias-Müller-Institute of Psychology, University of Göttingen, Germany; [2]Pain Management Clinic at the Red Cross Hospital, Kassel, Germany

Correspondence: Maryam Shaygan

Georg-Elias-Müller-Institute of Psychology, University of Göttingen, Göttingen, Germany

Tel +49 551 39 33717

Fax +49 551 39 3544

Email maryam.shaygan@psych.uni-goettingen.de

Abstract

Background: A large number of population-based studies of chronic pain considered neuropathic sensory symptoms to be associated with a high level of pain intensity and negative affectivity. The present study examines the question of whether this association previously found in non-selected samples of chronic pain patients can also be found in chronic pain patients with underlying pathology of neuropathic sensory symptoms.

Methods: Neuropathic sensory symptoms in 306 patients with chronic pain diagnosed as typical neuropathic pain, radiculopathy, fibromyalgia or nociceptive back pain were assessed using the Pain DETECT Questionnaire. Two separate cluster analyses were performed to identify subgroups of patients with different *levels* of self-reported neuropathic sensory symptoms and furthermore to identify subgroups of patients with distinct *patterns* of neuropathic sensory symptoms (adjusted for individual response bias regarding specific symptoms).

Results: ANOVA results in typical neuropathic pain, radiculopathy and fibromyalgia showed no significant differences between the 3 levels of neuropathic sensory symptoms regarding pain intensity, pain chronicity, pain catastrophizing, pain acceptance and depressive symptoms. However, in nociceptive back pain patients, significant differences were found for all variables except pain chronicity. When controlling for the response bias of patients in ratings of symptoms, none of the patterns of neuropathic sensory symptoms were associated with pain and psychological factors.

Conclusions: Neuropathic sensory symptoms are not closely associated with higher levels of pain intensity and cognitive-emotional evaluations in chronic pain patients with underlying pathology of neuropathic sensory symptoms. The findings are discussed in term of differential response bias in patients with vs. without verified neuropathic sensory symptoms by clinical examination, medical tests or underlying pathology of disease. Our results lend support to the importance of using adjusted scores thereby eliminating the response bias when investigating self-reported neuropathic symptoms by patients.

Keywords: Self-reported neuropathic sensory symptoms, pain-related features, psychological factors, response bias

Introduction

Neuropathic pain is defined as 'pain caused by a lesion or disease affecting the somatosensory system'[1] manifested by sensory signs and symptoms such as hyperalgesia, burning and prickling sensations. Boureau et al[2], stated that verbal descriptors of experienced sensory symptoms reliably distinguish neuropathic pain from other types of pain. Several studies, however, found similar self-reported sensory symptoms in otherwise diagnosed pain such as fibromyalgia[3].

A large number of population-based studies of chronic pain reported a high level of pain intensity as well anxiety and depressive symptoms in respondents who scored high on neuropathic sensory symptoms assessed by self-report[4-7]. These studies concluded that the neuropathic character of pain is denoted by a high level of intensity as well as negative affectivity. However, some clinical studies did not support these findings when comparing medically diagnosed neuropathic and non-neuropathic pain[8-10]. Consequently, two questions were raised: First, do neuropathic sensory symptoms assessed by screening tools reliably distinguish neuropathic pain from non-neuropathic types of pain? The present study assessed self-reported neuropathic sensory symptoms in patients with "typical neuropathic pain" (TNP), radiculopathy (RAD), fibromyalgia (FM) and nociceptive back pain (nBP). We expected that these symptoms would distinguish TNP not from RAD and FM but from nBP. RAD is caused by compression or lesion of a dorsal root or its ganglion and considered as a syndrome with both nociceptive and neuropathic components of pain (mixed pain syndrome[11-13]). Although in the majority of FM patients, no nerve lesions can be demonstrated, the presence of neuropathic sensory symptoms (eg, allodynia, hyperalgesia) in these patients can be explained in terms of pathogenic mechanisms such as impaired small fiber function and a dysfunction of endogenous systems modulating afferent activity[14-16]. In a more recent study, Uceyler et al[14], suggested a neuropathic nature of pain in FM syndrome. However, the classification of FM as neuropathic pain is a subject of controversy and debate among researchers[1,17].

A further question was whether the association between a high score of self-reported neuropathic sensory symptoms with a high level of pain intensity and negative affectivity previously found in non-selected samples of chronic pain patients can also be found in chronic pain patients with underlying pathology of neuropathic sensory symptoms such as TNP, RAD and also FM.

Symptom reports are well known to be influenced by a general negative response tendency, revealed by a dominance of responses at the negative pole of a rating scale which is based on a person's disposition to disclose and report negative aspects of oneself, including both emotional and physical symptoms. In this context, a general negative self-appraisal seems to play an important role. Such biases may inflate correlations among symptoms[18]. However, later studies suggested a considerable variation in how strongly different symptoms are influenced by this response bias. For example, response bias has been suggested to more strongly relate with the report of symptoms without any identified pathology than with symptoms that can be verified by clinical examination or medical tests[19-21].

In conclusion, it is argued that not only does the character of pain determine the symptom report, but also an individual tendency to select specific response categories, in this case preferring the endpoints of a response scale independent of the item content. This could have determined the positive correlation between self-reported neuropathic sensory symptoms with pain intensity and negative affectivity found in large population-based studies. This association should be examined in patients with an underlying pathology of neuropathic sensory symptoms.

In the present study, we wanted to analyse the relation between the level of neuropathic sensory symptoms with other pain related parameters like intensity and chronicity as well psychological factors (depression, catastrophizing, pain acceptance) in four mentioned diagnostic groups, ie, TNP, RAD, FM and nBP. Cluster analysis was used to classify patients of these diagnostic groups based on self-reported intensity of neuropathic sensory symptoms (clustering 1). We hypothesised that only nBP patients who scored high on neuropathic sensory symptoms would report a high level of pain-related features and also psychological factors driven by the previously explained response bias. In all other diagnostic groups, significant associations were not expected.

In order to control for the response bias, a second clustering approach (clustering 2) based on adjusted scores of neuropathic sensory symptoms using individual means was performed. This enabled us to subgroup the patients of the different diagnostic groups based on their distinct patterns of neuropathic sensory symptoms after having eliminated the individual response bias regarding the symptoms. Studies concerning the association of different patterns of neuropathic sensory symptoms with

different parameters of pain and psychological factors are rare. A recent symptom-based study on chronic low back pain demonstrated no association between distinct patterns of neuropathic sensory symptoms with depression and anxiety[22]. We wanted to find out whether the different diagnostic groups in our study are characterised by specific patterns of neuropathic sensory symptoms (after elimination of the general response bias). We expected that these symptom patterns should be represented differently in the diagnostic groups. However, since the general response bias was eliminated, none of the symptom patterns should be associated with higher levels of pain related parameters or psychological factors.

Methods

This cross-sectional study was conducted in a multidisciplinary tertiary care centre, comprising experts in pain medicine, psychology and neighbouring professions. In-patients presenting with chronic pain, diagnosed by anesthesiologists/ neurologists, were asked to complete various questionnaires, after having signed informed consent regarding their participation in the study. Ethical approval was obtained from the Ethics Committee of the Georg-Elias-Mueller Institute of Psychology.

Sample selection

From April 2012 to February 2013, 344 patients suffering from a chronic pain condition were referred to the pain treatment centre. Chronic pain conditions included TNP, RAD, FM or nBP assessed by the pain specialists who determined the pain diagnoses based on history, clinical bedside examinations and whatever diagnostic methods were considered appropriate (eg, electrophysiological evaluation, imaging techniques, etc.). A total of 78 patients with one of the following neurological syndromes were included into the study: postherpetic neuralgia (PHN, which was confirmed if patients had persistent pain in an area previously affected by acute herpes zoster rash), complex regional pain syndrome type II (CRPS II, according to clinical criteria)[23], central neuropathic pain (defined as pain caused by a demonstrable lesion in the central nervous system in an area anatomically attributable to the lesion), polyneuropathy (PNP, according to clinical criteria)[24] and trigeminal neuralgia (according to International Headache Classification criteria 2003). Patients with chronic low back pain were divided in two groups: with (RAD) or

without (nBP) typical dermatomal pain (radiating beyond the knee, pain evoked by stretching of the femoral nerve) as well as clinical signs of nerve root involvement, including sensory or motor deficits in the leg and a decrease or loss of tendon reflexes. Moreover, available results of spinal imaging and further investigations such as electromyography were also taken into account. Fibromyalgia was diagnosed on the basis of the American College of Rheumatology criteria[26] (ACR). Of the 344 patients, 306 were considered for inclusion in the study. Criteria for inclusion were: age above 18 years and having a chronic pain condition according to ICD-10 criteria (F45.41 or R52.1-2, International Statistical Classification of Diseases and Related Health Problems, 2012)[27]. The following exclusion criteria were applied: a pain history less than 6 months, presence of a malignant disease, severe medical or psychiatric illness interfering with the pain assessment, another painful disorder or neurological disease that might have interfered with the pain assessment, and inability to comprehend the German language.

Data assessment

In addition to standard demographic inquiry, the following questionnaires were applied:

Neuropathic sensory symptoms were assessed by the Pain DETECT Questionnaire (PDQ[4]). The PDQ is a self-report questionnaire including nine items asking about the intensity and quality of pain. The questions address the presence of seven sensory symptoms rated on a 0–5 rating scale (never to very strong): 1. burning pain, 2. paresthesias, 3. mechanical allodynia, 4. spontaneous pain attacks, 5. thermal hyperalgesia, 6. numbness, 7. pressure hyperalgesia. The PDQ also comprises two questions regarding the course of pain and radiation pain. The scale was validated in a sample of patients with either neuropathic pain, including post-herpetic neuralgia, polyneuropathy, nerve trauma and low back pain (LBP where the source of pain is in lumbar vertebrae, sacrum and/or coccyx) or nociceptive pain including visceral pain, osteoarthritis, inflammatory arthropathies and non-neuropathic LBP. The instrument indicated sensitivity as well specificity of 84% when identifying patients with medically diagnosed neuropathic pain. The questionnaire demonstrated adequate internal consistency (Cronbach's alpha= 0.83[4]).

The average pain intensity was assessed by an 11-point numeric rating scale[28] (NRS; 0 (no pain) to 10 (worst imaginable pain)).

Pain chronicity was assessed by the Mainz Pain Staging System[29] (MPSS). The MPSS defines three stages of pain chronicity based on ten questions (in terms of 4 axes). Patients were requested to describe the occurrence of pain, pain duration and changes in pain intensity *(axis 1, temporal dimension)*; pain distribution *(axis 2, spatial dimension)*; drug use and number of previous drug withdrawal *(axis 3, drug taking behaviour)*; change of personal physician, pain related hospitalizations, pain related operations and pain related rehabilitation *(axis 4, utilization of the health care system).* Patients were assisted by a physician to complete the questions. The sum of the 4 axes varies in the range of 4–12. The instrument was validated in a study by Pfingsten et al with 542 patients with different diagnoses[30].

Depressive symptoms were assessed by the German short version[31] of the Center for Epidemiological Studies Depression Scale[32] (CES-D). It is a 15-item self-report scale from 0 (rarely) to 3 (most of the time) designed to measure depressive symptoms during the past seven days. Validity and reliability (Cronbach's alpha= 0.91) were good[31].

Catastrophizing cognitions concerning pain were measured with the German version of the Pain Catastrophizing Scale[33] (PCS, subscale "helplessness"). The subscale "helplessness" describes the feeling of inability to cope with the pain. It consists of 6 items answered on a 5-point scale ranging from 0 (not at all) to 4 (all the time). This subscale showed good internal consistency (Cronbach alpha= 0.89) as well convergent validity[33].

Pain acceptance was measured by 10 items from the German version of the Chronic Pain Acceptance Questionnaire (items 1, 2, 6, 9, 11, 12, 13, 14, 15, 18; CPAQ-D)[34]. These items showed the highest correlation with the total score of the questionnaire[34]. Items were answered on a 7-point scale ranging from 0 (never) to 6 (always), with an internal consistency of $\alpha = 0.73$.

Statistical Analysis

One-way analyses of variance (ANOVAs), post-hoc Tukey's tests and chi-square tests were conducted to explore differences between the four diagnostic groups regarding demographic and clinical variables.

To distinguish subgroups of patients with different levels of self-reported neuropathic sensory symptoms across the 4 diagnostic groups (clustering 1), a hierarchical cluster analysis including the seven sensory symptoms taken from the Pain DETECT Questionnaire was performed. The commonly recommended hierarchical WARD-approach with a squared Euclidian distance measure was used[35]. Agglomeration coefficients were investigated to establish the optimal cluster solution. The point at which the percentage of change was largest between steps determines the most appropriate cluster solution[36]. A cut-off point for essential clusters was set at about 10% of evaluated cases. Multinominal regression analysis was conducted to examine associations between the levels of self-reported neuropathic sensory symptoms (clusters as predictors) with diagnostic groups (criterion). Furthermore, ANOVAs were performed to investigate differences between these clusters regarding pain related and psychological variables (separately for each diagnostic group as well as for total sample of patients as a comparison with non-selected samples of chronic pain).

For the purpose of identifying relevant subgroups of patients with different patterns of neuropathic sensory symptoms, a further hierarchical cluster analysis (clustering 2) was conducted on the basis of adjusted scores using the individual mean of the seven sensory symptoms, i.e. the rating of each item by the patient was subtracted from the individual mean of all seven items rated by the same patient, thus eliminating the response bias of patients. This cluster analysis was followed by multiple discriminant analysis including the seven sensory symptoms as independent variables (criterion: clusters), to ensure the stability of the cluster solution[35]. ANOVAs and chi-square tests were performed to explore differences between the identified clusters regarding various pain and psychological variables as well regarding their frequency in each diagnostic group. All analyses were conducted by SPSS software, version 19. The significance level was set at $p<0.05$.

Results

Study Sample

Of the 344 patients, a total of 306 with TNP, RAD, FM or nBP fulfilled the inclusion criteria. Thirty eight patients had to be excluded from the study: 11 patients because they had a pain history of less than 6 months, 16 patients in whom tumour or other medical or psychiatric illness interfering with the pain assessment was diagnosed (e.g., Alzheimer's disease, Schizophrenia), 6 patients because of their inability to comprehend the German language and 5 patients who refused to participate. The mean age of the patients was 59.2 years (SD=13.2). ANOVA and post-hoc tests showed significant differences between TNP and FM patients regarding age (p=0.02), the latter being younger on average. The majority of patients were female (65%). Separate chi-square tests demonstrated a lower percentage of women in TNP compared to nBP (p=0.007) and FM (p=0.000, see Table 1). Also, results of the ANOVA and post-hoc tests revealed significant differences between FM vs. nBP and FM vs. TNP regarding pain chronicity (p=0.000) and between FM vs. RAD and FM vs. TNP regarding depressive symptoms (p=0.006, see Table 1). The neuropathic character (assessed by the PDQ total score) of nBP was significantly lower than in all other diagnostic groups (p=0.02, see Table 1). No group differences were found regarding pain history (p=0.12), pain intensity (p=0.69), pain acceptance (p=0.07) or catastrophizing (p=0.09, see Table 1).

- Please insert Table 1 –

Cluster analysis 1: Subgroups of patients with different levels of self-reported neuropathic sensory symptoms

Based on the agglomeration coefficients for hierarchical cluster analysis, three distinct clusters emerged which were characterised by either a low (M_{Low}=1.38, SD=0.69), moderate ($M_{Moderate}$=2.51, SD=0.50) or high (M_{High}=3.36, SD=0.65) level of intensity of self-reported neuropathic sensory symptoms which differed significantly from one another (F (2,295)=267.72, p=0.000).

Multinominal logistic regression analysis

Multinominal logistic regression (criterion: diagnostic groups) with TNP as a reference group revealed that the levels of self-reported neuropathic sensory symptoms only contributed to distinguishing TNP from nBP and not from RAD and FM. The model explained about 19% of the total variance (Table 2).

- Please insert Table 2 –

Association of self-reported neuropathic sensory symptoms with pain and psychological variables in the four diagnostic groups

Results of the ANOVA showed no significant differences between the three levels of neuropathic sensory symptoms regarding pain intensity, pain chronicity, pain catastrophizing, pain acceptance and depressive symptoms (all *p*s > 0.05) in TNP, RAD and FM (see Table 3 for more detail).

However, in nBP patients, significant differences were found regarding all variables, except pain chronicity (see Table 3 for further details). Accordingly, post-hoc tests demonstrated significant differences between low vs. high level of neuropathic sensory symptoms for pain intensity and pain catastrophizing, between low vs. moderate and high level of neuropathic sensory symptoms for pain acceptance and between low and moderate vs. high level of neuropathic sensory symptoms for depressive symptoms.

ANOVAs comparing all pain patients in the three levels of neuropathic sensory symptoms demonstrated significant differences regarding all variables, except with regard to pain catastrophizing (for details see Table 3). Post-hoc tests also revealed significant differences between low and moderate vs. high level of neuropathic sensory symptoms for pain intensity, pain chronicity and depressive symptoms and between low vs. high level of neuropathic sensory symptoms for pain acceptance.

- Please insert Table 3 –

Cluster analysis 2: Subgroups of patients with distinct patterns of neuropathic sensory symptoms

The cluster analysis based on adjusted scores of the seven sensory symptoms led to a four-cluster solution with distinct patterns of symptoms (Figure 1). Each of the 4 symptom patterns was present in every diagnostic group differing only by relative frequency. Cluster 1 was characterised by a high intensity of prickling sensations (M_{adj}= 0.98), pain attacks (M_{adj}= 0.98) and numbness (M_{adj}= 0.62) compared to the other sensory symptoms. This pattern of symptoms occurred nearly two times more frequently in TNP (26%) than in FM (15%), in nBP (13.3%) and in RAD (12.9%; X^2=6.33, df=3, p=0.09, see Figure 1). Patients who had been classified into cluster 2 reported particularly high levels of pain attacks (M_{adj}= 1.56) and pressure hyperalgesia (M_{adj}= 0.97). All other symptoms were close to the mean, except burning pain which was less severe. In patients with nBP (44.9%), FM (38.3%) and RAD (28.6%), this symptom pattern was more frequent than in TNP patients (14.3%; X^2=23.87, df=3, p=0.000, see Figure 1). Cluster 3 was characterised by an overall "flat profile", i.e. no item deviated much from the individual mean (see Figure 1). This pattern of symptoms evenly distributed over all four diagnostic groups (X^2=6.06, df=3, p=0.10, see Figure 1). The dominant symptom of cluster 4 was a severe burning pain (M_{adj}= 2.05). Pain attacks (M_{adj}= 0.98) and thermal pain (M_{adj}= 0.67) were also above the individual mean. All other symptoms were below average. This symptom pattern prevailed in TNP (19.5%), in RAD (15.7%) and in FM (13.3%, see Figure 1).

A discriminant analysis with the seven neuropathic sensory symptoms as independent variables (criterion: the 4 patterns of neuropathic sensory symptoms) led to 3 significant discriminating functions (p=0.000 for each function) with Wilks' lambda of 0.16, 0.36 and 0.63 and eigenvalues of 1.24, 0.75 and 0.57. Eighty-eight percent of the patients were classified correctly. Burning pain (β=0.99), thermal hyperalgesia (β=0.91) and pain attacks (β=0.84) were the best predictors for the clusters (symptom patterns). But also, prickling sensations (β=0.56), pressure hyperalgesia (β=0.55), numbness (β=0.48) and allodynia (β=0.40) contributed significantly to the discrimination of the four clusters.

The results of the ANOVAs showed no significant differences regarding pain intensity (p=0.95), pain chronicity (p=0.11), pain catastrophizing (p=0.87), pain acceptance (p=0.46) and depressive symptoms (p=0.78) when comparing the four clusters based on adjusted scores.

- Please insert Figure 1 –

Discussion

The present study demonstrates that neuropathic sensory symptoms do not contribute to the degree of pain intensity, pain chronicity and negative affectivity in a clinical sample of patients with underlying pathology of neuropathic sensory symptoms, ie, TNP, RAD and FM. Our findings also highlight the fact that high ratings of self-reported neuropathic sensory symptoms are not necessarily associated with major neuropathic characteristics of pain but are also related to a negative response tendency in patients without any identifiable underlying pathology of neuropathic sensory symptoms, ie, nBP. These results demonstrate the importance of taking advantage of response bias-adjusted scores when investigating self-reported neuropathic symptoms by patients.

The assumption that neuropathic sensory symptoms would differentiate TNP from nBP was confirmed by the results of regression analysis (Table 2). Patients medically diagnosed with nBP also revealed the lowest neuropathic score assessed by the Pain DETECT Questionnaire differing significantly from all other diagnostic groups (TNP, RAD, FM) which are supposed to present pain with underlying pathology of neuropathic sensory symptoms (Table 1). Neuropathic sensory symptoms, however, did not distinguish TNP from FM. Although in the majority of FM patients no nerve lesion can be detected[37], numerous studies demonstrated similarities between neuropathic pain patients and FM patients with regard to the experience of sensory symptoms[3]. Vierck suggested that changes in the milieu of muscles and other deep somatic structures in FM might lead to a similar state of hyperactivity in nociceptive neurons as is observed after nerve damage[37]. Moreover, Staud, using functional MRI, provided strong support for neuroplastic CNS changes in FM[38]. However, it must be stressed that the classification of FM as a variant of neuropathic pain is a subject of controversy among researchers[1,17].

As hypothesised, the three levels of self-reported neuropathic sensory symptoms in chronic pain patients with underlying pathology of neuropathic sensory symptoms did not differ in pain intensity and

chronicity, depression, pain acceptance and catastrophizing. Thus, neuropathic sensory symptoms do not contribute per se to the character of pain-related features and cognitive-emotional processes. This interpretation finds support in some clinical studies[8-10] as well as our own findings (Table 1) indicating no significant differences between medically diagnosed neuropathic and non-neuropathic pain regarding pain intensity, pain chronicity and psychological factors. Other possible explanations for this result may be that negative emotions and maladaptive appraisals do not play an important role in the report of *sensory* descriptors of pain such as neuropathic sensory symptoms. In accordance with this interpretation, Sullivan found that pain catastrophizing in neuropathic pain patients was not associated with the sensory subscale of the McGill Pain Questionnaire but only with the affective aspects[39]. They suggested that the mechanism of pain catastrophizing is specifically related to the affective dimension of pain. Functional imaging studies with FM also demonstrated that neither a high level of pain catastrophizing[40] nor the presence of a clinically diagnosed major depression[41] were associated with the sensory aspects of pain processing.

In contrast to this finding, in patients with nBP an association between high levels of neuropathic sensory symptoms with high levels of pain intensity, depression, pain catastrophizing and with less acceptance of pain was observed suggesting a general negative response tendency among patients with nBP who scored high on neuropathic sensory symptoms without any identifiable underlying neuropathology. Ambiguity about the origin and significance of neuropathic sensory symptoms among patients with nBP may explain the biased response tendency regarding these symptoms particularly among those nBP patients with negative affect and self-appraisals. According to Social Comparison Theory[42] and Temporal Comparison Theory[43,44], individuals need comparison standards to evaluate their opinions, skills, social status, as well as their physical state. Petersen et al, proposed the comparison standards as a predictor of symptom presentations and contended that in evaluating a bodily state, individuals have to use reference standards, such as the personal experience of symptoms in the past, or beliefs about the perception of sensations by relevant others, such as patients or healthy individuals[45]. It can be, therefore argued that those nBP patients with negative affect and self-appraisals were most likely influenced by a biased response tendency regarding neuropathic sensory symptoms. The finding that the

three levels of neuropathic sensory symptoms in nBP did not differentiate pain chronicity which was not obtained by self-report may provide additional evidence for the argument above.

Altogether, our findings suggest that a high level of neuropathic sensory symptoms in patients with underlying pathology of neuropathic sensory symptoms does not automatically result in a high intensity of pain related characteristics and psychological dysfunctional features but that the group of patients (nBP) with a general negative response tendency determine such an association which was partly found in other studies, especially when mixed patients were analysed. This spurious positive association can also be seen in our total sample of patients as the consequence of the discussed effect. Further studies therefore should control for this effect of differential response bias in their samples.

With the second clustering approach, response bias-adjusted scores were created. This enabled us to characterise different subgroups of patients with common patterns of neuropathic sensory symptoms. Consistent with earlier studies[9], none of the symptom patterns was exclusively seen in the groups with diagnosed neuropathic or nociceptive pain. Nevertheless, the distributions of symptom patterns differed between different diagnostic groups. For example, symptom pattern 4 occurred only in 2% of the patients with nBP whereas nearly half of the nBP patients demonstrated the symptom pattern characterised by a high level of pain attacks and pressure hyperalgesia (cluster 2). In any case, we found that neither the symptom patterns frequently occurring in neuropathic pain nor symptom patterns frequently occurring in nociceptive back pain were associated with a higher level of pain-related and psychological factors. This finding gives reason to further question a genuine association of neuropathic sensory symptoms with high levels of pain and psychological factors in patients with underlying pathology of neuropathic sensory symptoms. At the same time, it highlights the adequacy of our strategy for analysis.

Intriguingly, about 40% of the chronic pain patients showed a “flat profile” of neuropathic sensory symptoms. The “flat profile” indicates that the patient responded in a similar way to all items of the Pain DETECT Questionnaire. This pattern was demonstrated by a similar percentage of subgroups of patients from the four diagnostic groups, a finding that has been reported before[46]. Possibly, a psychological phenomenon, ie, the tendency to adhere to a similar rating style regardless of item content, is responsible for this observation. For a more accurate interpretation, we compared patients demonstrating a “flat

profile" with different levels of neuropathic sensory symptoms (in clustering 1). Interestingly, among nBP patients who scored "high" (in clustering 1) as well as "flat" on neuropathic sensory symptoms, we found a higher level of depressive symptoms (p=0.004), pain catastrophizing (p=0.04) as well as less acceptance of pain (p=0.04). Consistent with this finding, Cohen et al proposed that negative emotions may not only result in a negative response bias as discussed before but also lead to an undifferentiated interpretation of symptoms[47]. Such differences were not found regarding TNP, RAD and FM with a "flat "and also "high" pattern of neuropathic sensory symptoms. This result can be interpreted that a "flat & high" pattern of neuropathic sensory symptoms is not necessarily based on a response bias particularly in the case of symptoms supported by underlying pathology.

Before considering the implications of our findings, several limitations of this study have to be acknowledged. The sample size was relatively small, and thus the reliability of the findings has to be questioned until other studies can replicate them. An additional limitation relates to the applied instrument, since the PDQ has not been validated regarding FM. Furthermore, our sample of patients was recruited from a single clinic and this selection might have affected the results.

In summary, our data seems to highlight the conclusion that neuropathic sensory symptoms do not contribute to the degree of pain and psychological dysfunctional features in a clinical sample of patients with underlying pathology of neuropathic sensory symptoms. Moreover, the present study corroborates previous findings that response bias may more strongly relate with the report of symptoms without any identified pathology as well as symptoms which were not experienced by patients in the past than with symptoms that can be verified by clinical examination or medical tests. These findings should have implications for symptom-based studies of neuropathic pain to include a relevant sample of patients when investigating the association of these symptoms with other indicators of health status. The results also highlight the importance of using adjusted scores to eliminate the response bias when investigating self-reported symptoms by patients.

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Author contributions

M. Shaygan contributed to study design, statistical analysis, data interpretation and paper writing.

A. Böger contributed to patient selection, examination of patients and paper commenting.

B. Kröner-Herwig contributed to study design, data interpretation, paper commenting and revision of the manuscript.

Disclosure

The author reports no conflicts of interest in this work.

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Table 1. Demographic and clinical characteristics of patients (Results of one-way analysis of variance (ANOVA), post-hoc Tukey's tests and chi-square test)

	TNP n = 78	RAD n = 68	FM n = 61	nBP n = 99	F(df) / X^2 (df)	Tukey test (p< 0.05)
Age (M ± SD)	61.05±12.8	59.5±13.6	54.78±10.1	60.3±14.3	F (3/ 302) = 3.08*	FM < TNP
Sex, n (%)						
Female	47.4%	64.8%	82.5%	67.7%	X^2 (3) = 18.40***	–
Pain history (years)	7.6±5.1	7.3±5.6	9.5±6.5	8.9±8	F (3/ 305) = 1.75†	–
NRS (M ± SD)	6.63±1.9	6.83±1.7	6.91±1.6	6.63±2.0	F (3/ 300) = .47†	–
MPSS (M ± SD)	8.72±1.1	8.92±1.3	9.28±1.1	8.45±1.1	F (3/ 288) = 6.11***	nBP, TNP < FM
PDQ (M ± SD)	19.01±7.2	20.32±6.5	19.50±6.9	13.27±6.6	F (3/ 299) = 19.42***	nBP < RAD, TNP, FM
PCS-H (M ± SD)	12.06±5.2	10.93±5.7	13.63±4.9	12.33±5.2	F (3/ 231) = 1.84†	–
CPAQ (M ± SD)	32.93±10.1	32.06±9.9	27.41±10.8	29.64±9.6	F (3/ 227) = 2.46†	–
ADS-K (M ± SD)	15.63±8.9	14.52±9.6	21.93±10.1	17.34±8.8	F (3/ 230) = 4.64**	RAD, TNP < FM

Note. TNP = typical neuropathic pain; RAD = radiculopathy; FM = fibromyalgia; nBP = nociceptive back pain; NRS, Numeric Rating Scale; MPSS, Mainz Pain Staging System; PDQ, Pain DETECT Questionnaire; PCS-H, Pain Catastrophizing Scale-Helplessness; CPAQ, Chronic Pain Acceptance Questionnaire; ADS-K, Allgemeine Depressionsskala-Kurz Version ******* p< 0.001; ****** p< 0.01; ***** p<0.05; † not significant

Table 2. Multinominal logistic regression analysis; Odds Ratio, Confidence Intervals (95%), Significance and Nagelkerke

Level of self-reported neuropathic sensory symptoms	Diagnostic group (Ref = typical neuropathic pain)			Nagelkerke
	Radiculopathy (RAD)	Fibromyalgia (FM)	Nociceptive back pain (nBP)	
Moderate level (M=2.51)[a]	1.06 (0.37-3.05) †	0.90 (0.30-2.70) †	0.24 (0.10-0.55)**	0.19***
High level (M=3.36)[a]	0.86 (0.28-2.64) †	1.18 (0.38-3.68) †	0.05 (0.01-0.16)***	
Ref: Low level (M=1.38)[a]				

Note.; [a]Mean score of the self-reported neuropathic sensory symptoms (sum of the 7 sensory symptoms/ 7); RAD = radiculopathy; FM = fibromyalgia; nBP = nociceptive back pain ******* p< 0.001; ****** p< 0.01; † not significant

Table 3. Means and SDs of various pain and psychological variables in patients with different levels of self-reported neuropathic sensory symptoms across the four diagnostic groups (clustering 1)

		"Cluster 1" Low level of neuropathic sensory symptoms (M=1.38)[a]	"Cluster 2" Moderate level of neuropathic sensory symptoms (M=2.51)[a]	"Cluster 3" High level of neuropathic sensory symptoms (M=3.36)[a]	F (df)	Post-hoc "LSD"
Typical neuropathic pain (TNP)	NRS (M±SD)	5.87±2.85	6.41±1.75	6.96±1.92	1.15 (2,70)†	–
	MPSS (M±SD)	8.25±1.48	8.73±1.05	8.77±1.18	0.68 (2,70)†	–
	PCS-H (M±SD)	11.50±2.00	12.86±5.70	10.46±5.70	.88 (2,40)†	–
	CPAQ (M±SD)	33.80±10.29	33.95±10.21	32.64±11.18	0.07 (2,37)†	–
	ADS-K (M±SD)	15.00±1.41	16.72±9.72	15.21±10.41	0.16 (2,40)†	–
Radiculopathy (RAD)	NRS (M±SD)	6.62±1.59	6.68±1.77	7.20±1.47	0.69 (2,63)†	–
	MPSS (M±SD)	8.42±0.97	8.89±1.44	9.26±1.32	1.03 (2,61)†	–
	PCS-H (M±SD)	9.33±3.82	10.80±5.71	12.23±6.21	0.66 (2,55)†	–
	CPAQ (M±SD)	37.66±12.45	33.17±9.30	27.58±10.11	2.93 (2,55)†	–
	ADS-K (M±SD)	14.20±4.65	12.82±9.33	18.94±10.59	2.39 (2,54)†	–
Fibromyalgia (FM)	NRS (M±SD)	6.28±1.60	6.53±1.66	7.50±1.44	3.03 (2,55)†	–
	MPSS (M±SD)	9.28±0.75	8.92±1.23	9.70±1.08	3.04 (2,55) †	–
	PCS-H (M±SD)	10.80±2.16	13.40±5.47	16.37±4.71	2.11 (2,25)†	–
	CPAQ (M±SD)	31.40±11.80	27.60±10.97	26.14±11.52	0.33 (2,24)†	–
	ADS-K (M±SD)	17.60±10.26	20.53±9.54	26.12±10.93	1.28 (2,25)†	–
Nociceptive back pain (nBP)	NRS (M±SD)	6.06±1.82	6.89±2.12	8.00±2.23	3.76 (2,95)*	1 < 3
	MPSS (M±SD)	8.33±1.16	8.42±1.05	9.14±1.06	1.60 (2,86)†	–
	PCS-H (M±SD)	11.04±5.99	12.93±4.28	16.00±4.20	3.50 (2,95)*	1 < 3
	CPAQ (M±SD)	32.75±11.47	27.91±6.85	23.14±7.58	5.00 (2,95)**	(2,3) < 1
	ADS-K (M±SD)	15.29±8.53	17.61±7.79	25.85±10.63	4.97 (2,95)**	(1,2) < 3
Total	NRS (M±SD)	6.19±1.93	6.65±1.86	7.25±1.68	6.09 (2,293)**	(1,2) < 3
	MPSS (M±SD)	8.44±1.15	8.72±1.21	9.22±1.22	7.76 (2,281)***	(1,2) < 3
	PCS-H (M±SD)	10.96±5.18	12.35±5.19	13.02±5.93	2.22 (2,224)†	–
	CPAQ (M±SD)	33.26±10.91	30.50±9.15	28.06±10.60	3.57 (2,220)*	3 < 1
	ADS-K (M±SD)	15.38±7.77	16.41±9.11	20.17±11.27	3.82 (2,223)*	(1,2) < 3

Note.[a]Mean score of the self-reported neuropathic sensory symptoms (sum of the 7 sensory symptoms/ 7); TNP = typical neuropathic pain; RAD = radiculopathy; FM = fibromyalgia; nBP = nociceptive back pain; NRS, Numeric Rating Scale; MPSS, Mainz Pain Staging System; PCS-H, Pain Catastrophizing Scale-Helplessness; CPAQ, Chronic Pain Acceptance Questionnaire; ADS-K, Allgemeine Depressionsskala-Kurz Version; ******* p< 0.001; ****** p< 0.01; ***** p<0.05; † not significant

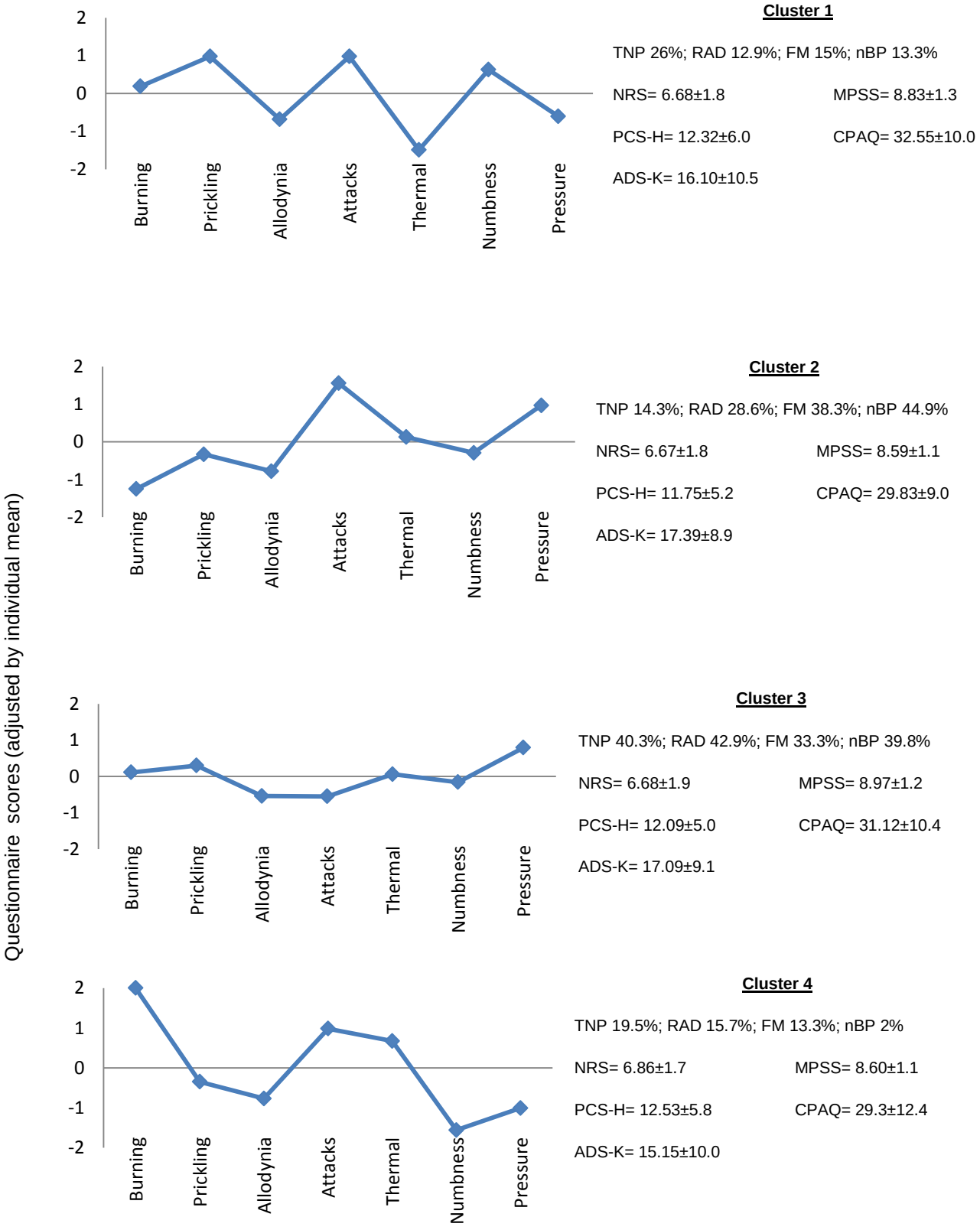

Figure 1. Subgroups of chronic pain patients with distinct patterns of neuropathic sensory symptoms using the Pain DETECT Questionnaire (clustering 2)

Note: Vertical axis: adjusted scores of neuropathic sensory symptoms, Horizontal axis marked as 0: average of seven adjusted scores of neuropathic sensory symptoms; TNP: typical neuropathic pain; RAD: radiculopathy; FM: fibromyalgia; nBP: nociceptive back pain; NRS, Numeric Rating Scale; MPSS, Mainz Pain Staging System; PCS-H, Pain Catastrophizing Scale-Helplessness; CPAQ, Chronic Pain Acceptance Questionnaire; ADS-K, Allgemeine

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Curriculum Vitae/Lebenslauf

Personal Data

Name	Maryam Shaygan
Date of Birth	18.09.1982
Place of Birth	Shiraz
Nationality	Iranian
Marital Status	Married
E mail	Maryam.shaygan@psych.uni-goettingen.de

Education

Bachelor of Science in Nursing (2004-2008)	Faculty of Nursing, Medical University of Isfahan, Isfahan, Iran
Master of Science in Psychiatric Nursing (2008-2010)	Faculty of Nursing, Medical University of Shiraz, Shiraz, Iran Thesis title: Effect of a psycho-educational intervention for family members on caregiver burdens and psychiatric symptoms in patients with schizophrenia Supervisor: Prof. Dr. Farkhondeh Sharif
Doctor of Philosophy 2011-Now	Department of Clinical Psychology and Psychotherapy, George August University, Göttingen, Germany Thesis title: Chronic pain with neuropathic characteristic Supervisor: Prof. Dr. Birgit Kröner-Herwig

Research Support and Honours

Nikon Company grant "Modulation of Pain Experience: The effects of mental representations of social support on pain experience", 2013

Top student in BSN program, Faculty of Nursing, Medical University of Isfahan.

First Top student in MSN program, Faculty of Nursing, Medical University of Shiraz.

Publications

Shaygan, M., Böger, A., & Kröner-Herwig, B. (accepted). Neuropathic sensory symptoms: Association with pain and psychological factors, *Neuropsychiatric Disease and Treatment.*

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