

# **Development and validation of diagnostic tools for adolescent chronic pain patients**

Dissertation zur Erlangung  
des Doktorgrades (Dr. rer. nat.)  
des Fachbereichs Humanwissenschaften  
der Universität Osnabrück

vorgelegt von

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Osnabrück, 2013

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## Summary

Chronic pain in children and adolescents is common; approximately 5% of children and adolescents report chronic pain along with moderate to high pain-related disability. Chronic pain is a subjective experience and can best be explained by a bio-psycho-social approach, which suggests reciprocal relations between different levels of this multidimensional phenomenon. The different dimensions of chronic pain need to be considered for a comprehensive assessment. Due to the subjective nature of pain, the child's self-report is usually considered the best available and most valid estimate of the pain experience. A reliable and multidimensional assessment is an indispensable requirement for treatment planning.

To date, questionnaires in German language are available to assess a wide range of relevant parameters in pediatric chronic pain. However, so far, no validated self-report tool exists to assess sensory and affective pain perception in children. These two parameters are of relevance since they describe aspects of the biological as well as the psychological dimension of chronic pain. Furthermore, a comprehensive diagnostic approach combining parameters from the three dimensions of chronic pain does not yet exist for children and adolescents. Such a comprehensive approach could be used for sample descriptions and standardized comparisons across different populations; it could serve as an approach for treatment planning or to classify outcome.

This doctoral thesis is aimed at further developing the available diagnostic measures for older children and adolescents with chronic pain based on the above mentioned gaps in pediatric pain assessment. Research was performed on three patient samples. Sample 1 includes data from a prospective assessment at the German Pediatric Pain Centre from August 2008 to March 2009 ( $N_1=139$ ). Sample 2 includes retrospective data from patients who were treated at the German Pediatric Pain Centre from July 2005 to June 2010 ( $N_2=1242$ ). Sample 3 consists of pediatric pain patients who started an intensive interdisciplinary inpatient treatment between November 2009 and July 2011 ( $N_3=83$ ).

In a first study, a tool to assess sensory and affective pain perception, the *Pain Perception Scale for Adolescents*, was adapted and validated in an adolescent clinical sample (Sample 1). The *Pain*

*Pain Perception Scale for Adolescents* allows pain patients to provide a valid and reliable self-report of parameters for both the biological and psychological dimensions of pain. In a second study, this tool was applied to a further sample of adolescents with migraine and tension-type headache (subsample of Sample 2). It was demonstrated that, contrary to the official headache classification guidelines, the sensory pain perception in this sample did not differentiate between migraine and tension-type headache. To develop a multidimensional assessment approach, in a third study, an adult classification system (*Chronic Pain Grading*) was applied to a sample of pediatric pain patients (Sample 2). This approach proved useful as a valid measure for a brief operationalization of pain problem severity, including pain intensity and pain-related disability only, and as an outcome measure. However, it displayed major shortcomings with regards to treatment stratification. To further develop an approach for treatment stratification and treatment planning, a fourth study focused on developing a new multidimensional approach for subgroup classification (subsample of Sample 2). The stability of subgroups was demonstrated in a cross-validation with an independent sample (Sample 1). Furthermore, the identified subgroups displayed distinct treatment outcomes after a standardized treatment program (Sample 3).

In conclusion, this doctoral thesis offers an addition to diagnostic measures for older children and adolescents with chronic pain by adding the *Pain Perception Scale for Adolescents* and by proving the validity of the *Chronic Pain Grading* for the application in this patient group. These tools allow a valid description of adolescents' subjective pain experience. Results from this doctoral thesis also indicate that the findings from adults cannot be readily transferred to children and adolescents. The final output of this doctoral thesis is a bio-psycho-social classification approach that identifies subgroups of adolescents with chronic pain with treatment relevant differences. This is a first step toward the development of subgroup-specific treatment.

## 1. Introduction

### 1.1 Chronic pain in children and adolescents

Chronic pain is a serious health problem in children and adolescents<sup>1</sup> which also has a high economic impact (King et al., 2011; Sled, Eccleston, Beecham, Knapp, & Jordan, 2005; Toliver-Sokol, Murray, Wilson, Lewandowski, & Palermo, 2011). Research efforts in pediatric chronic pain have greatly increased in the recent decades (Howard, 2003). This has led to advancement in the understanding of pediatric chronic pain and to advancement in the development of diagnostic measures and treatment (Howard, 2003; McGrath et al., 2008; Walker, 2008). However, many aspects remain unexplored. So far, there is not even a final agreement on the definition of chronic pain. Furthermore, despite age-related differences in many chronic pain conditions and different treatment requirements in pediatric pain management, treatment is often based on empirical findings from adult studies (Miro, Huguet, & Nieto, 2007; Walker, 2008).

#### 1.1.1 Definition

For children as well as adults, *pain in general* is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey & Bogduk, 1994, p.210). The most accepted definition of *chronic pain* and its distinction from acute pain is based on a time criterion. Pain that persists or reoccurs for three months and longer is considered chronic pain (Merskey & Bogduk, 1994). Chronic pain is not a uniform condition. It may be a symptom of an underlying chronic disease such as juvenile idiopathic arthritis<sup>2</sup> (Petty et al., 2004), but chronic pain may also become an independent disease itself (Lieb, Mastaler, & Wittchen, 1998). Common pain conditions in children are tension-type headache<sup>3</sup> (Kröner-Herwig, Heinrich, & Morris,

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<sup>1</sup> In the following, the term “children” will entail children and adolescents unless otherwise specified.

<sup>2</sup> Juvenile idiopathic arthritis is a chronic painful inflammatory disease primarily affecting the joints. Disease onset is before the age of 16 years. The origin of the condition is unknown (idiopathic). (Petty et al., 2004)

<sup>3</sup> Tension-type headache is the most common primary headache usually with a low to moderate pain intensity (International Headache Society [IHS], 2004).

2007), migraine<sup>4</sup> (Kröner-Herwig et al., 2007), functional abdominal pain<sup>5</sup> (Chitkara, Rawat, & Talley, 2005) and lower back pain (Watson et al., 2002). Furthermore, irrespective of the pain location, mental and behavioral pain disorders, such as the somatoform pain disorder (International Classification of Disorders, ICD-10, F45.4; World Health Organisation [WHO], 1992) and the chronic pain syndrome with somatic and psychological factors (International Classification of Disorders German Modification, ICD-10-GM, F45.41; Deutsches Institut für Medizinische Dokumentation und Information [DIMDI], 2009), are often diagnosed at specialized pediatric pain centers (Hechler et al., 2013; Lieb et al., 1998; Zernikow, Wager, et al., 2012).

### **1.1.2 Epidemiology of chronic pain**

The prevalence rates of chronic pain in children highly differ between studies depending on the research focus (e.g., definition and sample) and research design (e.g., data assessment and time frame) (Du, Knopf, Zhuang, & Ellert, 2011; Haraldstad, Sorum, Eide, Natvig, & Helseth, 2011; Huguet & Miro, 2008; Perquin et al., 2000; Roth-Isigkeit, Thyen, Raspe, Stöven, & Schmucker, 2004). Whereas a Norwegian study reported chronic pain in 21% of all school children between the ages of 8 and 18 (Haraldstad et al., 2011), a German study stated a prevalence rate of chronic pain as high as 46% for school children in a similar age range (10 to 18 years) (Roth-Isigkeit et al., 2004). The variety in prevalence rates may be explained by differences in the definition of chronic pain (e.g., time criterion of three months plus a minimum pain frequency), differences in the samples (e.g., age range) and differences in data assessment (e.g., interview vs. questionnaire and self-report vs. proxy-report) as well as differences in the time period of reporting (King et al., 2011). Despite this large variety, it has become apparent that chronic pain is “overwhelmingly prevalent in children and adolescents and should be recognized as a major health concern in this population” (King et al., 2011, p.2737). In addition, it can be assumed that chronic pain in children is a growing problem and that the prevalence rates have increased over the past decades (Bandell Hoekstra et al., 2001; Coffelt, Bauer, & Carroll,

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<sup>4</sup> Migraine is a primary headache disorder, occurring in attacks ranging between 4 and 72 hours. In migraine headaches the pain intensity is moderate to high and attacks are accompanied by various attendant symptoms. (IHS, 2004)

<sup>5</sup> Chronic functional abdominal pain is defined as ongoing abdominal pain without a known medical explanation (Drossman, 2006).

2013; King et al., 2011; Luntamo, Sourander, Santalahti, Aromaa, & Helenius, 2012; Sillanpää & Anttila, 1996).

Headache is the most common pain condition in children (King et al., 2011; Kröner-Herwig et al., 2007). Other types of pain, such as abdominal, back or musculoskeletal pain occur less often compared with headache (King et al., 2011). In addition to single pain sides, pain in more than one location is also often observed in children with chronic pain (Ghandour, Overpeck, Huang, Kogan, & Scheidt, 2004; King et al., 2011; Mikkelsen et al., 2008; Petersen, Brulin, & Bergstrom, 2006). Girls generally experience pain more often than boys, and the prevalence of chronic pain increases with age (King et al., 2011). Though in some children, the chronic pain condition persists into adulthood (Harreby et al., 1999; Hestbaek, Leboeuf-Yde, Kyvik, Manniche, & Sci, 2006; Mulvaney, Lambert, Garber, & Walker, 2006; Walker, Dengler-Crish, Rippel, & Bruehl, 2010), other children may experience a spontaneous remission without treatment (Gijsbers, Kneepkens, Schweizer, Benninga, & Büller, 2011; Mikkelsen et al., 2008). For back pain, it was demonstrated that its occurrence in adolescence goes along with a four times increased risk of back pain in adulthood. For functional abdominal pain, a tertiary care study reports that about 14% of patients presenting for an initial appointment still experienced pain five years later (Mulvaney et al., 2006). Another study identified a group at risk for long lasting functional abdominal pain; about one quarter of the initial sample were assigned to this group at risk (Walker, Sherman, Bruehl, Garber, & Smith, 2012). Spontaneous remission, on the other hand, was reported ranging between 25% for recurrent abdominal pain (Gijsbers et al., 2011) and 48% for widespread pain (Mikkelsen et al., 2008).

### ***Interpretation of prevalence rates***

When interpreting prevalence rates of epidemiological studies, it has to be kept in mind that not all children being classified as children with chronic pain can be considered chronic pain patients, i.e., children in need of treatment due to the pain condition.

Not all children with persistent pain visit a health care provider or take medication (Ellert, Neuhauser, & Roth-Isigkeit, 2007; Huguet & Miro, 2008; Perquin et al., 2001; Toliver-Sokol et al., 2011). A German study reports that 54% of all children with recurrent pain between the ages of 3 to 10 years and 36%

of all adolescents with recurrent pain between the ages of 11 to 17 years visit a physician because of their pain problem (Ellert et al., 2007). In a Dutch study, 31% of the children with chronic pain between 0 and 18 years of age visit a general practitioner in a three-month period, 14% visited a specialized doctor, mainly a pediatrician, 12% a psychotherapist and 3% a social worker or psychologist (Perquin et al., 2001). The numbers are slightly lower in an American epidemiological study, where primary care treatment was sought by 16% of all children with chronic pain in a six-month period, specialized care by 3% and mental healthcare by 2% (Toliver-Sokol et al., 2011). In addition to doctor visits, taking pain medication is very common in children and adolescents with chronic pain. Approximately half of all children with chronic pain regularly use pain medication (Huguet & Miro, 2008; Ellert et al., 2007; Perquin et al., 2001). When the severity of the pain problem increases, the likelihood of taking pain medication rises (Huguet & Miro, 2008). Whereas 44% of children with a low severity of chronic pain take medication, the number exceeds 80% in highly impaired children (Huguet & Miro, 2008). The numbers of medication users are similar for patients presenting to a tertiary pediatric pain center (76%) (Zernikow, Wager, et al., 2012). What is most worrying about this number is the sizable fraction of patients where pharmacological treatment is not indicated. Approximately 30% of the children taking analgesics do this without indication when they first visit a tertiary care center (Zernikow, Wager, et al., 2012).

To judge the severity of a chronic pain problem, pain-related disability and distress associated with chronic pain are important factors (Eccleston, Wastell, Crombez, & Jordan, 2008). An epidemiological study by Huguet and Miro (2008) demonstrated that not all children experiencing pain for three months or longer also experienced pain-related disability. Whereas 37% of the children had chronic pain (i.e., permanent or recurrent pain for at least three months), only 4% reported moderate pain-related disability, and 1% actually reported high pain-related disability (Huguet & Miro, 2008). It can be assumed that only these children experience serious impairment due to pain and actually do require specialized treatment. Currently, the study by Huguet and Miro (2008) can most likely be considered the best prevalence estimate of a clinically relevant chronic pain problem in children, i.e. chronic pain along with impairment in the child's everyday life. The study sample covers the age range from 8 to 16

years, includes all locations of pain and offers an extended operationalization of chronic pain, including pain-related disability (Huguet & Miro, 2008). Converting these numbers to the German population, we can expect approximately 350 000 children between 8 and 16 years of age to experience chronic pain with moderate to severe pain-related disability (data for the year 2012; Statistisches Bundesamt, 2013).

### **1.1.3 Multidimensionality of chronic pain and factors influencing the pain experience**

The traditional biomedical approach of pain, assuming that the degree of tissue damage translates directly into the severity of the pain experience and that pain with no pathophysiology indicates a sole psychological origin, has long been refuted (Turk & Okifuji, 1999). It has become obvious that in acute pain with an underlying physical abnormality, there is only a small association between the patient's degree of functional impairment and the severity of tissue damage (Turk & Okifuji, 1999). This indicates that a pain experience is the result of a complex individual process and exclusively subjective (Coghill, McHaffie, & Yen, 2003; Turk & Okifuji, 1999). Different areas of the central nervous system are involved in the processing of pain, i.e., somatosensory areas as well as emotional areas (e.g., the limbic system) (Coghill et al., 2003; Legrain, Iannetti, Plaghki, & Mouraux, 2011; Melzack, 2005). This network of affective as well as somatosensory structures suggests that pain is never a pure sensory perception.

The multidimensionality of chronic pain can best be described using a bio-psycho-social model (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). This model gives consideration to the fact that the overall experience and impact of chronic pain is influenced by the interaction of biological processes, psychological factors and the social environment.

#### ***Biological aspects of chronic pain***

There are a number of chronic diseases in which the pathophysiology may cause chronic nociceptive input to the brain. Among these diseases are chronic inflammatory diseases (e.g., ulcerative colitis<sup>6</sup>,

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<sup>6</sup> Ulcerative colitis is a form of an inflammatory bowel disease of unknown origin. It is a disease of the colon that includes characteristic ulcers or open sores. The main symptom of active disease is constant bloody diarrhea. It goes along with different degrees of abdominal pain. (Langan, Gotsch, Krafczyk, & Skillinge, 2007)

Crohn's disease<sup>7</sup> and juvenile idiopathic arthritis), genetic disorders (e.g., epidermolysis bullosa<sup>8</sup> and osteogenesis imperfecta<sup>9</sup>), degenerative conditions (e.g., arthrosis<sup>10</sup>) and cancer (Baumgart & Sandborn, 2012; Birchfield, 2001; Fine, 2010; Langan et al., 2007; Petty et al., 2004; Rauch & Glorieux, 2004).

#### Minor physiological abnormalities in functional conditions

Even in conditions considered functional, e.g., gastrointestinal conditions with no obvious underlying pathophysiology such as inflammation, tissue damage, metabolic or neoplastic processes (Drossman, 2006), physiological abnormalities play an important role in the development and exacerbation of chronic pain conditions. Functional gastrointestinal disorders are associated with certain minor physical abnormalities such as constipation or decreased bowel contractions and, on the other end of the spectrum, increased contractions and diarrhea (Devanarayana, Rajindrajith, Rathnamalala, Samaraweera, & Benninga, 2012; Devanarayana, Rajindrajith, Perera, Nishanthanie, & Benninga, 2013; Gijbbers et al., 2011; Lomax, Sharkey, & Furness, 2010). These symptoms may be mediated by abnormal functioning of the autonomic nervous system (Lomax et al., 2010). Low vagal activity may lead to decreased bowel contractions, reduced motility and constipation, whereas high vagal activity may lead to increased contractions and diarrhea (Lomax et al., 2010).

In children with functional dyspepsia, gastric motility is often altered, reduced or accelerated (Bufler, Gross, & Uhlig, 2011; Chitkara et al., 2003; Devanarayana, De Silva, & De Silva, 2008). Children with irritable bowel syndrome<sup>11</sup> or functional abdominal pain are more likely to have food allergies (Saps, Lu, & Bonilla, 2011), fructose or lactose malabsorption (Putkonen, Yao, & Gibson, 2013; Van Tilburg &

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<sup>7</sup> Crohn's disease is an inflammatory bowel disease of unknown origin causing a wide variety of symptoms; most common symptoms are abdominal pain, (bloody) diarrhea, vomiting and weight loss (Baumgart & Sandborn, 2012).

<sup>8</sup> Epidermolysis bullosa is an inherited connective tissue disease causing blisters in the skin and mucosal membranes, resulting in painful friction and skin fragility. Its severity ranges from mild to lethal. (Fine, 2010)

<sup>9</sup> Osteogenesis imperfecta is a congenital bone disorder of increased bone fragility and low bone mass. The severity ranges from mild to lethal. (Rauch & Glorieux, 2004)

<sup>10</sup> Arthrosis (also known as osteoarthritis) is a degenerative condition associated with aging. In this condition the cartilage of the joints are affected. Main symptoms are pain and stiffness. (Birchfield, 2001)

<sup>11</sup> Irritable bowel syndrome is characterized by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. This condition belongs to the group of functional bowel disorders, i.e., it has no known organic cause. (Drossman, 2006)

Felix, 2013), altered intestinal microbiomes (Saulnier et al., 2011), increased gastrointestinal permeability (Shulman, Eakin, Czyzewski, Jarrett, & Ou, 2008), subclinical gut inflammation (Olafsdottir, Aksnes, Fluge, & Berstad, 2002; Shulman, et al., 2008) or subtle changes in local gut immunology with an increased mast cell count (Henderson et al., 2012; Gijbsbers et al., 2011; Schurman & Friesen, 2010). In up to one-third of all patients with irritable bowel syndrome, symptoms begin after an acute gastrointestinal infection (Gwee, 2010; Saps et al., 2008). It is proposed that a inflammation-immunological phenomenon plays a major role in the development of post-infectious irritable bowel syndrome (Gwee, 2010).

In children with tension-type headache an increased muscle tone in the head and neck area can be observed (Alonso-Blanco et al., 2011; Soe, Thomsen, Tornoe, & Skov, 2013). There are conflicting findings about the interaction between joint hypermobility and musculoskeletal pain in children. Though some studies report a strong correlation, especially in obese children (Tobias, Deere, Palmer, Clark, & Clinch, 2013), others challenge these findings. A systematic review of several studies discovered no association for children with a European background, but did discover an association for children with an Afro-Asian background (McCluskey, O'Kane, Hann, Weekes, & Rooney, 2012). In children with chronic low back pain, low grade spondylolysis<sup>12</sup> and spondylolisthesis<sup>13</sup> are observed more often than in pain-free children (Faingold et al., 2004).

#### Changes in the nervous system

Alterations in body function – even minor ones – may increase nociceptive (A $\delta$  or C fibers) or sensory (A $\beta$  fibers) input to the spinal cord and the brain. In some children, this may lead to peripheral and/or central pain sensitization (Levy & Van Tilburg, 2012; Metsahonkala et al., 2006; Singh et al., 2012). Sensitization can be explained by the permanent experience of pain which causes changes in the (central) nervous system. These changes represent an increased sensitivity to painful and normally

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<sup>12</sup> Spondylolysis is defined as a defect in the pars interarticularis of a vertebra, which appears to be secondary to a stress fracture. A bilateral defect would result in spondylolisthesis of varying degrees. (Faingold, Saigal, Azouz, Morales, & Albuquerque, 2004)

<sup>13</sup> Spondylolisthesis is the anterior or posterior displacement of a vertebra or the vertebral column in relation to the vertebrae below. (Faingold et al., 2004)

non-painful stimuli, causing a reduction in pain threshold and an increased response to suprathreshold stimuli. Evidence for the phenomenon of sensitization in chronic pain has been provided in numerous studies (Gatchel et al., 2007; Loeser & Treede, 2008; Soe et al., 2013; Walker et al., 2012; Woolf, 2011). In children with various functional gastrointestinal disorders, visceral and more generalized pain sensitization have been observed (Castilloux, Noble, & Faure, 2008; Di Lorenzo et al., 2001; Faure & Wieckowska, 2007; Hoffman, Vos, & Tack, 2007; Van Ginkel, Voskuil, Benninga, Taminiau, & Boeckstaens, 2001). In adults with irritable bowel syndrome, diminished pain inhibition has also been detected in several studies (Wilder-Smith, 2011); a lowered inhibition results in a more intense pain experience. However, not all studies support the assumption of sensitization in pediatric chronic pain conditions (Soe et al., 2013). Tsao, Evans, Seidman and Zeltzer (2012) demonstrated that children with and without chronic pain did not differ in their pain responses (pain intensity and pain tolerance) to standardized pain tasks involving thermal heat, pressure and cold pain stimuli. Rather, the children with chronic pain were more likely to tolerate a cold pressor task compared with healthy controls (Tsao, Evans, Seidman, & Zeltzer, 2012). In a study by Soe and colleagues (2013), children with chronic tension-type headache did not display significantly increased sensitivity to pressure and pressure pain.

#### Heritability and chronic pain

Chronic pain in children also has a biologic-genetic dimension. Heritability is specifically important in migraine (Russell, 2008; Stam, Haan, van den Maagdenberg, Ferrari, & Terwindt, 2009), but also plays a role in functional gastrointestinal disorders (Grudell et al., 2008; Levy & Van Tilburg, 2012) or musculoskeletal pain (Champion et al., 2012; Diatchenko, Fillingim, Smith, & Maixner, 2013). Twin studies suggest that there may also be a genetic deterrent to central sensitization (Woolf, 2011). However, knowledge on relevant genes is still vague and sufficient research evidence is still lacking (Woolf, 2011).

#### ***Psychological aspects of chronic pain***

The psychological dimension of chronic pain includes the child's emotions, cognitions and behavior resulting therefrom. These factors are highly individual and influence the child's pain experience

(Gatchel et al., 2007; Miro et al., 2007). Importantly, they are also highly reciprocal, which makes it impossible to clearly separate the three.

### Emotions

Pain is, due to its evolutionary function, closely associated with emotions, specifically feelings of fear and threat (Williams, 2002). This close connection is also represented in the tight cortical connection between somatosensory and affective areas (Legrain et al., 2011). Pediatric pain experts consider depressive and anxious traits important factors in the development or maintenance of chronic pain and disability (Miro et al., 2007), which is underlined by the fact that pediatric chronic pain patients often report increased scores for depression and anxiety (Hirschfeld et al., 2013; Zernikow, Wager, et al., 2012). The specific role of emotional distress in chronic pain is not yet fully understood. Pediatric longitudinal studies suggest that depression and anxiety are predictive of recurrent pain trajectories (Larsson & Sund, 2005; Mulvaney et al., 2006; Stanford, Chambers, Biesanz, & Chen, 2008). Though some adult studies support these findings (Magni, Moreschi, Rigatti-Luchini, & Merkey, 1994; Polatin, Kinney, Gatchel, Lillo, & Mayer, 1993), others suggest that chronic pain can cause depression (Atkinson, Slater, Patterson, Grant, & Garfin, 1991; Magni et al., 1994). Therefore, it is assumed that several aspects play an intervening role (Bair, Robinson, Katon, & Kroenke, 2003; Gatchel et al., 2007). Once chronic pain and depression or anxiety has developed, they may interact reciprocally, worsening each other over the course of illness (Stanford et al., 2008).

In addition to the general emotional distress related to pain, *pain-specific* emotions also deserve special attention. One such pain-specific emotion is the fear of pain. It results when a child is appraising a stimulus that is related to pain as threatening (Asmundson, Noel, Petter, & Parkerson, 2012; Simons, Sieberg, Carpino, Logan, & Berde, 2011). This fear is highly influenced by cognitions such as catastrophizing thoughts (Simons & Kaczynski, 2012) and often leads to avoidance behavior and further inactivity (Asmundson et al., 2012); both aspects are described in more detail below. An increased fear of pain is associated with increased pain-related disability (Martin, McGrath, Brown, & Katz, 2007; Simons et al., 2011). Negative emotions such as fear of pain may further contribute to

muscle tension and physiological arousal, which again may exacerbate and maintain pain (Vlaeyen & Linton, 2000).

### Cognitions

As mentioned above, emotions are reciprocally related to cognitive-interpretive processes (Asmundson et al., 2012; Gatchel et al., 2007). Unlike the emotional dimension, chronic pain research on cognition has rarely been performed on *general* cognitive factors. There are hints that children with chronic pain have a higher intelligence compared with the population norm (Ho, Bennett, Cox, & Poole, 2009). In the long term, however, this relation seems to reverse: a longitudinal study found that higher intelligence in childhood is a protective factor for chronic wide-spread pain in adulthood (Gale, Deary, Cooper, & Batty, 2012).

Unlike general cognitive factors, *pain-specific* cognitions have been extensively examined. Appraisals are one focus of these pain-specific cognitions; they refer to the subjective judgment of a situation and are not driven exclusively by the actual sensory experience of pain but rather by one's own judgment of coping resources and hence the controllability or acceptance of pain (Gatchel et al., 2007; Hayes, Strosahl, & Wilson, 2012). Appraisals are determined by underlying beliefs, which develop over a lifetime and are highly influenced by the parents' beliefs a child is confronted with during childhood (Wilson, Lewandowski, & Palermo, 2011). Typical maladaptive beliefs of chronic pain patients are "pain is a signal of harm and activity should be avoided", "pain leads to disability", "pain is uncontrollable" and "pain is a permanent condition" (Crombez et al., 2003; Turner, Jensen, & Romano, 2000).

There is disagreement about whether pain catastrophizing should be considered a pain-specific appraisal in specific, pain-related situations or rather a set of maladaptive beliefs which are stable across situations and have developed over the lifetime (Sullivan et al., 2001). Pain catastrophizing is, however, defined as a cognitive style characterized by increased focusing on pain and exaggerated or fearful appraisals of pain symptoms and their consequences (Sullivan, Bishop, & Pivik, 1995). Pediatric pain experts consider pain catastrophizing a relevant factor in the development and maintenance of chronic pain (Miro et al., 2007). Pain catastrophizing is associated with increased pain intensity, disability and increased emotional burden (Crombez et al., 2003; Eccleston, Crombez, Scotford, Clinch,

& Connell, 2004; Hermann, Hohmeister, Zohsel, Ebinger, & Flor, 2007). Importantly, conclusions on the causal relation cannot be drawn due to the study design of previous research.

Pain beliefs and appraisals have strong impact on cognitive or behavioral coping strategies (Hechler et al., 2008; Walker, Smith, Garber, & Claar, 2007). Cognitive coping strategies to prevent negative emotions may aim at accommodation, i.e., changing the appraisal of a situation to accept it (Walker et al., 2007). Other typical helpful pain-related cognitive coping strategies are positive self-statements or mental distraction. The latter two coping strategies along with behavioral distraction can be subsumed under problem-focused coping, which aims at dealing with stressors and changing the circumstances (Reid, Gilbert, & McGrath, 1998).

### Pain Behavior

Children with a problem-focused coping style usually show an active pain coping behavior; this coping style is associated with reduced pain and disability (Chambers, Taddio, Uman, & McMurtry, 2009; Hermann et al., 2007; Walker et al., 2007; Reid et al., 1998). Children with a reduced ability for problem-focused coping will not show such active coping behavior, but rather engage in accommodative or passive coping (Walker et al., 2007). Accommodative coping may be functional in some respect (Hayes, Luoma, Bond, Masuda, & Lillis, 2006), but passive pain coping cannot be considered functional and is positively associated with pronounced disability, somatic symptoms and increased depression (Kaminsky, Robertson, & Dewey, 2006; Simons, Claar, & Logan, 2008; Walker et al., 2007; Walker, Garber, & Van Slyke, 1997). Passive pain coping behavior includes behavioral disengagement, self-isolation and activity avoidance (Walker et al., 1997). Whether children with pain show accommodative or passive coping depends on their ability for emotion-focused coping. Passive pain coping will dominate the pain behavior if a child is low on emotion-focused coping, i.e., is not able to accommodate. Passive pain coping further mediates the association between anxiety and disability, i.e., adolescents with chronic pain and comorbid anxiety engaging in passive pain coping may exhibit greater disability (Kaczynski, Simons, & Claar, 2011). The causal relation of these findings is not yet known. Adolescents with chronic pain and comorbid anxiety may be more likely to engage in negative thinking and activity avoidance, which are typical passive coping strategies, because these reactions

are common cognitive and behavioral responses to the emotional experience of anxiety. It may also be that negative thinking and activity avoidance increase anxiety, which may interfere with adaptive functioning. It is most likely that the relations between anxiety, pain coping and disability are bidirectional and have a reciprocal influence on each other (Kaczynski et al., 2011).

#### A comprehensive model of emotions, cognitions and behavior

The close and reciprocal relationship of emotions, cognitions and behavior is also illustrated in the *Fear-Avoidance Model* of chronic pain (Asmundson et al., 2012; Vlaeyen & Linton, 2000). This model – primarily developed for musculoskeletal pain but also transferable to other pain complaints – postulates that the fear of pain plays a central role in the maintenance and exacerbation of chronic pain. According to this model, not the sensory experience of pain itself but the dysfunctional appraisals about pain and its consequences, such as catastrophizing thoughts, increase pain-related fears. This leads to avoidance behavior to escape situations that may trigger pain. Through operant conditioning, this short-term reinforcement by the reduction of suffering associated with certain activities will cause the persistence of avoidance behavior and the functional disability. Avoidance, however, is a maladaptive response if it persists and leads to a general decrease of activity and physical fitness as well as increased fear and other psychological consequences that contribute to disability and persisting pain (Asmundson et al., 2012; Vlaeyen & Linton, 2000). The pediatric specification of this model highlights the reciprocal relationship between the child's behavior and psychological responses with the parental behavior and their psychological responses (Asmundson et al., 2012). The effects of various components of the pediatric Fear-Avoidance Model have been tested empirically (Asmundson et al., 2012; Simons & Kaczynski, 2012). Research could, for example, prove the influence of the child's pain-related anxiety and fear of pain on functional disability (Asmundson et al., 2012; Simons & Kaczynski, 2012). It was also demonstrated that parent protective pain behavior that is perceived by the child as a signal of parent fear or anxiety, is associated with the child's functional disability (Asmundson et al., 2012).

***Social aspects of chronic pain***

As in adults, the social context has an important impact on the development and maintenance of chronic pain in children (Goubert, Eccleston, Vervoort, Jordan, & Crombez, 2006). The child's social context is specifically affected by the parents (instead of the spouse in adults) and family, peers and school (instead of work in adults). Research concerning the social environment illustrates that parents and peers can have positive as well as negative impact on the child's pain problem (Miro et al., 2007). Importantly, the behavior of others never has an exclusive effect on the child. Rather the child's characteristics and social circumstances have to be taken into account and a reciprocal relation can be expected (Hermann, Zohsel, Hohmeister, & Flor, 2008).

**Parental psychological factors**

Being confronted with a child in pain will elicit certain emotional reactions in parents (Goubert et al., 2005). These emotions can be oriented to the self (e.g., parental distress or anxiety) but can also be oriented to the child in pain (e.g., sympathy). These two emotional responses have different motivational/behavioral consequences. While self-oriented responses may more likely cause behavior to reduce personal distress based on an egoistic motivation, the experience of sympathy may more likely cause altruistic motivation with the goal to help the child (Goubert et al., 2005). The way parents will respond is highly driven by their previous experience, their beliefs and appraisals regarding the child's pain. The emotional response will further influence parental cognitions and behavior. As for children, an important parental cognition is pain catastrophizing toward the child's pain (Miro et al., 2007; Vervoort et al., 2011). This cognition is associated with increased solicitous behavior (Goubert, Vervoort, Ruddle, & Crombez, 2012) and attention toward the pain (Caes, Vervoort, Trost, & Goubert, 2012). Parents who catastrophize are less likely to encourage their child to participate in daily activities (Caes, Vervoort, Eccleston, & Goubert, 2012), leading to increased disability (Goubert et al., 2006).

In regards to parental behavior, some studies indicate that solicitous or protective parental behavior in response to the child's pain is associated with increased pain and pain behavior of the child (Carter & Threlkeld, 2012; Kaczynski, Claar, & LeBel, 2013; Peterson & Palermo, 2004; Sieberg, Williams, & Simons, 2011; Walker, Levy, & Whitehead, 2006; Walker & Zeman, 1992; Wilson et al., 2011). However,

other studies report no association between solicitous parental behavior and the child's pain (Merlijn et al., 2006; Reid, McGrath, & Lang, 2005). And conversely, other studies again describe maternal solicitousness and distracting behaviors being associated with more adaptive coping behavior such as positive self-statements and problem-solving in children (Hermann et al., 2008). These conflicting findings may arise due to factors mediating the relation between parental behavior and the child's response. A study by Simons and colleagues (2008) demonstrated that adolescents without a fixed pain behavior pattern (i.e., infrequently using passive or active coping strategies) are especially vulnerable to the effects of parenting behavior and that parental protective behavior is associated with higher levels of disability and somatic symptoms specifically in these children.

While directing attention away from pain is generally positive (Reid et al., 1998) and supports active coping (Hermann et al., 2008), it may, however, also have an adverse effect when parents ignore or minimize the child's pain problem. Discouraging parental behavior, i.e., parents not taking their child's pain problem seriously, is associated with depressive and anxious mood and with catastrophizing thoughts in children with recurrent pain complaints (Hermann et al., 2008). Given that the causal relation between parental behavior and the child's reaction is not yet understood, findings can be interpreted in different ways. Emotionally distressed pediatric pain patients may be more sensitive to this parent behavior, and the negative mood may be a reaction to being ignored. However, discouraging parental behavior may also be a reciprocal effect wherein parents get increasingly frustrated and helpless when their child is in a negative mood (Hermann et al., 2008).

#### Familial accumulation of chronic pain

Several studies demonstrate a familial accumulation of chronic pain, i.e., children of parents with chronic pain have an increased risk to develop chronic pain themselves (Galli, Canzano, Scalisi, & Guidetti, 2009; Hoftun, Romundstad, & Rygg, 2013; Schanberg et al., 2001). Some of the above mentioned aspects (e.g., emotions, beliefs and behavior) might play a role in this context. For example, children of parents with a pain history have a higher tendency of catastrophizing thoughts (Schanberg et al., 2001). Furthermore, parents experiencing chronic pain themselves may display different behavior towards the child, e.g., may tend to overprotective behavior (Goubert et al., 2005).

Observational learning may also contribute to this accumulation (Goubert, Vlaeyen, Crombez, & Craig, 2011). In addition, hereditary factors, such as the vulnerability for certain pain conditions (e.g., migraine) or a genetic influence on central sensitization, may also present one aspect adding to this accumulation (Gatchel et al., 2007; Hoftun et al., 2013; Russell, 2008; Woolf, 2011; see paragraph 1.1.3 “Multidimensionality of chronic pain...”, subheading “Heritability and chronic pain”). It is most likely that different factors interact (Gatchel et al., 2007).

#### A comprehensive family model

Studies suggest a consistent positive association between family dysfunction and high impairment (Lewandowski, Palermo, Stinson, Handley, & Chambers, 2010). A first attempt to explain the complexity of relations is the integrative model of the family's role in chronic pain and pain-related impairment suggested by Palermo and Chambers (2005). So far, this framework is based on theoretical assumptions and not on empirical evidence. This model integrates operant-behavioral theories of parent behavior in a broader family system theory and proposes a complex relationship between family factors and pain – starting at the individual, followed by dyadic relations, and finally the whole family system. On the individual level, this model focuses parenting variables such as parenting style or parental reinforcement. The next level represents dyadic relationships between parents and the child. These dyadic relationships are further embedded within a more global familial environment (e.g., family functioning). This model highlights the reciprocal influence of pain, its effects on the child and on the family, as well as child characteristics (e.g., age, gender), parental factors (e.g., parental pain history) and family factors that interact between the different levels. The relationships and interactions between the different levels highly depend on the developmental status of the child. However, the model remains on a quite general level of explanation. It is not specified how interactions between the different levels are shaped. Taken together, the framework by Palermo and Chambers (2005) suggests an impact of the social context on the maintenance of the child's pain, while the child's illness also has an impact on the family environment (e.g., burden to his/her parents). Specific ideas on the kind of reciprocal associations are not discussed and need further clarification. Therefore, future research needs to fill this framework with more detailed explanations and empirical findings.

## Peers and school

Beyond the family system, peers and school may also be associated with the development and maintenance of pediatric chronic pain. However, studies explicitly investigating the impact of the peer group are scarce (Forgeron et al., 2010). Generally, children with chronic pain have fewer friends compared with healthy children and are less involved in peer activities (Forgeron et al., 2010). Some studies report an increased rate of victimization in children with chronic pain (Greco, Freeman, & Dufton, 2007; Hjern, Alfvén, & Östberg, 2008). However, the causal relationship of these findings and their impact on the development and maintenance of chronic pain is not yet understood (Forgeron et al., 2010). Peer victimization may trigger pain symptoms, but an ill child may also be more likely to be victimized due to his/her vulnerability (Forgeron et al., 2010).

A study by Merlijn and colleagues (2003) suggests that peers reward and amplify pain-free behavior. The researchers demonstrated that peers pay attention to their friends' suffering and chronic pain especially during episodes free of pain, whereas they reduce their attention during pain episodes (Merlijn et al., 2003). Based on this, Forgeron et al. (2011) determined that children with chronic pain often feel misunderstood by their peers; they desire increased attention and understanding especially when in pain. Though a reduction of peer attention during pain episodes could be considered a protective factor with regards to learning theory, it may still lead to social exclusion and loneliness in children with chronic pain and hence cause depression (Forgeron et al., 2011; MacDonald & Leary, 2005).

The general limitation in activity in children with chronic pain also affects school attendance (Huguet & Miro, 2008; Logan, Simons, Stein, & Chastain, 2008; Logan, Simons, & Carpino, 2011; Zernikow, Wager, et al., 2012). Irregular attendance of school results in numerous consequences for the child (Logan & Simons, 2010). Frequently, school performance drops markedly, children have a lower perception of their own academic performance and are less able to address the classroom demands (Logan et al., 2008; Sato et al., 2007). All this highly endangers the pupil's educational development. In addition, children missing school regularly become increasingly isolated from their classmates and lose contact with peers (Forgeron et al., 2010; Sato et al., 2007).

### Miscellaneous context factors

Furthermore, contextual stress is considered a relevant factor in the development and maintenance of chronic pain in children (Boey & Goh, 2001; Ghandour et al., 2004; Miro et al., 2007). A low socioeconomic status may be one cause of an increased stress level. Findings on the association between socioeconomic status and pain prevalence are not definite (King et al., 2011). Some findings support the idea that low socioeconomic status is associated with increased chronic pain (Bugdayci et al., 2005), whereas other studies could not replicate these findings (Hoftun et al., 2013; Kristjansdottir & Wahlberg, 1993). However, a recent study suggests that treatment seeking may be associated with socioeconomic status; longer distances to a specialized treatment center are travelled by parents with a high educational skill level (Wager, Ruhe et al., 2013). These findings suggest social injustice in treatment seeking; lower socioeconomic status may be associated with a lower accessibility of specialized treatment.

### ***Relevance of the bio-psycho-social model of chronic pain***

The bio-psycho-social model of chronic pain can be summarized as follows: Biological aspects in common pediatric chronic pain conditions often present minor physiological abnormalities. Importantly, they are not specific to children with chronic pain and will not occur in all affected children. In many children with chronic pain, biological markers are not detectable – or may be beyond the current state of knowledge. However, even if minor abnormalities are detected, they usually do not explain the severity of the pain problem, such as pain intensity or pain-related disability. Peripheral and central sensitizations, as well as an impaired pain inhibition, are often observed in chronic pain patients. Furthermore, emotions and cognitions have a high impact on the pain experience and influence each other. They also have an impact on pain behavior, which will again affect emotions and cognitions. Psychological processes are determined by the individual's disposition, past experiences and current circumstances. Beyond biological and psychological factors, social context factors play an important role in the development and maintenance of chronic pain in children. Parents, family, school and peers are relevant factors in pediatric chronic pain.

After all, the discussed biological, psychological and social factors can only be considered components in the full understanding of chronic pain in children. However, they are important additions for a better understanding of the origin and maintenance of chronic pain. One should keep in mind that all these factors will interact in a complex way. To really capture the pain experience one has to consider different levels: the individual (the child), relevant dyads (e.g., with the parents or peers) and the social context (the whole environment including family, peers, etc.) (Miro et al., 2007; Palermo & Chambers, 2005).

This bio-psycho-social model of the development and maintenance of chronic pain is relevant for the pain assessment derived from these theoretical assumptions (see paragraph 1.2 “Pain assessment”) and for the treatment of chronic pain (see paragraph 1.3 “Pain treatment”).

## **1.2 Pain assessment**

An accurate and comprehensive assessment of chronic pain is an important requirement for adequate treatment (Turk & Okifuji, 1999). However, the comprehensive assessment of chronic pain is a huge challenge. It is impossible to achieve a truly objective assessment of pain because of its subjective nature (Coghill et al., 2003; Turk & Okifuji, 1999). Therefore, the individual’s self-report is usually considered the best available and most valid estimate of the pain experience (Coghill et al., 2003). Nevertheless, additional measures, e.g., electroencephalography (EEG) or (functional) magnetic resonance imaging (MRI), are applied in pain research and clinical practice (Gatchel et al., 2007). These rather objective diagnostic approaches can illustrate the structure and/or activity of the nervous system, but will, however, not allow a final conclusion regarding the patient’s pain perception (Turk & Okifuji, 1999). The activation and structure of certain brain areas (Legrain et al., 2011) can neither be directly interpreted with regards to the perception of pain characteristics nor to cognitive and emotional correlates (Gatchel et al., 2007; Harrison, Beggs, & Stevens, 2012). Besides objective measures, pain perception can also be approached by semi-objective measures. These measures, e.g., quantitative sensory testing (QST), offer a fixed protocol for a standardized assessment, but still rely on the child’s self-report regarding the pain perception (Blankenburg et al., 2010).

Nevertheless, questionnaires remain an important tool in the assessment of chronic pain. Though self-reporting is considered the gold standard, it is often not accomplishable in younger children. A reliable report of pain intensity can be achieved from 4 years onwards (McGrath et al., 2008; Stinson, Kavanagh, Yamada, Gill, & Stevens, 2006; von Baeyer, 2009a). The report of more complex items requires a higher developmental status (McGrath et al., 2008; Schroeder et al., 2010). In the assessment of pediatric chronic pain, different developmental stages require adapted questionnaire versions (McGrath et al., 2008; Schroeder et al., 2010; Walker, 2008). Either the assessment of younger children must be briefer and less complex compared with older children and adolescents or the child version has to provide different wording, i.e., appropriate for this age group (Schroeder et al., 2010). Alternatively, parent proxy-reporting can be used for younger children (Schroeder et al., 2010).

In each individual, the biological, psychological and social aspects of chronic pain are differently developed and characteristics of one dimension do not allow a conclusion on the other dimensions. Therefore, a comprehensive assessment of chronic pain should comprise all three dimensions of chronic pain (Turk & Okifuji, 1999). In the following section, the most important assessment standards for children with chronic pain will be outlined and divided into the biological, psychological and social aspects of chronic pain.

### **1.2.1 Assessment of biological aspects of chronic pain**

The assessment of biological aspects in chronic pain has two major objectives: First, to rule out defined underlying diseases contributing to the chronic pain condition and second, to “directly” measure pain.

#### **Identification of specific organic pathology**

Pain can occur due to structural changes, tissue or nerve damage or other pathophysiology. Therefore, a comprehensive medical examination is essential to rule out an underlying causative pathology (Wager, Kriszto, Dobe, Hechler, & Zernikow, 2013). As mentioned above, pathophysiology can often not be found in chronic pain patients. However, many physicians believe and therefore (unintentionally) suggest to the patient that chronic pain has a specific treatable organic cause. They also believe and suggest that this organic cause needs to be detected through a vigorous medical diagnostic process. Accordingly, a large number of medical diagnostic approaches, such as MRI of the

brain, will be performed in children, even without any clinical indication (Lewis & Koch, 2010; Martens et al., 2012; Rho et al., 2011; Schaefer et al., 2012). This common problem can be explained by a lack of discrimination between acute and chronic pain. Unlike chronic pain, acute pain is usually a sign for some type of pathophysiology (Schäfer, 2009). In chronic pain patients, however, overdiagnosis and multiple organic diagnostic investigations may even worsen the problem; it may cause further chronification of the pain syndrome known as iatrogenic chronification (Schaefer et al., 2012). Therefore, it is very important to apply sufficient, but not exaggerated, diagnostic procedures in chronic pain patients. One way to optimize medical diagnostics is the use of *red flags*. Red flags are clinical indicators of possible serious underlying medical conditions requiring further diagnostic procedures and interventions.

For most recurrent or chronic pain conditions in children (e.g., different types of headache, abdominal or musculoskeletal pain), red flags are defined. To reliably identify red flags, taking a comprehensive medical history and a broad physical examination are required (Carville, Padhi, Reason, & Underwood, 2012; Di Lorenzo et al., 2005). When red flags are detected, further diagnostic approaches are justified to rule out malignancies, infections or autoimmune diseases (Ahmed, Martinez, Cahill, Chong, & Whitehouse, 2010; Carville et al., 2012; Di Lorenzo et al., 2005; Ebinger, 2010). Minor alterations in body function, such as subclinical gut inflammation in functional abdominal pain (Olafsdottir et al., 2002; Shulman et al., 2008), increased muscle tone in tension-type headache (Alonso-Blanco et al., 2011; Soe et al., 2013) or joint hypermobility in musculoskeletal pain (McCluskey et al., 2012; Tobias et al., 2013) are either detectable by physical examination or only detectable by the use of invasive diagnostic procedures. Given that causative treatment for these conditions does not exist anyway (see paragraph 1.3.1 “Medical interventions”), an invasive approach is not justified in the absence of red flags. In neuropathic pain, the underlying pathology involves the peripheral or central nervous system. Objective or semi-objective investigations such as MRI, nerve conduction velocity testing or QST are used to characterize the underlying pathophysiology in more detail and guide the treatment decision (Backonja et al., 2013).

Following red flags and diagnostic guidelines may protect children with chronic pain from unnecessary diagnostic procedures and prevent iatrogenic chronification. In addition, a bio-psycho-social understanding of chronic pain instead of the search for the one organic cause may help to prevent the patient's somatic fixation, i.e., only seeing the biological dimension as a possible cause for chronic pain.

#### Semi-objective approaches to identify sensitization

There are semi-objective measures for detecting the function of the nervous system. They are considered semi-objective since these diagnostic approaches follow a standardized protocol, but do rely on the patient's self-report, e.g., regarding pain intensity or other pain qualities. One such semi-objective approach is QST. It allows measuring perceptual functioning of almost all somatosensory modalities. QST examines the functioning of larger fibers ( $A\beta$ ) and smaller ones ( $A\delta$ , C) to detect neuropathies (Blankenburg et al., 2010). Although it is an important tool to detect peripheral and central pain sensitization and the function of the descending pain inhibition, to date, it is mainly applied in research studies (Sethna, Meier, Zurakowski, & Berde, 2007; Walker et al., 2009). Other semi-objective measures for this application are pain provocation tasks such as cold pressor tests (Tsao et al., 2013) or rectal distention (Kanazawa et al., 2008). These tests are also mainly applied in research and not in clinical practice. One reason for the lack of clinical application may be that these semi-objective approaches are costly and time consuming, difficult to operationalize and some are invasive (Blankenburg et al., 2010; Kanazawa et al., 2008; Tsao et al., 2013).

#### Subjective assessment of biological processes

Though some approaches produce rather objective results (e.g., functional MRI) or at least semi-objective results (e.g., QST) with regards to pathophysiology, there is no diagnostic medical procedure to "directly" measure a person's subjective pain perception (Ebinger, 2010; Gatchel et al., 2007). Therefore, clinicians and researchers also greatly rely on the patient's self-report. Subjective measures are another way to indirectly describe biological processes that cause a prototypic pain. The description of pain quality and intensity are indicators of pathophysiology. Neuropathic pain, for example, is characterized by a burning, tingling or prickling pain quality (Baron & Tölle, 2008; Boureau, Doubrere, & Luu, 1990). According to the International Headache Society, migraine is defined as a

sudden periodic headache, with moderate to severe pain intensity and pulsating pain quality, whereas tension-type headache is a mild to moderate pain with a pressing and specifically not pulsating pain quality (International Headache Society [IHS], 2004). Therefore, sensory pain perception is especially relevant with regards to pain diagnoses.

Even though considered subjective, these measures still appear to hold reliable information and were demonstrated to correlate with objective measures. The subjective report of pain intensity, for example, is considered the most reliable index to measure it (Coghill et al., 2003). A functional MRI study has proven the validity of pain self-reports in adults by revealing a high concordance between specific brain activities and reported pain magnitudes (Coghill et al., 2003). Furthermore, pediatric studies in acute pain have demonstrated that the report of pain intensity correlates with the severity of painful procedures (Miro, Castarlenas, & Huguet, 2009). The before mentioned studies are examples of acute pain. Whether these results can be readily transferred to chronic pain is questionable. Sound validation studies in chronic pain are impossible due to a missing gold standard (Jensen, Turner, Romano, & Fisher, 1999; von Baeyer, 2006). Given that many factors influence the pain perception, it is unlikely that a self-report of pain intensity in chronic pain really reflects the intensity of the pure pain experience. However, pain intensity in chronic pain is one important indicator of the perceived severity of the pain problem (Von Korff, Ormel, Keefe, & Dworkin, 1992).

#### Assessment of pain intensity and pain quality

There are numerous validated tools to assess pain intensity in older children and adolescents. Most commonly the numeric rating scale and the visual analogue scale are applied (von Baeyer, 2009b). Both tools have good psychometric properties for the assessment of pain intensity in older children (Miro et al., 2009; Stinson et al., 2006).

The quality of pain can be verbally described. The first to create a list of pain-relevant adjectives was Melzack (1975). Since then, different lists have been developed for the application in adults (Dworkin et al., 2009; Melzack, 1987; Wilkie, Savedra, Holzemer, Tesler, & Paul, 1990). Adaption for their use in children has also been promoted in the English language (Savedra, Holzemer, Tesler, & Wilkie, 1993; Varni, Thompson, & Hanson, 1987). These measures usually capture the sensory, affective and

evaluative pain perception (Savedra et al., 1993; Varni et al., 1987). With regards to the biological dimension of pain, sensory pain perception describing the quality of pain can be considered a relevant marker to detect a specific pain pathology; e.g., pain caused by a structural change in the peripheral nervous system (neuropathic pain) often is described as burning, tingling or prickling (Baron & Tölle, 2008; Bennett et al., 2007; Hallström & Norrbrink, 2011). However, no validated tool in the German language for the assessment of sensory pain perception in children has been previously available.

### **1.2.2 Assessment of psychological aspects of chronic pain**

Instruments to assess emotions, cognitions and behavior regarding pain are progressively developed and validated (Palermo & Eccleston, 2009). In this paragraph, the most common instruments for older children and adolescents (>10 years) are presented. If not mentioned otherwise, the discussed questionnaires are in the German language.

#### Assessment of affective traits

As mentioned above, depressive and anxious symptoms are important in the development and maintenance of chronic pain. Therefore, depression and anxiety screening tools are suggested as standard measures in the assessment of pediatric chronic pain by the Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (McGrath et al., 2008). However, general emotional constructs, such as depression or anxiety, are difficult to assess in the context of chronic pain. One basic problem is the overlap between emotional distress symptoms and chronic pain symptoms. Depression and chronic pain share neurological pathways and neurotransmitters, and most important, they also have common behavioral symptoms, such as decreased activity or disease-related disability (Bair et al., 2003). Furthermore, the somatic symptoms of chronic pain may influence the scoring of a depression tool. Recently, Logan and colleagues (2013) investigated the factor structure of an established English language depression-screening tool (*Children's Depression Inventory*; Kovacs, 1981). Although they generally suggest its validity in pediatric chronic pain patients and do not advise the elimination of items, they note the importance of careful interpretation of results as it remains unclear whether certain somatic symptoms and their consequences truly reflect depression or are rather linked to the chronic pain experience itself (Logan et al., 2013). The total score may be elevated

without an underlying clinical depression and subscales, including somatic items or items broaching the issue of inactivity, have to be interpreted with reservations. An overlap between anxiety and chronic pain is also supposed. In animal studies, researchers demonstrated that anxious behavior is overlapping with chronic pain symptoms and that both states involve the same dysbalance of noradrenalin as a neurotransmitter and the activation of the same brain area, the nucleus locus coeruleus (Alba-Delgado et al., 2013). The nucleus locus coeruleus is a relevant structure in pain transmission and also part of the central “stress circuitry” involved in the pathophysiology of depression and anxiety disorders (Alba-Delgado et al., 2013).

#### Assessment of pain-specific affect

One possibility to avoid the overlap between symptoms of emotional distress and chronic pain is to measure the affective state directly related to pain perception. Affective pain perception is an important facet of the emotional dimension of pain (Legrain et al., 2011; Melzack, 2005). People cannot only describe pain in its sensory characteristics, such as intensity or quality, but also with affective features such as “horrible”, “annoying”, “exhausting” or “terrifying” (Melzack, 2005). This affective component of pain perception captures the direct emotional impact of pain on the individual, i.e., the individual psychological burden and the concurrent suffering due to pain (Geissner, 1996). Questionnaires exploring sensory pain perception usually also include a scale for affective pain perception (Savedra et al., 1993; Varni et al., 1987). A questionnaire to assess pain-specific affect was thus far not available for use in children in the German language.

The assessment of pain-related fear in children is highly recommended, due to its important role in the explanation of the Fear-Avoidance Model (Asmundson et al., 2012), which postulates pain-related fears as a trigger for avoidance behavior to escape pain-associated situations (explained in more detail in paragraph 1.1.3 “Multidimensionality of chronic pain and factors influencing the pain experience”, subheading “A comprehensive model of emotions, cognitions and behavior”). A validation study of the German translation of a validated English tool (*Fear of Pain Questionnaire*; Simons et al., 2011) is currently in progress (Ebeling et al., 2012).

### Assessment of pain-specific cognitions and behavior

Instruments to assess pain-related cognitions and mental coping strategies are available. Children are commonly questioned regarding their catastrophizing thoughts related to pain (*Pain-Related Cognitions Questionnaire for Children*; Hermann et al., 2007; Varni et al., 1996). Questionnaires also allow the assessment of cognitive coping strategies; these tools provide information on positive self-statements or positive self-instructions (e.g., *Pain-Related Cognitions Questionnaire for Children*; Hermann et al., 2007; *Pediatric Pain Coping Inventory Revised*; Hechler et al., 2008).

On the behavioral level, different coping strategies, such as passive pain coping and seeking social support can also be described by questionnaire self-reporting (*Pediatric Pain Coping Inventory Revised*; Hechler et al., 2008; Varni et al., 1996). Lastly, problem-solving, a construct including cognitive and behavioral coping, has also been operationalized in a questionnaire (*Pain-Related Cognitions Questionnaire for Children*; Hermann et al., 2007). Besides coping, pain behavior further concerns limitations in daily activity. A questionnaire to assess the construct of pain-related disability in everyday life is available in a self-report format (*Paediatric Pain Disability Index*; Hübner et al., 2009). It assesses the frequency of the child being kept from various everyday activities.

### **1.2.3 Assessment of social aspects of chronic pain**

The social environment can be assessed through the self-reports of attachment figures (e.g., by parental report on catastrophizing thoughts regarding the child's pain) and the child's self-reporting with regards to the relationship with family members, peers or school, as well as parents' or teachers' proxy-reporting on the child and structural facts.

### Assessment of parental parameters

The assessment of parental emotions is not common in the clinical setting of pediatric chronic pain. However, some research concerning the emotional status of parents whose child has chronic pain does exist and suggests emotional impairment also in parents (e.g., Eccleston et al., 2004; Kashikar-Zuck et al., 2008). Still, in the clinical context this information is difficult to obtain. Rather than giving information on their own emotional status, parents are generally more willing to report on topics obviously related to their child's pain such as their own pain-related cognitions and their behavior

towards the child. Information regarding the extent of parental catastrophizing (*Parental Catastrophizing Scale*; Hechler, Vervoort, et al., 2011) or parental behavior in response to the child's pain including solicitousness, distracting and discouraging behavior (*Pain-related Parent Behavior Inventory*; Hermann et al., 2008) can be assessed through questionnaires. The child's view on the family system can also be assessed. The relation with parents and the atmosphere at home are operationalized in the health-related quality of life *Kidscreen* questionnaire (Subscale "Parents and Home Life"; Ravens-Sieberer, 2006).

#### Assessment of peer and school parameters

With regards to the role of peers, validated tools are rare even in the English language. The patient's peers are not asked, although their perspective may add further details to the whole picture. Instead, the pain patient reports on his/her perception of peer-relations (*Kidscreen* subscale "Peer Relationships"; Ravens-Sieberer, 2006).

School absence is a relevant marker for the severity of a pain problem and for treatment outcomes. The best measure of days missed in school would be school records. However, Logan and colleagues (2008) have demonstrated that children's and parents' report of school absence are sufficient, i.e., comparable to official school records. The same applies for the estimate of academic performance (Logan et al., 2008). Via self-reporting, children can further describe their own perception of their cognitive capacity, learning and concentration. In addition, feelings of being rejected by peers at school can be assessed by the *Kidscreen* subscales "School Environment" and "Social Acceptance" (Ravens-Sieberer, 2006).

#### **1.2.4 Comprehensive measures of chronic pain**

Given that chronic pain is a complex construct, there are also efforts to develop multidimensional measures. These multidimensional measures allow classifying chronic pain patients into homogenous subgroups. Such classification systems may serve several goals: First, they can offer a comprehensive and simple description of samples and allow standardized comparison across different populations; second, they could serve as an approach for treatment planning, i.e., patient groups are referred to

specific treatments based on their characteristics; third, such comprehensive measures could also be used as an approach to classify outcome (Von Korff et al., 1992).

#### Classification systems for adults

In adults, the *Mainz Pain Staging System* (Gerbershagen, 1986) and the *Chronic Pain Grading* (Von Korff et al., 1992) are examples of such classification approaches. The *Mainz Pain Staging System* is a German approach widely used for adult pain patients (Frettlöh, Maier, Gockel, Zenz, & Hüppe, 2009; Michalski & Hinz, 2006; Nilges & Nagel, 2007). It classifies patients into different stages of chronicity based on temporal and spatial aspects of pain, drug-taking behavior and utilization of the health care system (Gerbershagen, 1986). This approach describes and classifies chronification as a gradual process which is, however, not dependent on pain duration. One disadvantage of this approach is the limited sensitivity to change because the *Mainz Pain Staging System* includes a life-time exploration of health care utilization (Pfungsten, Schöps, Wille, Terp, & Hildebrandt, 2000). Therefore, patients are less likely to be classified into a lower grade after successful treatment when there has been a wide range of previous treatment. This fact is contradictory to the concept of healing and is not in line with the general understanding of chronification as a bidirectional process (Pfungsten et al., 2000). Due to this limitation, the *Mainz Pain Staging System* cannot be used as an outcome measure. However, it can serve as an approach for sample description and comparison and allows a good overview of chronification and medical history (Frettlöh et al., 2009; Hüppe et al., 2001). The *Mainz Pain Staging System* furthermore offers important suggestions for treatment planning (Gerbershagen, 1986). However, an empirical examination of the utility for treatment stratification, i.e., targeting treatment options based on patient characteristics, has not been conducted thus far. Concerning the multidimensional approach of chronic pain, the *Mainz Pain Staging System* is strongly oriented toward previous treatment and does not consider the psychological or social aspects of chronic pain.

The *Chronic Pain Grading* classifies people with chronic pain into different severity grades based on pain intensity and disability (Von Korff et al., 1992). There is sufficient evidence for its validity in adult patients (Elliott, Smith, Smith, & Chambers, 2000; Hawker, Mian, Kendzerska, & French, 2011; Muller, Thomas, Dunn, & Mallen, 2013; Penny, Purves, Smith, Chambers, & Smith, 1999; Smith et al., 1997).

Also, a German version of this classification approach was validated in an adult sample (Klasen, Hallner, Schaub, Willburger, & Hasenbring, 2004). This brief and easy to apply classification, including two of the most relevant aspects of chronic pain, pain intensity and disability, allows describing and comparing samples and can be used as an outcome measure (Hawker et al., 2011; Muller et al., 2013). Thus far, the *Chronic Pain Grading* has not been tested for treatment stratification, but can be used as a prognostic measure for the course of pain when combined with a more complex risk score measure (Dunn, Croft, Main, & Von Korff, 2008; Von Korff & Miglioretti, 2005). The *Chronic Pain Grading* only covers the behavioral aspect of the psychological dimension (disability), leaving emotions or cognitions unconsidered. It also does not include a component of the social dimension of chronic pain.

#### Development of a classification for children

There are two possible methods for establishing a classification approach for pediatric chronic pain. The first method is to adapt the adult classification system for use in children. The second method is to develop a new approach.

With regards to the first method, the adaption of the *Mainz Pain Staging System* to a pediatric sample does not appear meaningful given that the *Mainz Pain Staging System* has not proven to be change sensitive and therefore cannot be applied as an outcome measure. Furthermore, it includes factors, such as previous drug withdrawal or number of pain-related operations and rehabilitation efforts, which only apply to a very small number of patients in the pediatric setting and would therefore not offer a good discrimination between individuals and homogenous subgroups.

Huguet and Miro (2008) followed the method of adapting an adult classification system and applied the *Chronic Pain Grading* to a sample of school children. Pain intensity was measured according to the adult version via numeric rating scale. The disability measure in the original *Chronic Pain Grading* includes interference with daily activity and work. One limitation of the adapted version by Huguet and Miro (2008) is that they did not include school interference into the disability measure in the pediatric *Chronic Pain Grading* as a replacement for work in the adult version. They only used a general disability measure without including school. Furthermore, the adapted version was only tested in an epidemiological sample with a low number of severely affected children ( $n=28$ ). An optimization of the

conceptual design as well as the application in a clinical pain sample is necessary to make conclusions on the quality of this grading system for use in children with chronic pain. The application for treatment stratification and as an outcome measure also requires the application in a clinical sample.

The second method, i.e., developing a new classification approach, may be considered when the first method does not offer a classification system that serves the three expected goals mentioned above (i.e., sample description, treatment planning and outcome measure). A new approach for the classification of pediatric patients with chronic pain should be based on theoretical assumptions (choice of factors by literature search) and explorative statistical testing. A goal of such an approach could be to identify more homogenous subgroups within a heterogeneous sample of children with chronic pain.

To date, there are several attempts to follow such an approach. Recently, Walker and colleagues (2012) published a cluster analysis of children with abdominal pain. They clustered children with abdominal pain with the main goal of determining whether these groups vary in their long-term outcome. They identified three patient groups mainly differing in their general degree of pain intensity, frequency and duration as well as on psychological parameters including catastrophizing, negative affect and coping. They demonstrated that the long-term outcome differed between groups (Walker et al., 2012). The results of this work are promising with regards to the usefulness of a cluster analytic approach. However, this work has major shortcomings. The drop-out rate was very high (>50%), the follow-up interval is not properly described and has a large range of several years. The construct validity was not properly tested (i.e., it was tested by the use of parental proxy-reports of child measures that were included in the cluster solution), neither was the utility as an outcome measure and for treatment stratification. This work only comprised children with abdominal pain and used a high number of parameters, nine in total. While this comprehensive approach includes sensory, cognitive, affective and behavioral aspects of pain, the high number of parameters makes it impractical for use in clinical practice.

Another previous approach was performed by Vowles, Jordan and Eccleston (2009). They also calculated a cluster analysis to develop a pain problem severity classification for pediatric chronic pain

patients. This approach included psychological variables based on a multidimensional questionnaire (*Bath Adolescent Pain Questionnaire*; Eccleston et al., 2005) and identified four distinct groups differing in daily functioning, emotional functioning, family functioning and development. These findings are hampered by the fact that they are based on children with musculoskeletal pain only, and no proper cross-validation was performed to test the stability of the cluster solution. This cluster solution also included a high number of parameters, seven in total, which makes it impractical for use in the clinical setting. Pain intensity was not included in this severity grading, though simultaneous analyses indicated an increase of pain intensity with increasing severity. This suggests that pain intensity might be a valuable addition.

### **1.2.5 Further development of pain assessment tools**

In summary, a paucity of German questionnaires to assess chronic pain in pediatric samples is available. To add to the existing diagnostic tools, a valid self-reporting tool to assess sensory and affective pain perception is required. Furthermore, the comprehensive assessment of chronic pain and the identification of subgroups appear promising for making treatment recommendations and measuring outcome. There are a few pain classification systems that have been developed and validated in adult samples. For one, the *Chronic Pain Grading*, an optimized adaption for children seems reasonable along with a validation in a clinical sample. Recently, some additional classifications have been newly developed in pediatric samples. However, these are very specific in their application, i.e., only developed for certain pain conditions. In addition, they are not useful in clinical practice due to their length. A further testing of the *Chronic Pain Grading* in a clinical pediatric sample and, when necessary, a new development of an easy to apply classification system for pediatric patients with different chronic pain conditions appears to be warranted.

## **1.3 Pain treatment**

According to the bio-psycho-social model, chronic pain will never be caused or maintained by just one dimension. A comprehensive assessment helps to identify the relevant parameters on each dimension and to decide which aspects need to be addressed in treatment. Treatment will then usually require

different modules to be combined (Leo, Srinivasan, & Parekh, 2011). A general goal of chronic pain treatment is the reduction and management of pain symptoms as well as reduction of disability, improvement of psychological well-being and the reestablishment of role functioning, including school or work (Hechler et al., 2013; Eccleston, Malleson, Clinch, Connell, & Sourbut, 2003). Treatment goals are also the further prevention of unnecessary or even harmful interventions or (invasive) diagnostic procedures (Zernikow, Dobe, et al., 2012) and the reduction of the economic burden for the individual and the society (Hechler et al., 2013).

Treatment modules for chronic pain can be split up into medical interventions aimed at the modification of biological components of pain, psychological interventions aimed at changing psychological processes and improving social impairment as well as social interventions.

### **1.3.1 Medical interventions**

In defined painful diseases such as juvenile idiopathic arthritis, inflammatory bowel disease or cancer, a successful causative treatment will reduce or abolish pain in many cases. However, even when the underlying condition is best treated, some children still experience chronic pain; e.g., children with juvenile idiopathic arthritis may still experience pain even when the inflammatory process is well controlled through disease-modifying drugs and signs of an active disease are no longer detectable (Faure & Giguere, 2008; Stinson, Luca, & Jibb, 2012).

When minor abnormalities of body function are detected in children with different chronic pain conditions, most medical therapies intending to improve body function and to reduce pathophysiology have proven ineffective with regards to the pain problem. For example, the causative treatment of constipation, lactose intolerance or helicobacter pylori colonization, such as high fiber or lactose free diets or helicobacter pylori eradication therapy, have been ineffective in reducing pain and pain-related disability (Bufler et al., 2011; Huertas-Ceballos, MacArthur, & Logan, 2009). The implications for the treatment of chronic pain are that a comprehensive education on the chronic pain condition should include pathophysiology. Importantly, the patient should be informed that the evidence of therapies targeting minor abnormalities is limited or cannot be provided at all. Sometimes, therapies

aimed at altered body function can be used in a supplementary manner, but in most cases, they will not provide a satisfying cure for the chronic pain condition (Bufler et al., 2011).

### Pharmacological interventions

Pharmacological interventions are only indicated when a causative treatment of the pathophysiology of pain is possible or in the case nociceptive processing can be directly influenced by the drug (Dobe, Kriszto, & Zernikow, 2013; Huertas-Ceballos, Logan, Bennett, & MacArthur, 2008). Four major groups of drugs can be distinguished: triptans, non-opioids, opioids and adjuvants. The chemical structure of *triptans* is similar to serotonin, and their action is mediated by the activation of serotonin receptors. Triptans are approved and effective for the treatment of migraine and cluster headache<sup>14</sup> (Eiland & Hunt, 2010). *Non-opioids*, e.g., the active agent ibuprofen, influence inflammatory processes that play a role, for instance, in migraine, juvenile idiopathic arthritis or cancer pain. In these applications, they are effective (Anthony & Schanberg, 2005; Toldo, De Carlo, Bolzonella, Sartori, & Battistella, 2012; Zernikow et al., 2006). *Opioids*, on the other hand, influence the transmission and processing of nociceptive stimuli. The use of opioids has proven effective specifically in acute pain conditions, such as postoperative pain or pain in burns (American Academy of Pediatrics & American Pain Society, 2001; Drake, Anderson, Anker, & Zernikow, 2013; Duedahl & Hansen, 2007), and cancer pain (Caraceni et al., 2012; WHO, 2012; Zernikow, Michel, Craig, & Anderson, 2009). Opioids are also often applied in the treatment of longstanding non-cancer pain in adults, although findings on the effectiveness of opioids in this context are conflicting (Kissin, 2013; Reinecke & Sorgatz, 2009). Though some patients with longstanding non-cancer pain report a reduction of pain intensity under opioids, these reductions in pain intensity are usually not accompanied by a reduction in functional disability (Reinecke & Sorgatz, 2009). Because of the low evidence of its effectiveness and the high probability of side effects, such as fatigue or constipation, long-term opioid treatment in non-cancer pain patients is only recommended in rare cases and with careful consideration (Reinecke & Sorgatz, 2009). *Adjuvant drugs*, such as anticonvulsants and antidepressants, play a major role in the treatment of neuropathic pain. In adults,

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<sup>14</sup> Cluster headache is a primary headache with unilateral very intense headache attacks lasting between 15 minutes to 3 hours (IHS, 2004).

they are generally applied for patients with post-zoster neuralgia or diabetic neuropathy (Attal et al., 2010; Dworkin et al., 2010; Moore, Derry, Aldington, Cole, & Wiffen, 2012). It is important to note that those conditions are rare in children. In other pediatric chronic pain conditions, such as headache or abdominal pain, adjuvants have not proven effective (Kaminski, Kamper, Thaler, Chapman, & Gartlehner, 2011; Toldo et al., 2012). On rare occasions and in orphan diseases such as osteogenesis imperfecta, adjuvants may be useful and are sometimes recommended (Drake et al., 2013).

#### Invasive medical interventions

Invasive medical interventions in the treatment of chronic pain conditions have limited evidence – even in adults (Dworkin et al., 2013). In severe cerebral palsy<sup>15</sup>, localized cancer pain or very rare cases of complex regional pain syndrome (CRPS)<sup>16</sup>, the application of intrathecal medications, such as baclofen or opioids, the use of regional anesthesia or sympathetic blocks might be effective in the context of a comprehensive multidisciplinary pain treatment. However, even in those situations, interventions may be effective for only a very limited number of patients (Hoving et al., 2009; Zernikow, Dobe, et al., 2012). Generally, the risk and burden of the interventions have to be carefully balanced against the anticipated success (Zernikow, Dobe, et al., 2012). Furthermore, the lack of evidence should be taken into account when making such a treatment decision.

#### Complementary medical interventions

There are various different complementary therapies that are offered to chronic pain patients – adults and children. The evidence of those interventions is low to moderate at best (Waterhouse, Tsao, & Zeltzer, 2009). For specific pain conditions, limited evidence for acupuncture has been described in adults (Hopton & MacPherson, 2010; Hutchinson, Ball, Andrews, & Jones, 2012; Lee & Raja, 2011; Vickers et al., 2012). Other interventions with at least some type of evidence in children and/or adults

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<sup>15</sup> Cerebral palsy is a neurodevelopmental condition beginning in early childhood and persisting through the lifespan. A non-progressive defect or lesion of the immature brain cause central motor dysfunction, i.e., impairment of muscle tone (mainly spasticity), posture and movement. (Severe) Pain may occur in some patients. (Bax, Goldstein, Rosenbaum, Leviton, & Paneth, 2005)

<sup>16</sup> CRPS is a chronic systemic disease of the limbs characterized by severe pain, swelling, and changes in the skin. It is usually generated by an aberrant response to tissue injury. Three major pathophysiological pathways have been identified: aberrant inflammatory mechanisms, vasomotor dysfunction and maladaptive neuroplasticity. It also has a strong psychological component. (Marinus et al., 2011)

are physiotherapy (Campos, Amaria, Campbell, & McGrath, 2012; Clinch & Eccleston, 2009), aerobic exercise (Stephens et al., 2008; Sullivan, Scheman, Venesy, & Davin, 2012), transcutaneous electrical nerve stimulation (Bennett, Hughes, & Johnson, 2011) and Yoga (Haaz & Bartlett, 2011; Kuttner et al., 2006). In musculoskeletal pain, physiotherapy is an important component in multiprofessional treatment programs (Eccleston et al., 2003; Logan et al., 2012).

In cases where no pathophysiology needs to be modified, either because it does not exist or because pharmacological or medical interventions cannot directly influence the pathophysiology, medical interventions should aim at preventing the patient and/or the family from seeking unnecessary or even harmful medical treatments and diagnostic procedures. One objective of interventions aimed at the biological dimension of chronic pain is to aid the patient and the family to lose their somatic fixation, i.e., to understand that chronic pain is a multidimensional event that cannot be cured solely by pharmacological and medical interventions (Dobe et al., 2013).

### **1.3.2 Psychological interventions**

Even in conditions with a clear underlying pathophysiology, the complementation by psychological treatment and social interventions will be necessary to achieve best treatment outcomes because medical interventions alone will not address the psychological or social dimension of chronic pain (Kashikar-Zuck et al., 2012).

#### General efficacy

Psychological therapy aims at modifying thoughts, beliefs or behavioral responses to symptoms and the effects of illness; it may also have a secondary effect on biological factors (Noto, Kudo, & Hirota, 2010; Thornton, Andersen, Schuler, & Carson, 2009; Vachon-Presseau et al., 2013). The most relevant psychological therapies in the context of chronic pain treatment are cognitive behavioral therapy, acceptance and commitment therapy, biofeedback and hypnotherapy (Eccleston, Palermo, Williams, et al., 2012). Thus far, the efficacy of psychological treatment in pediatric chronic pain is only supported by a low amount of high-quality empirical evidence. A Cochrane Review has summarized the major findings of the available randomized controlled trials (Eccleston, Palermo, Williams, et al., 2012). According to the Cochrane Review, there is good evidence for the efficacy of psychological

interventions in chronic pain patients with various functional pain conditions as well as in patients with underlying physical conditions (Eccleston, Palermo, Williams, et al., 2012). Psychological interventions generally lead to a reduction in pain intensity. However, the reduction in pain-related disability and emotional distress is not consistent across interventions and studies; some studies report a reduction of disability and emotional distress, other studies describe no improvement in these outcome parameters (Eccleston, Palermo, Williams, et al., 2012).

### Cognitive behavioral therapy

Cognitive behavioral therapy aims to identify and alter the child's dysfunctional pain-related beliefs and appraisals (e.g., pain catastrophizing). It also aims to identify and alter negative affect and dysfunctional behavior to increase activity, school attendance or social involvement (Carter & Threlkeld, 2012; Gatchel et al., 2007). Typical cognitive behavioral therapy elements in the treatment of chronic pain are psychoeducation, changing cognitions regarding pain, learning new coping, distraction and relaxation strategies and reinforcement of non-pain behavior, such as attending school or performing daily activities (Palermo, Wilson, Peters, Lewandowski, & Somhegyi, 2009; Sieberg, Huguet, von Baeyer, & Seshia, 2012). Cognitive behavioral therapy has been proven effective in terms of symptom reduction in a group setting (Kröner-Herwig & Denecke, 2002) and as a single intervention (Levy et al., 2010) for children with different pain complaints. Cognitive behavioral therapy elements have also been applied in internet-based interventions with children with various pain problems (Palermo et al., 2009). Palermo and colleagues (2009) demonstrated that a group receiving internet-based cognitive behavioral therapy elements achieved a significantly greater reduction in pain-related disability and pain intensity compared with a group only receiving standard medical care. Furthermore, cognitive behavioral therapy is effective in chronic pain with underlying medical conditions, such as juvenile idiopathic arthritis (Kashikar-Zuck, Swain, Jones, & Graham, 2005; Kashikar-Zuck et al., 2012). Patients increase their ability to cope with pain, reduce disability and depressive symptoms (Kashikar-Zuck et al., 2012).

### Acceptance and commitment therapy

Acceptance and commitment therapy is a specific cognitive behavioral approach primarily targeting the belief system. It is based on the fact that certain negative reactions toward pain, such as negative thoughts or feelings and body sensations, cannot be changed. Acceptance and commitment therapy promotes acceptance of these negative reactions to facilitate engagement in meaningful activities even when they are painful or fear provoking (Hayes et al., 2006). By accepting negative reactions, patients are able to distance themselves from pain and distress and are more likely to perform activities and specifically tasks that are meaningful and valued (Hayes et al., 2006). In a sample of 10- to 18-year-olds, this approach led to reduced pain-related disability and pain intensity; it further improved the perceived functional ability and quality of life and decreased fear of re-injury (Wicksell, Melin, & Olsson, 2007; Wicksell, Melin, Lekander, & Olsson, 2009).

### Biofeedback

Biofeedback therapy can be considered both a psychological and a physiological intervention. This approach gives (mostly visual) feedback on physiological processes that are not directly accessible to a person's perception, such as muscular tension, skin resistance, heart rate, respiratory rate or skin temperature (Sieberg et al., 2012). The continual feedback of physiological processes enhances body awareness, improves self-regulation of pain-related physiological processes (e.g., reduces muscular tension) and can be applied in the training of stress and emotion regulation (Culbert, 1996; Sieberg et al., 2012). Biofeedback is very often applied in the treatment of chronic pain and has proven highly effective in reducing pain intensity in children with recurrent headache or abdominal pain (Eccleston, Palermo, Williams, et al., 2012; Palermo, Eccleston, Lewandowski, Williams, & Morley, 2010; Trautmann, Lackschewitz, & Kröner-Herwig, 2006; Weydert, Ball, & Davis, 2003).

### Hypnotherapy

Hypnosis is another approach in the treatment of chronic pain that has proven effective in reducing pain intensity in children with headache and abdominal pain (Kohen, 2010; Rutten, Reitsma, Vlieger, & Benninga, 2013; Vlieger, Menko-Frankenhuys, Wolfkamp, Tromp, & Benninga, 2007; Vlieger, Rutten, Govers, Frankenhuys, & Benninga, 2012). Hypnotherapeutic interventions include visual imagery,

hypnoanesthesia, distancing, distraction techniques and reframing (Sieberg et al., 2012). These interventions induce a state of relaxation and reduce psychological stress (Gonsalkorale, 2006). They can also control and normalize physical functions and decrease the awareness toward pain signals (Gonsalkorale, 2006; Sieberg et al., 2012).

### **1.3.3 Social interventions**

Given that the family system is an important factor for the maintenance of the chronic pain condition, it is often recommended to be addressed in treatment (Dobe et al., 2013). Therefore, many psychological pain interventions with children include parents or the whole family, however, to a different degree (Eccleston, Palermo, Williams, et al., 2012; Eccleston, Palermo, Fisher, & Law, 2012). Generally, it has proven effective to include parents in the pain treatment (Duarte et al., 2006; Eccleston, Palermo, Fisher, et al., 2012; Palermo et al., 2009). For instance, dysfunctional pain-related beliefs and appraisals of parents as well as negative affect and dysfunctional behavior can be altered by cognitive behavioral therapy (Carter & Threlkeld, 2012). A Cochrane Review indicates that psychological therapies including parents have a positive effect on the child's pain symptoms, the parent behavior as well as the parental mental health condition (Eccleston, Palermo, Fisher, et al., 2012).

In pain therapy, school is another important treatment focus (Eccleston, Palermo, Williams, et al., 2012; Hechler et al., 2013). Some inpatient programs include school for daily therapy sessions (Hechler et al., 2013). In addition, exposure to home school can be one therapy module (Dobe et al., 2013). Because many chronic pain patients have a large number of school absences over a long period of time, they may require intensive training to be re-integrated.

### **1.3.4 Multimodal interventions**

Multidisciplinary pain treatment programs for children combining several of the above described modules "have recently become a standard of care" (Eccleston, Palermo, Williams, et al., 2012, p.5) and are offered in inpatient (Hechler et al., 2013), day-care (Eccleston et al., 2003; Logan et al., 2012) or less intense outpatient settings (Hechler, Martin, et al., 2011). These programs suggest a structured combination of different modules and include professionals from several disciplines (Eccleston et al.,

2003; Hechler et al., 2013; Maynard, Amari, Wieczorek, Christensen, & Slifer, 2009). The included modules and the treatment focus differ between treatment programs. For instance, a program explicitly aimed at children with musculoskeletal pain has more focus on physiotherapy (Eccleston et al., 2003) compared to a program for children with various pain conditions (Hechler et al., 2013). Generally, the combination of treatment modules should match the patient's needs (Leo et al., 2011; Turk, 2005).

An intensive interdisciplinary pain treatment program may be indicated, especially in highly impaired chronic pain patients not responding to outpatient treatment (Hechler et al., 2013; Maynard et al., 2009; Zernikow, Wager, et al., 2012). These intensive pain programs involve all professions in the daily treatment. The treatment team interacts with the patient over a longer period of time and across various situations. For severely impaired patients, this approach is effective not only for primary pain outcomes, such as pain-related disability and pain intensity, but also for a reduction of emotional distress (Eccleston et al., 2003; Hechler et al., 2013; Logan et al., 2012). For less severely impaired patients, an outpatient approach seems to be sufficient and effective (Hechler, Martin, et al., 2011).

### **1.3.5 Treatment matched to the patient's needs**

Given that different treatment approaches are available, the pain therapist needs to make a recommendation for the one approach that is supposed to be the most sufficient and most effective. Furthermore, the recommended treatment needs to be accepted by the patient. Several factors should be taken into account when making a treatment recommendation (Gatchel et al., 2007; Gerbershagen, 1986; Turk, 2005; Wager, Ruhe, et al., 2013): Is there a treatable physiological cause to the pain problem? How severe is the patient's impairment? Is the patient motivated for treatment? Which treatment approaches have been unsuccessful in the past? Which ones have been somewhat successful? Is the suggested treatment option available to the patient, e.g., does the patient's family have the financial and time resources to seek a specific treatment?

To date, no study has yet systematically investigated the match between certain patient characteristics and adequate pediatric pain treatment, i.e., the treatment with the best effectiveness for a subgroup of patients with similar characteristics. Therefore, therapy recommendation for idiopathic chronic pain

is given on the therapist's clinical judgment. This may possibly be adequate when the therapist is highly experienced with pain treatment. However, primary care health professionals or less experienced physicians and therapists will not have enough knowledge and skill to decide on the adequate treatment (Bhatia, Brennan, Abrahams, & Gilder, 2008). One way to simplify treatment stratification is to identify relatively homogenous subgroups of patients in need of a similar treatment (Walker et al., 2012). A screening approach to classify patients into well-defined subgroups would support the treatment decision and ease the stratification process.

In multimodal interdisciplinary treatment programs, it may be warranted to match the choice and focus of treatment modules to the patient's needs (Hechler, Martin, et al., 2011; Hirschfeld et al., 2013). Supposedly, not every patient requires every treatment module. A different treatment focus for subgroups of pediatric pain patients may be necessary (Walker et al., 2012). Therefore, more flexibility in designing treatment may be warranted to really match a multimodal interdisciplinary pain treatment program to the patient's needs.

## 2. Aims of the thesis

The overall aim of this doctoral thesis is to complement the available diagnostic measures for older children and adolescents with chronic pain. Advancement of the assessment of chronic pain comprises two aspects. First, it includes the development and validation of tools measuring single chronic pain parameters. As a validated self-reporting tool for the assessment of sensory and affective pain perception was missing, it was the goal of this thesis to develop such a tool. Once these single measures could be properly described, a second objective comprises the adaption and development of new comprehensive assessment approaches covering different dimensions of the chronic pain problem. These comprehensive approaches may allow the classification of pediatric chronic pain patients and be used for treatment planning or as an outcome measure.

In detail, the aims of the thesis were as follows:

1. To validate a diagnostic tool for the assessment of sensory and affective pain perception (*Pain Perception Scale for Adolescents*)
2. To test the diagnostic utility of the *Pain Perception Scale for Adolescents* for classifying the primary headache diagnoses migraine and tension-type headache
3. To test the applicability of an established severity measure (*Chronic Pain Grading*) in a clinical sample of pediatric chronic pain patients, and to test its ability for treatment planning and as an outcome measure
4. To develop a new classification of pediatric pain patients to identify distinct profiles of adolescents with chronic pain that may be relevant with respect to treatment planning

These goals were achieved by four research projects using data from three patient samples. Sample 1 includes data from a prospective assessment at the German Pediatric Pain Centre from August 2008 to March 2009 ( $N_1=139$ ). Sample 2 contains retrospective data from patients who were treated at the German Pediatric Pain Centre from July 2005 to June 2010 ( $N_2=1242$ ). Sample 3 consists of inpatients only who started treatment at the German Pediatric Pain Centre between November 2009 and July 2011 ( $N_3=83$ ).

In a first study, a tool to assess sensory and affective pain perception, the *Pain Perception Scale for Adolescents*, was adapted and validated in an adolescent clinical sample (Sample 1). In a second study, this tool was applied to a further sample of adolescents with migraine and tension-type headache (subsample of Sample 2). To develop a multidimensional assessment approach, in a third study, an adult classification system (*Chronic Pain Grading*) was applied to a sample of pediatric chronic pain patients (Sample 2). To further develop an approach for treatment stratification and treatment planning, a fourth study focused on developing a new multidimensional approach for subgroup classification (subsample of Sample 2). The stability of subgroups was demonstrated in a cross-validation with an independent sample (Sample 1). Furthermore, treatment outcomes for the identified subgroups were investigated after a standardized treatment program (Sample 3).

The four manuscripts have been submitted to or published in peer-reviewed journals.

### 3. Main body (Journal articles)

The following journal articles were included in this doctoral thesis:

1. **Wager, J.**, Tietze, A.-L., Hamann, M., Schroeder, S., Vocks, S., Kosfelder, J., Zernikow, B., & Hechler, T. (2010). Schmerzempfindung bei Jugendlichen mit chronischen funktionellen Schmerzen: Adaptation und psychometrische Überprüfung der Schmerzempfindungsskala (SES) nach Geissner. *Der Schmerz*, 24(3), 236-250.  
Impact Factor (2010): 1.17; 5-year Impact Factor: 1.0
2. **Wager, J.**, Hirschfeld, G., & Zernikow, B. (2013). Tension-type headache or migraine? Adolescents' pain descriptions are of little help. *Headache*, 53(2), 322-332.  
Impact Factor (2012): 2.524; 5-year Impact Factor: 2.496
3. **Wager, J.**, Hechler, T., Darlington, A. S., Hirschfeld, G., Vocks, S., & Zernikow, B. (2013). Classifying the severity of paediatric chronic pain – An application of the chronic pain grading. *European Journal of Pain*, 17(9), 1393-1402.  
Impact Factor (2012): 3.067; 5-year Impact Factor: 4.267
4. **Wager, J.**, Zernikow, B., Darlington, A. S., Vocks, S., & Hechler, T. Identifying subgroups of pediatric chronic pain patients – A cluster analytic approach. *European Journal of Pain*, *submitted*.  
Impact Factor (2012): 3.067; 5-year Impact Factor: 4.267

### **3.1 Schmerzempfindung bei Jugendlichen mit chronischen funktionellen Schmerzen – Adaption und psychometrische Überprüfung der Schmerzempfindungsskala (SES) nach Geissner.**

**Wager, J.,** Tietze, A.-L., Hamann, M., Schroeder, S., Vocks, S., Kosfelder, J., Zernikow, B., & Hechler, T. (2010). *Der Schmerz*, 24(3), 236-250. doi: 10.1007/s00482-010-0920-4.

#### **Zusammenfassung**

*Hintergrund.* Die Schmerzempfindung ist ein zentraler Aspekt der Multidimensionalität chronischer Schmerzen. Bis dato gibt es kein validiertes Instrument zur Erfassung der Schmerzempfindung für Jugendliche im deutschsprachigen Raum. Ziel dieser Studie ist es, die bei Erwachsenen etablierte Schmerzempfindungsskala von Geissner (SES) für Jugendliche mit chronischen Schmerzen zu überprüfen und zu adaptieren, um ein Messinstrument zur Diagnostik und Evaluation von Behandlungserfolgen zur Verfügung zu stellen.

*Material und Methoden.* Anhand eines Samples mit 139 Jugendlichen wurde eine Hauptkomponentenanalyse mit anschließenden Reliabilitäts- und Itemanalysen durchgeführt. Zur Überprüfung der Validität wurden Alters- und Geschlechtseffekte, Korrelationen mit schmerzverwandten Konstrukten, Unterschiede zwischen Behandlungsgruppen (ambulant vs. stationär) und Übereinstimmungen zwischen Jugendlichen und Eltern analysiert.

*Ergebnisse.* Die durchgeführten Analysen ergaben eine 2-faktorielle Lösung mit einem affektiven und einem sensorischen Faktor; 3 weitere sensorische Einzelitems wurden zusätzlich in die Endversion aufgenommen. Die Skalen weisen eine gute interne Konsistenz auf. Innerhalb der Validitätsanalysen zeigen sich hypothesenkonforme Beziehungen zu Schmerzcharakteristika, emotionalen und kognitiven Variablen sowie zu schmerzbezogener Beeinträchtigung. Ambulant und stationär behandelte Jugendliche unterscheiden sich bezüglich der affektiven Schmerzempfindung. Die Übereinstimmung zwischen Eltern und Jugendlichen ist hoch.

*Schlussfolgerung.* Mit dem adaptierten Fragebogen steht erstmalig ein validiertes deutschsprachiges Instrument zur Erfassung der Schmerzempfindung bei Jugendlichen mit chronischen Schmerzen zur

Verfügung (Schmerzempfindungsskala für Jugendliche, SES-J). Aufgrund seiner guten psychometrischen Charakteristika und Praktikabilität eignet sich dieser Fragebogen für die klinische Anwendung.

## **Abstract**

*Background.* Pain perception is a central aspect of the multidimensional model of chronic pain. Up to now, validated measurement tools are lacking in the German language for measuring pain perception in adolescents. The aim of this study was to examine and adapt the well-established Pain Perception Scale for Adults by Geissner (SES) for use in adolescents with chronic pain to provide a measure for clinical diagnosis and evaluation of treatment effects.

*Material and methods.* Principal component, reliability and item analyses were conducted on a sample with 139 adolescents. To test validity, age and sex effects, correlations with pain-related constructs, differences between treatment groups (inpatients vs outpatients) and concordance between adolescents and their parents were analysed.

*Results.* Findings support a two-factor solution with one affective and one sensory factor; three additional sensory items were included in the final version. The scales show good internal consistency. Consistent with hypotheses, we found significant correlations with pain characteristics, emotional and cognitive variables as well as pain-related disability. Inpatients and outpatients show a significant difference in affective pain perception. Concordance between parents and adolescents was high.

*Conclusion.* With this questionnaire, there is now a validated German assessment tool to measure pain perception in adolescents with chronic pain (Pain Perception Scale for Adolescents, SES-J). Due to its practicability, it is suitable for clinical application.

### **3.2 Tension-type headache or migraine? Adolescents' pain descriptions are of little help.**

**Wager, J., Hirschfeld, G., & Zernikow, B. (2013).** *Headache*, 53(2), 322-332. doi: 10.1111/j.1526-4610.2012.02224.x.

#### **Abstract**

*Objective.* The aim of this study was to investigate the utility of pain descriptors (pain quality, pain intensity) assessed in a questionnaire to discriminate tension-type headache (TTH) from TTH plus migraine in a sample of adolescents.

*Background.* Epidemiological studies assess pain characteristics via questionnaire and estimate prevalence rates based on these pain descriptions. According to International Headache Society criteria, the subjective pain quality and intensity for TTH and migraine differs and therefore should be able to discriminate the 2 diagnoses. The discriminative ability between TTH and TTH plus migraine may be a special challenge.

*Design and methods.* One hundred twenty-two adolescents with pure TTH and 110 adolescents with TTH plus migraine aged 11-18 years presenting to a tertiary pediatric pain clinic were included in the study. Questionnaire reports of pain intensity and quality were compared with physician's diagnosis as the gold standard. Mean differences as well as receiver operating characteristics were analyzed.

*Results.* Adolescents with TTH plus migraine reported more pulsating and less intense pain compared with pure TTH. Receiver operating characteristic analysis indicated that pain descriptors did not discriminate between groups. Diagnostic utility of descriptors was similarly low for older adolescents and parental proxy reports.

*Conclusions.* Pain intensity and quality assessed by questionnaires are not suitable to discriminate TTH from TTH plus migraine. This may lead to inaccurate prevalence estimates in epidemiological studies and may mislead practitioners in forming diagnostic hypotheses. The exclusion of these pain descriptors in questionnaires should be considered. More research systematically assessing the diagnostic utility of verbal pain descriptors in primary care and epidemiological samples is needed.

### **3.3 Classifying the severity of pediatric chronic pain – An application of the Chronic Pain Grading.**

**Wager, J.,** Hechler, T., Darlington, A. S., Hirschfeld, G., Vocks, S., & Zernikow, B. (2013). *European Journal of Pain*, 17(9), 1393-1402. doi: 10.1002/j.1532-2149.2013.00314.x.

#### **Abstract**

*Background.* The chronic pain grading (CPG), a standard approach to classify the severity of pain conditions in adults, combines the characteristics of pain intensity and pain-related disability. However, in children and adolescents, the CPG has only been validated in a school sample, but not in the actual target population, i.e., clinical populations with pain.

*Methods.* In the present study, we applied the CPG to a tertiary sample of adolescents with chronic pain (n = 1242). Construct validity, sensitivity to change and prognostic utility were examined.

*Results.* Results indicate that most adolescents were equally classified into the three higher severity grades. Higher CPG classification was associated with more pain locations, higher pain frequency, longer pain duration, extensive use of health care and more depressive symptoms. Adolescents with a high CPG received recommendations for inpatient treatment more often; however, the prognostic utility for therapy recommendation – as operationalized in this study – was low. Sensitivity to change was assessed via reassessment at follow-up for a subsample of 490 adolescents. The majority of adolescents improved to a less severe CPG; changes were more common in the high severity range.

*Conclusion.* The CPG may be applied to adolescent tertiary care samples and to assess outcomes in clinical trials. However, in this study it was not appropriate to assign adolescent patients to different treatment options. Future work should focus on developing a comprehensive assessment tool for assigning patients to different treatments.

### **3.4 Identifying subgroups of pediatric chronic pain patients – A cluster analytic approach.**

**Wager, J.,** Zernikow, B., Darlington, A. S., Vocks, S., & Hechler, T. *European Journal of Pain*, submitted.

#### **Abstract**

*Background.* Pediatric chronic pain patients are a heterogeneous group. Patients respond differently to standardized treatments.

*Objectives.* This study aimed to identify subgroups of adolescent chronic pain patients who were distinguishable by specific patient and pain characteristics.

*Methods.* Within a pediatric sample (Sample A,  $N_A=266$ ), subgroups were identified by a cluster analytic approach. The stability of clusters was tested in a cross-validation with a second independent sample (Sample B,  $N_B=108$ ). In a third sample (Sample C,  $N_C=83$ ), differences in change scores of the outcome parameters pain intensity, pain-related disability and school absences were tested between cluster subgroups twelve months after a standardized treatment.

*Results.* Five cluster subgroups with distinct pain problems were identified. They differed in pain intensity, school absence, pain-related disability, passive pain coping and affective pain perception. Cluster 1 and Cluster 2 reported overall moderate pain problems and only differed with regard to passive pain coping, which was low in Cluster 1 and moderate in Cluster 2. Patients in Cluster 3 reported severe pain problems, including high pain-related disability and frequent school absences. Patients in Clusters 4 and 5 reported very severe pain problems; while Cluster 4 patients reported low school absences, Cluster 5 patients had very frequent school absences. A cross-validation of the cluster solution with an independent sample indicated its stability ( $Kappa=0.64$ ). Concerning treatment outcome after a standardized multidisciplinary treatment program, the five subgroups displayed distinct patterns in treatment outcome. The mean change scores were significantly different between subgroups ( $F(4,78)=5.88; p=.017$ ). Cluster 5 showed the best benefit from treatment.

*Conclusions.* The identified patient subgroups proved stable across samples. Depending on the subgroup classification, patients differed in therapy outcome. These results offer initial hints for the need of subgroup-specific treatment planning.

## 4. General discussion

The overall aim of this doctoral thesis was to complement and further develop the available diagnostic measures for older children and adolescents with chronic pain. The advancement of the pain assessment included two aspects: First, the adaption and validation of a tool measuring the sensory and affective pain perception; and second, the adaption and development of comprehensive assessment approaches covering different dimensions of the chronic pain problem. These comprehensive approaches were tested for their utility as a classification system, regarding their relevance for treatment planning and as an outcome measure in clinical trials.

### 4.1 Summary and integration of results

As discussed in the introduction section, although there is a paucity of German questionnaires available to assess chronic pain in older children and adolescents, certain additions are necessary to complement the available diagnostic measures. By covering the above-mentioned aims, this doctoral thesis offers an addition to the already established assessment tools.

#### Assessment of sensory and affective pain perception

The *Pain Perception Scale for Adolescents*, a German language tool for the assessment of sensory and affective pain perception in adolescents, was validated within the scope of this doctoral thesis (→ Article 1). This self-report questionnaire is a measure to improve the assessment of the biological and psychological dimensions of chronic pain. Concerning the biological dimension of pain, it was demonstrated that this tool allows a valid and reliable assessment of sensory pain perception, specifically pain with a rhythmic or pulsating quality. Although stable factors for other sensory pain sensations could not be identified, three single items describing the pain quality were included in the final version of the *Pain Perception Scale for Adolescents* (pressing, burning, stabbing) to allow information for differential diagnoses of neuropathic pain and tension-type headache (Baron & Tölle, 2008; Bennett et al., 2007; IHS, 2004). The pulsating and pressing pain qualities are considered specifically important in diagnosing primary headaches (IHS, 2004). However, these diagnostic criteria, developed based on adult research, did not prove helpful in diagnosing children's primary headaches

(→ Article 2). Sensory pain perception in children did not match the criteria developed for adults for primary headache. This finding underlines the important knowledge that findings from chronic pain in adults cannot be readily transferred to children and adolescents. Due to their developmental stage, children and adolescents may differ from adults with regards to their pain perception or their ability to describe sensory sensations (Maytal, Young, Shechter, & Lipton, 1997). Therefore, assessment tools and diagnostic criteria need to be developed and validated for this specific age group. If not done so, this may have detrimental effects, e.g., prevalence data on primary headache in children based on the adult criteria may differ from the actual prevalence of these conditions.

The *Pain Perception Scale for Adolescents* also assesses affective pain perception (→ Article 1). Therefore, it offers a brief tool to measure pain-specific affect. Measuring affective pain perception is one way to minimize the overlap between the symptoms of emotional distress and chronic pain (see comprehensive discussion in paragraph 1.1.3 “Multidimensionality of chronic pain...”, subheading “Psychological aspects of chronic pain”). The affective component of pain perception captures the direct emotional impact of pain on the individual (Geissner, 1996) and is a good way to measure the individual psychological burden and the concurrent suffering due to pain.

#### Development and adaption of comprehensive diagnostic approaches

Besides the development and validation of single measures, it is warranted to provide measures including the different dimensions of the bio-psycho-social model of chronic pain. Previous research demonstrated that such an approach can be used to identify subgroups of children with chronic pain (Vowles et al., 2009; Walker et al., 2012). In the scope of this doctoral thesis, two different approaches to derive classification systems are presented. On the one hand, a very brief approach, the *Chronic Pain Grading*, only including pain intensity and disability and not covering psychological factors, was adopted for use in a pediatric clinical sample and was demonstrated to be useful in giving a valid description of pain severity and as an outcome measure (→ Article 3). However, the *Chronic Pain Grading* did not prove useful in treatment stratification. One reason may be the missing psychological dimension. Therefore, an advancement of this very brief classification system was developed, adding the psychological parameters affective pain perception and passive pain coping (→ Article 4). A

multidimensional cluster solution identified five distinct patient groups. These patient groups displayed distinct differences in long-term outcome. The results of the cluster solution are a first step in the development of a comprehensive self-reporting assessment approach covering biological, psychological and social aspects of chronic pain that may be useful for treatment planning.

#### **4.1.1 The subjectivity of pain**

The description of the pain experience in older children and adolescents is the central focus of this doctoral thesis. As mentioned in the introduction, the assessment of chronic pain can never be truly objective because of its subjective nature (Coghill et al., 2003; Turk & Okifuji, 1999). Objective or semi-objective measures will never give information on the subjective experience of the individual's pain problem. To describe the unique nature of an individual's pain problem, the use of self-reporting of the subjective pain experience is unavoidable (Coghill et al., 2003). The necessity of self-reported pain has been highlighted in several works. Consistently, it has been demonstrated that reports on physical perceptions, mood and social interactions differ greatly between children and their parents, whereas observable behavior-based parameters have a better agreement between self- and proxy-report (Hourigan, Goodman, & Southam-Gerow, 2011; Jokovic, Locker, & Guyatt, 2004; Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005; Peterson & Noel, 2012; Verrips, Vogels, Ouden, Paneth, & Verloove-Vanhorick, 2000). It may be difficult for a parent to gain insight into their child's social and emotional functioning (Verrips et al., 2000). Understanding someone else's pain requires sensitivity and empathy, which is influenced by many contextual factors, previous events and experiences (Goubert et al., 2005). Understanding the own child may be specifically difficult during adolescence when children generally exchange less information concerning their personal situation with their parents (Keijsers, Branje, Frijns, Finkenauer, & Meeus, 2010; Smetana, Metzger, Gettman, & Campione-Barr, 2006). This may cause a lack of insight for parents into their children's lives (Jokovic et al., 2004). Disagreement between self- and proxy-reports suggests that the pain experience assessed by a child is a different construct than the pain experience described by the parents, i.e., self- and proxy-report measure different realities or perspectives (Jokovic et al., 2004; Verrips et al., 2000). Therefore, it is very important to ask the child directly about his/her pain experience.

#### **4.1.2 Benefits of comprehensive pain assessment**

Within the scope of this doctoral thesis, the available self-reporting measures for chronic pain were complemented, so that the child can describe the subjective pain experience in its entirety, including biological, psychological and social aspects. In addition to the high validity of self-reports, this comprehensive assessment serves several additional goals. First, a comprehensive assessment helps a patient to feel safe, understood and taken seriously (Wager, Kriszio, et al., 2013). Especially children with chronic pain often have a long medical history (Zernikow, Wager, et al., 2012); they have experienced a great deal of unsuccessful treatment, false promises, or have even experienced accusation that their pain is not real and that they are lying about the pain (Zernikow, Wager, et al., 2012). Many patients have most likely lost their trust in the health care system (Dell'Api, Rennick, & Rosmus, 2007). A diagnostic assessment triggering a feeling of safety and understanding is essential for a good relation between patient and pain therapist. Second, asking patients in detail about their pain condition even may help them to better understand their pain and factors influencing it. Most patients are not aware of the multidimensionality of chronic pain when they first visit a specialist. Being asked about different psychological and social components may help to get a feeling for the interrelationship before even being started with psychoeducation. Third, good pain assessment is essential to plan adequate treatment (Schroeder et al., 2010). Therefore, the pain therapist needs to understand the cause of suffering and the effect of chronic pain on the patient's life (McCracken & Turk, 2002; Turk & Okifuji, 1999).

#### **4.1.3 Subgroups of chronic pain patients**

Even though the experience of pain is subjective to each individual, there are still groups of chronic pain patients who share common features and patterns in their pain experience (→ Article 4). For instance, there is one group that is characterized by frequent school absences and high pain-related disability, along with low affective pain perception and moderate pain intensity and passive pain coping. Another group displays a different pattern; they are generally experiencing a more severe pain problem with high pain intensity, highly affective pain perception and moderate pain-related disability. Importantly, compared to the first mentioned group, patients classified into the second group have a

remarkably lower frequency of school absences. Although they experience high pain intensity and are also impaired in their daily activities, they still visit school. Within the two subgroups described, characteristic pain profiles are relatively homogenous.

In addition to subgroups of pediatric patient with chronic pain identified within the scope of this doctoral thesis, there are other approaches that detected individuals with similar pain profiles within a heterogeneous group of pediatric pain patients (Huguet & Miro, 2008; Vowles et al., 2009; Walker et al., 2012). Walker et al. (2012), for example, identified three subgroups of children with chronic abdominal pain. These groups are described as 1) high pain dysfunctional, 2) high pain adaptive and 3) low pain adaptive. The first group (high pain dysfunctional) reported high levels of abdominal pain, experienced their pain as highly threatening, reported extremely high levels of pain catastrophizing and had little ability to cope. The second group (high pain adaptive) had a comparably high level of abdominal pain, but they experienced pain as less threatening, had less catastrophizing thoughts and a greater confidence in their ability to cope with the pain. A direct comparison of these two groups revealed that the second group reported lower levels of negative affect and impairment compared to the first group. Differences between these groups could also be identified at follow up; the first group experienced more symptoms of abdominal pain compared to the second group. According to these findings, differences in the long-term outcome between subgroups of chronic pain patients were also detected in this doctoral thesis. These findings demonstrate the clinical relevance of the identification of subgroups.

#### **4.1.4 Implications of chronic pain subgroups**

To evaluate chronic pain as a subjective phenomenon and at the same time recognize that there are certain patterns reoccurring in individuals, means important additions to the understanding and treatment of chronic pain in children. The identification of subgroups of pediatric chronic pain patients may be valuable for several applications.

First, the identification of subgroups may help to generate different models for the development and maintenance of chronic pain for certain subgroups (Turk, 2005). There are various factors making chronic pain more likely in a child. A risk factor for developing chronic pain after a surgical procedure

is pain unpleasantness, i.e., negative affect associated with the acute pain, whereas a risk factor for maintaining the pain condition is anxiety sensitivity (Pagé, Stinson, Campbell, Isaac, & Katz, 2013). Cross-sectional epidemiological research has identified several factors associated with chronic pain in children. Those factors are depression and anxiety symptoms, parental chronic pain or psychopathology, smoking, drinking alcohol, overweight/obesity and adverse life events (Deere et al., 2012; Hoftun, Romundstad, & Rygg, 2012; Hoftun et al., 2013; Seshia, 2012). Epidemiological longitudinal data to predict chronic pain in children does not exist. Therefore, it is not known if subgroups of chronic pain patients have different risk factors (Hoftun et al., 2012). However, research efforts concerning this question are low and definitely require further investigation because identifying risk factors for certain subgroups of chronic pain may increase the predictive quality. In particular, psychosocial and environmental factors that influence the development of chronic pain should receive more attention (King et al., 2011).

Second, once a better understanding of risk factors and the development of pain in certain subgroups is accomplished, prevention programs can be based on this knowledge (Hoftun et al., 2012; King et al., 2011; Miro et al., 2007). The children most in need of certain medical or psychological interventions can be identified (King et al., 2011). Knowledge of these risk factors can also increase the general awareness toward pediatric chronic pain in the general population and in health care professionals.

Third, identifying subgroups of children with chronic pain can help to optimize referral patterns. As mentioned in the introduction, between 30% and 50% of all children and adolescents with chronic pain seek help in the health care system (Ellert et al., 2007). Those are generally the children with a more severe pain problem (Huguet & Miro, 2008). Primary care pediatricians or general practitioners are usually the first contact for a child with chronic pain (Bhatia et al., 2008; Perquin et al., 2001; Toliver-Sokol et al., 2011). It is up to them to treat the patient or, in case they do not expect their treatment to be effective, they need to refer the patient to another health professional. A recent study revealed that the number of patients with chronic pain symptoms in pediatric inpatient settings is increasing (Coffelt et al., 2013). Knowledge on chronic pediatric pain in primary care is low (Bhatia et al., 2008). With a low amount of knowledge, it is very difficult to apply a good treatment or to make good referral

recommendations. These problems can also be assumed in the German health care system. In a recent study, we demonstrated that it takes a long time for children to present to a specialized treatment center (Zernikow, Wager, et al., 2012). To optimize these referral patterns, brief and easy to apply screening tools detecting subgroups with specific treatment needs, have to be developed. These tools can serve primary care physicians to classify the patient's pain problem severity to make a treatment recommendation based on predefined guidelines.

Fourth, the identification of chronic pain patient subgroups may be an important step for the further development of pain treatment. As described in the introduction, there is a paucity of treatment modules aimed at the different dimensions of chronic pain. Multimodal interdisciplinary treatment programs usually follow a predefined structure of treatment modules (Eccleston et al., 2003; Hechler et al., 2013; Maynard et al., 2009). However, it can be assumed that the need for certain modules depends on the individual pain problem. As part of this doctoral thesis has shown (→ Article 4), subgroups of pediatric pain patients react very distinctly to a standardized inpatient treatment. Whereas some greatly benefit, others only display moderate changes in outcome parameters. This might be a hint for the necessity of treatment modulation for certain subgroups. As chronic pain subgroups share characteristic pain features, it would be efficient to develop treatment programs aimed at the subgroup's needs. Subgroup characteristics may be an important inspiration for tailoring treatment programs and for establishing a subgroup-specific therapy focus. Subgroup-specific treatment programs may help to further increase effectiveness of treatment.

## **4.2 Future perspectives**

This doctoral thesis added to the available diagnostic measures for older children and adolescents with chronic pain and, by identifying subgroups of pediatric chronic pain patients, established important motivations for the further modification of treatment approaches. However, results are not yet satisfying. New treatment concepts based on subgroup characteristics need to be developed. Once those treatment concepts are established, the efficacy of subgroup-tailored treatment needs to be investigated to find out whether the classification system assigns patients to the optimal treatment option. To test treatment efficacy in a randomized controlled trial, outcomes need to be compared

between patients who underwent the treatment suggested based on the classification system and those patients who received a different treatment than their classification supported.

Possibly, the classification approach developed within the scope of this doctoral thesis needs further modification to better assign patients to treatment options or to predict their course. One aspect not considered in the current cluster solution is parents or family, although experts agree that social factors are of utmost importance in the experience of chronic pain (Goubert et al., 2006). Importantly, when developing a tool, the balance between completeness and feasibility needs always to be deliberated. Therefore, future research should investigate whether adding family parameters increases the quality of subgroup classification. In case they greatly add to the quality, their inclusion should be considered. Once the classification system is extensively validated and applied in specialized care, an expansion and adaption of this classification system for use in primary care seems worthwhile. In this setting, it could be used as a screening tool to detect children in need of specialized treatment or other specific treatment options.

### **4.3 Conclusion**

This doctoral thesis offers an addition to already established diagnostic measures for older children and adolescents with chronic pain. The *Pain Perception Scale for Adolescents* and the *Chronic Pain Grading* can be considered valid approaches to measure the pain perception and pain problem severity in pediatric clinical samples. These tools are adequate for describing children with chronic pain and offer the child the opportunity to report his/her pain experience in detail. It is of importance to not just transfer knowledge from adults to children, but to perform independent research and to develop age-specific ideas, as there are relevant differences. The classification criteria for primary headaches, for example, cannot be readily transferred from adults to children.

The final output of this doctoral thesis is a bio-psycho-social classification approach that identifies subgroups of children with chronic pain. These subgroups display distinct outcome patterns after a standardized treatment. The results offer hints for the need for different treatment approaches and are a first step toward the development of such subgroup-tailored treatment.

## 5. References

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**Ich danke...**

... Boris Zernikow für die Unterstützung bei meiner Dissertation, sowie für die kritische und konstruktive Reflexion. Ich danke ihm auch für den Raum, den er mir gegeben hat, um eigene Ideen zu entwickeln und zu verwirklichen.

... Tanja Hechler für die tolle Heranführung an das wissenschaftliche Arbeiten, für ihre kritische und konstruktive Rückmeldung, die mir geholfen hat, meine Arbeit immer weiter zu verbessern. Mit ihrem Optimismus hat sie mir zudem viel Kraft gegeben, um auch bei Rückschlägen am Ball zu bleiben.

... Silja Vocks für die sehr gute Betreuung meiner Dissertation und für ihre hilfreichen, sorgfältigen und detaillierten Rückmeldungen.

... meinen Kollegen (Pia Schmidt, Ann-Kristin Ruhe, Anna-Lena Tietze, Gerrit Hirschfeld und Michael Otto) für ihre Unterstützung. Sie machen das Arbeiten im Büro immer wieder zu einem sehr schönen Erlebnis.

... meiner Familie und meinen Freunden für ihre Unterstützung und für ihre Geduld. Besonders danke ich ihnen dafür, dass sie mich erinnert haben, Pausen zu machen, und wir diese Pausen mit schönen gemeinsamen Aktivitäten gefüllt haben.

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