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CHILDREN AND ADOLESCENTS WITH CHRONIC PAIN: PARENTAL FACTORS, FUNCTIONING, AND NEURODEVELOPMENTAL COMORBIDITY

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Children and adolescents with chronic pain: parental factors, functioning, and neurodevelopmental comorbidity

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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"Occurrences in this domain are beyond the reach of exact prediction because of the variety of factors in operation, not because of any lack of order in nature."

Albert Einstein

For the participating children and parents.

ABSTRACT

Background: Pediatric chronic pain affects between 11 and 38% of all children. Although pain may result from injury or disease, the cause of chronic pain is commonly unclear. The interaction between biological, psychological, and social aspects has been emphasized as key to the understanding of the chronic pain experience, as well as risk and resilience factors. Pediatric chronic pain may result in significant impairment affecting both child and family functioning, and addressing family factors such as parental distress and protective behaviors, are generally considered important to pediatric chronic pain management. However, there is still a need to identify resilience factors that can be targeted in parental support programs, and to develop and evaluate effective parent support interventions. The complexity of the pain experience in pediatric chronic pain is well known with a large number of patients suffering from co-occurring disorders such as depression or insomnia. However, despite a considerable number of clinical observations suggesting an elevated prevalence of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) among children with chronic pain, and similarities in terms of clinical correlates, the empirical support has been scarce. More research on the co-occurrence of pediatric chronic pain, ADHD, and ASD, including relationships with functioning, is therefore warranted.

Purpose and aims: The purpose of the present research project was to identify and assess parental and child factors of importance for functioning and treatment effects in pediatric chronic pain. More specifically, the aims of the project were to: validate an instrument for parental psychological flexibility (Study I); evaluate the effects of a brief parental ACT-intervention on parent outcomes (Study II); assess the prevalence of clinically significant traits and symptoms of ASD and ADHD in children, and relations to pain- and demographic variables (Study III); and, to explore the relationships between traits and symptoms of ASD and ADHD, functioning, and health-related quality of life (HRQoL) (Study IV).

Methods: In Study 1, utilizing a cross-sectional design, the Parent Psychological Flexibility Questionnaire (PPFQ) was translated and psychometrically evaluated in a sample of parents ($n=263$) of children with chronic pain using principal component analysis (PCA), correlation and regression analyses, and analysis of internal consistency. In Study II, the effects of individual and group ACT-interventions for adolescents ($n=48$) with chronic pain, and a brief support program for their parents ($n=28$), were evaluated using a randomized (group/individual) uncontrolled pilot design and non-parametric analyses of differences between groups and over time. In Study III, the prevalence of clinically significant ASD-traits and ADHD-symptoms was evaluated in a descriptive cross-sectional study on children with chronic pain ($n=146$) and their parents ($n=146$). Differences in pain- and demographic variables between children below and above cutoff for clinically significant traits and symptoms of ADHD or ASD were also assessed. Study IV, using the same sample as Study III, examined the relationships between ASD-traits and ADHD-symptoms, functioning (depression and pain interference), and HRQoL in correlation- and regression analyses and with independent t-tests, and assessed the indirect effects of insomnia and psychological inflexibility on the relationships between ASD-traits or ADHD-symptoms as predictors and functioning and HRQoL as dependents.

Results: In Study 1, results supported a three-factor solution for the PPFQ with 10 items (PPFQ-10), showing good internal consistency and explaining a significant amount of

variance in the criteria variables anxiety (29%) and depression (35.6%). In Study II, significant improvements in parental pain reactivity and psychological flexibility were found with clinically significant changes in the direction of better functioning for 54-76% of parents, with no differences between individual and group formats. In Study III, 13.7% of the sample presented with clinically significant ASD-traits and 19.9% of the sample presented with clinically significant ADHD-symptoms. The combined prevalence of clinically significant ASD/ADHD-traits and symptoms was 26%. Children with clinically significant ASD-traits were more likely to be girls and clinically significant ADHD-symptoms showed no gender differences. In Study IV, children with clinically significant ASD-traits and ADHD-symptoms presented with significantly higher levels of depressive symptoms and pain interference, and significantly lower HRQoL, compared to the rest of the sample. ASD-traits and ADHD-symptoms explained a significant amount of variance in pain interference and depressive symptoms, as well as in HRQoL. Psychological inflexibility was shown to mediate the influence of both ADHD-symptoms and ASD-traits, and insomnia the effect of ADHD-symptoms, on depression, pain interference, and HRQoL.

Conclusions: Although tentative, the results suggests the utility of addressing parental psychological flexibility in relation to pediatric chronic pain. However, more research is warranted and future studies should e.g. evaluate the predictive utility of the PPFQ for child treatment outcomes, and evaluate if parental support programs that increase parental psychological flexibility also have positive effects on the children. Also, the results provide empirical support regarding elevated levels of clinically significant ADHD-symptoms and ASD-traits in pediatric chronic pain, and illustrate significant relationships between such traits and symptoms and functioning in children. Children with debilitating chronic pain, particularly girls, may be at risk for having a comorbid, and possibly undetected high-functioning neurodevelopmental disorder. Results thus suggest the utility of screening for neurodevelopmental disorders in children with chronic pain, and may indicate insomnia, and psychological flexibility as potential treatment targets to improve functioning and HRQoL. The results also warrant further research to e.g. validate these findings in larger studies, evaluate the utility of tailored interventions, and examine the shared neuropathophysiology of chronic pain and neurodevelopmental disorders, including dopamine function and sensory abnormalities.

LIST OF SCIENTIFIC PAPERS

- I. Wiwe Lipsker, C., Kanstrup, M., Holmström, L., Kemani, M., Wicksell, RK. (2016). The Parent Psychological Flexibility Questionnaire (PPFQ): Item Reduction and Validation in a Clinical Sample of Swedish Parents of Children with Chronic Pain. *Children*, 3(4): 32.
- II. Kanstrup, M., Wicksell, RK., Kemani, M., Wiwe Lipsker, C., Lekander, M., Holmström, L. (2016) A Clinical Pilot Study of Individual and Group Treatment for Adolescents with Chronic Pain and Their Parents: Effects of Acceptance and Commitment Therapy on Functioning. *Children*, 3(4): 30.
- III. Wiwe Lipsker, C., Bölte, S., Hirvikoski, T., Lekander, M., Holmström, L., Wicksell, RK. (2018). Prevalence of autism traits and attention-deficit hyperactivity disorder symptoms in a clinical sample of children and adolescents with chronic pain. *Journal of Pain Research*, 11:2827—2836.
- IV. Wiwe Lipsker, C., Hirvikoski, T., Bölte, S., Lekander, M., Holmström, L., Wicksell, RK. (Submitted for publication). The relationships between autistic traits and symptoms of ADHD, health-related quality of life, and functioning in pediatric chronic pain.

ASSOCIATED PAPER NOT INCLUDED IN THE THESIS

- I. Wiwe Lipsker, C., von Heijne, M., Bölte, S., Wicksell, RK. (2018). A case report and literature review of autism and attention deficit hyperactivity disorder in paediatric chronic pain. *Acta Paediatrica*, 107(5):753-758.

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LIST OF ABBREVIATIONS

ACT	Acceptance and commitment therapy
ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CES-DC	Center for Epidemiological Studies – Depression scale for Children
CNS	Central nervous system
CPP	Chronic primary pain
CBT	Cognitive behavioral therapy
FPD	Functional pain disorders
HPA	Hypothalamic-pituitary adrenal axis
HADS	Hospital Anxiety and Depression Scale
ISI	Insomnia Severity Index
LPQ	Lübeck Pain Questionnaire
NRS	Numerical Rating Scale
PPFQ	Parental Psychological Flexibility Questionnaire
PII	Pain Interference Index
PRS	Pain Reactivity Scale
PRS-P	Pain Reactivity Scale-Parent
PedsQL	Pediatric Quality of Life Inventory
PTSD	Post-traumatic stress disorder
PCA	Principal component analysis
PIPS	Psychological Inflexibility in Pain Scale
RFT	Relational Frame Theory
SMD	Sensory modulation disorders
SOR	Sensory over-responsivity
SRS	Social Responsiveness Scale
IASP	The International Association for the Study of Pain
PedIMMPACT	The Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
WHO	The World Health Organization
ICD-11	The 11 th revision of the International Classification of Diseases

1 INTRODUCTION

What is pediatric chronic pain and who has it? Despite being a major health problem, many questions regarding the experience of pain, the possible existence of an overall clinical phenotype in pediatric chronic pain, and how to effectively treat it, still remain unanswered. During my years working as a clinical psychologist with children¹ suffering from chronic pain and their parents at a tertiary pain clinic, I have seen the debilitating effects of chronic pain up close in its many different expressions, but also with important similarities across the patients and their parents. In my clinical work, it became increasingly clear that pediatric chronic pain is *not* primarily a condition that resides within the individual, but occurs in, and interacts with, a larger context such as family, parents, friends, and school. Based on my previous work with assessment and screening of attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), I observed in some of our chronic pain patients what I perceived were traits and behavioral difficulties indicative of ADHD and high functioning ASD. Over time, my impression was that the occurrence of these manifestations was relatively larger among our pediatric pain patients, than the normal prevalence of these disorders. In terms of clinical manifestations, in particular one child with severe chronic pain and comorbid ADHD and ASD [1], sparked a sense of urgency and interest in finding out more about the prevalence of neurodevelopmental disorders in pediatric chronic pain, and any relationships with functioning.

A clinician at heart, I have, with the support and encouragement of dedicated and knowledgeable colleagues and faculty funding, been given the opportunity to study these topics related to the context of pediatric chronic pain. In relation to the larger context, by studying aspects of parental functioning; and in relation to the individual, by studying the prevalence of traits and symptoms of ADHD and ASD in children, and relationships with functioning. Albeit a modest contribution to a large picture puzzle, it is my hope that my research will be of relevance in further development of methods to help children and adolescents that suffer from chronic pain.

Stockholm, January 2019

¹ The terms "child" and "children" here and throughout also includes adolescents (up to the age of 18), unless detailed specification is required or given.

2 BACKGROUND

2.1 PEDIATRIC CHRONIC PAIN

Chronic pain in children, most often defined from a temporal point of view as pain that persists or recurs for more than (usually) three months, may arise as a result of a chronic health condition, such as e.g. arthritis or sickle cell disease [2]. However, in the context of pediatric chronic pain, the terms functional and idiopathic are also well known and typically refer to a situation where the biological origin or pathophysiological mechanism is unclear [3, 4].

The many pain sub-diagnoses (e.g. chronic daily headaches, functional abdominal pain, fibromyalgia, etc.) that are fitted under the diagnostic umbrella of functional pain disorders (FPD) further reflect the heterogeneity of the pain expressions and possibly also the diagnostic uncertainty embedded in the FPD-label [5, 6]. Regardless of classification, however; functional, unexplained, or idiopathic pain, affects many children, as noted by several studies [6-8], but specific epidemiologic data on the broader construct of FPD is scarce, in part likely due to the uncertainty regarding a clear operationalization of overall FPD [9].

2.1.1 Definition and conceptualization of chronic primary pain - a classification for a "new" era

In 2016, a Task Force appointed by the International Association for the Study of Pain (IASP) and the World Health Organization (WHO), suggested a new systematic classification of chronic pain for the 11th revision of the *International Classification of Diseases* (ICD-11) [10] that has now been incorporated into the new ICD-11 under the label "Chronic primary pain" (CPP), with an appending classification just recently (January 2019) released by Nicholas et. al. [11]. In accordance with the previous definition of chronic pain [2], it is suggested that chronic pain should be defined as persistent or recurrent pain, lasting longer than 3 months. However, and different from the old perspective, the proposed CPP-diagnosis does not classify pain as defined by either a pathophysiological-, or a psychological cause. Instead, CPP is conceptualized as a complex disease with psychological, biological, and social factors interacting to produce the chronic pain experience [11]. This corresponds with the widely recognized biopsychological model of chronic pain [12], and is sensible also to the immediate patient-caregiver relationship, where e.g. parents of children with chronic pain have been found to perceive the lack of a clear pathophysiological mechanism as more worrisome when psychological reasons for pain are presented as the only alternative to pathophysiology [13].

Besides the three-month duration of pain in one or more body regions, the ICD-11 classification also specifies in the definition of CPP, that pain should not be better explained by another diagnosis, and that it should be "associated with significant emotional distress (...) and/or significant functional disability". These last specifications are important additions that are in accordance with the statements by *the Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials* (PedIMMPACT), declaring emotional functioning, physical functioning, and pain intensity as three of the primary outcome

variables to assess in clinical trials on pediatric chronic pain [14]. Several epidemiological studies on pediatric chronic pain have for instance focused mainly on pain symptoms and not on functional impairment, which may in turn limit the ability to generalize other findings from these studies to more severely impaired groups [15]. Also, such focus on symptoms does not seem to be in line with actual and recommended clinical practice for pediatric chronic pain, that usually employs a multidisciplinary targeting of several aspects of the chronic pain experience [16, 17], and may hamper the evolution towards a broader understanding of chronic pain in children. It is possible that this new classification may also aid in generating more consistent prevalence findings in epidemiological, as well as clinical studies on pediatric chronic pain, by encouraging new methodological approaches.

2.1.2 Prevalence

Several studies have sought to examine the overall prevalence of chronic pain in children, and have found it to be a common problem that appears to be increasing [18-21]. *The American Pain Society* estimates that between 20% and 35% of children around the world are affected by some type of chronic pain [22]. In the comprehensive review by King et al. (2011) [18] on the epidemiology of pediatric chronic pain, and a follow up summary in *the Encyclopedia of Pain* (2013) [23], the overall prevalence of pediatric chronic pain was set at between 11 and 38%. Prevalence rates, however, differed significantly between studies, many studies did not meet quality criteria, and there was a large variation in the methodology used, which made truly meaningful comparisons and syntheses difficult. Headaches, abdominal pain, and musculoskeletal pain were among the most common pain types (with headache being the most common). Notably, overall, the reported prevalence rates ranged between 8–83% [18]. For most pain types, although not abdominal pain, the pain prevalence increased with age [18]. Another large international study on the prevalence of chronic pain in adolescents by Swain et al. (2014) [24] found a similar pattern with headache being the most common pain type along with high prevalence numbers for abdominal and back pain, and many participants reported multi-site pain, with the highest odds of experiencing an additional pain found for headache and abdominal pain [24]. Overall, prevalence ranged between 37 - 54% for the various pain types (sites), however, the prevalence of children who experienced daily pain episodes was between 4 - 8% across all pain sites [24]. Concerning the separate study of the prevalence of idiopathic chronic pain, some attempts exist, including a Norwegian study in 7373 adolescents, of which 44.4% reported idiopathic chronic pain, 10.2% described daily (or almost daily) idiopathic pain, and 25.5% reported multi-site idiopathic pain [25].

In conclusion, precise and instructive estimates of pediatric chronic pain prevalence depend on definitions, which implies the relevance of operationalizing e.g. temporal and locational aspects of pain (duration, frequency, sites), *as well as* pain interference, which is a critical but still somewhat neglected dimension within prevalence research on pediatric chronic pain [23].

2.1.3 Gender differences

Chronic pain appears to be more common in girls than in boys in community as well as clinical samples [18, 21, 23, 26, 27]. In terms of pain location, this pattern also holds true, with a female-biased incidence for most pain sites [23]. Adolescent girls have also been

shown to report more multi-site pains [24]. Higher rates of pain and associated disability are seen in girls than boys [25, 28], as well as higher levels of anxiety sensitivity and pain catastrophizing [29, 30]. The reasons for these gender differences have not been clearly established. Catastrophizing has e.g. been associated with a higher degree of overt pain behavior in the social context and it has been suggested that this may illustrate a relevant gender aspect as girls have been found to express more overt pain behavior than boys, which may in turn lead to e.g. more pain reinforcing behaviors from others, including parents [31]. From the biological perspective, a recent study found chronic nonspecific pain to be more prevalent among girls with early menarche, than in those with normal, late, or no menarche [32], and early puberty has also previously been associated with more back pain in girls [33]. On a related note, it has previously been shown that the sex hormones estrogen and testosterone affect the chronic pain experience [34], and low testosterone levels have been associated with a higher risk for chronic pain in both mice and human models, where testosterone therapy was shown to affect central sensitization and decrease the pain response in women with fibromyalgia [35].

2.1.4 The biopsychosocial model of chronic pain

The biopsychological model of chronic pain constitutes an important frame of reference for understanding the role and function of both internal and external contextual factors in the development, experience, and chronification of, and disability in, pediatric chronic pain [12]. Hence, it serves as an important foundation for designing the pain assessment and interpreting the findings, as well as for the formulation of individualized multimodal treatment options [36, 37].

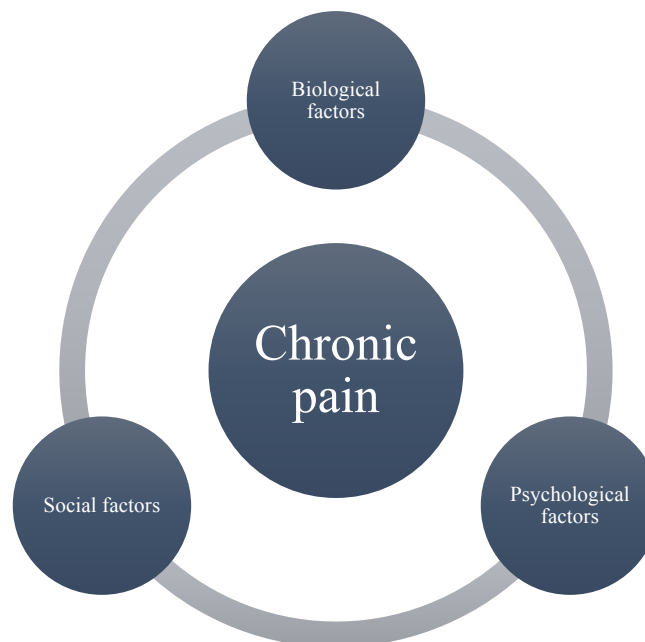


Figure 1. A simplified illustration of the biopsychosocial model of chronic pain.

In the model, pediatric chronic pain is conceptualized as the product of a number of processes of biological, social, and psychological character [12], including mood, catastrophizing, cognition, neuroplasticity and structure, family, parents, friends, and

school, etc. [36, 38]. In the following sections, some of these factors will be addressed in relation to pediatric chronic pain.

2.1.5 Parental and family factors

There is accumulating evidence that family factors, such as family functioning, parental distress, and parent behavior are of paramount importance in order to understand the development and persistence of pediatric pain [39-42].

Poor family functioning in pediatric chronic pain has been associated with high-conflict interactions within the family, low parental ability to engage in adaptive behaviors, and poor emotion regulation in parents [40, 42]. Furthermore, poor family functioning is more prevalent compared to families with healthy children [40, 43], and has also been linked to more functional disability in the child with chronic pain, including school absence and lower overall activity [42].

Moreover, there is increasing evidence describing the association between functional disability in children with chronic pain, and parental distress, including anxiety, pain catastrophizing, and depression [41, 44, 45]. For example, in one longitudinal study [46], the distress and avoidances behaviors of parents were shown to significantly predict child emotional- and school functioning 4 months after a multidisciplinary intervention. The inclusion of parental characteristics and behaviors in the assessment and treatment of children with chronic pain, therefore seems to be highly important to inform effective treatment options for the child [22, 46].

It is also common that parents of children with chronic pain suffer from chronic pain conditions themselves [47], and parents' own pain has been associated with an increased risk for anxiety and depression in children with chronic pain [48], as well as poorer outcomes than other children with non-afflicted parents in a number of areas, including coping [49].

Finally, research on shared family factors, such as genetics and family physical environment, have found some evidence of genetic risk factors for chronic pain [50], and some shared effect of environment [51]. Notably, however, the largest amount of variance was found to be explained by factors pertaining to the specific individual circumstances [51].

2.1.6 Comorbid mental health conditions

Psychiatric disorders are common in pediatric chronic pain [8, 52], and in particular in functionally impaired samples. A large study on an inpatient sample of children with chronic pain, e.g. found the prevalence of comorbid psychiatric diagnoses to be 44% [53].

In particular anxiety and depression have shown strong associations with chronic pain in children [54], along with post-traumatic stress disorder (PTSD) [55]. Depression has been strongly associated with functional disability and maladaptive coping [56], and anxiety has been shown to robustly predict school functioning over and above pain intensity [57]. Research further indicates that anxiety disorders may predate the onset of pain and thus

serve as a risk factor for the development of chronic pain [58, 59]. High anxiety has further been observed to "override" the association between pain intensity and functional disability as shown in one study where pain intensity predicted functional disability in the presence of low anxiety but not in the presence of high levels of anxiety [60]. Chronic pain in adolescence has also been associated with an increased risk for anxiety to persist into adulthood [61].

Also, although not considered a mental health disorder but rather a personality trait, higher levels of the inability to recognize and express own feelings (poor emotional awareness), known as alexithymia, have been found in children with chronic pain [62-64]. Alexithymia appears to be associated with anxiety and depression in chronic pain [62], and overall with an increased physiological arousal that is hypothesized to contribute to the onset of medical comorbidities [65]. The relationships between chronic pain and alexithymia, including implications for assessment and treatment in pediatric chronic pain, have however not been clearly established [62, 64].

2.1.7 Sleep disturbances

Much like pediatric chronic pain, pediatric sleep disturbances, including sleep deprivation/shorter periods of sleep (insomnia), comprise a variety of dysfunction-patterns and include several categories and subcategories of (sleep) disorders [66, 67], and is more prevalent among females [68]. Like chronic pain, sleep disturbances may also be conceptualized as the main disorder or as concurrent to another disorder [67]. The crucial importance of sleep for several aspects of child development has been shown in many studies [66, 69], including for mental health and physical growth, as well as immune system function and neurodevelopmental processes [70]. One study on healthy children (ages 5-12) showed a particularly heightened sensitivity in developing brain circuits to restrictions in sleep different from that of adults, indicating the importance of sleep for the maturing brain plasticity [71].

The importance of evaluating and treating sleep disorders is continuously being emphasized in the context of pediatric chronic pain [37, 72-74], where research shows that sleep disturbances are common [75]. The incidence of sleep disturbances in adolescents in chronic pain treatment has been found to be nearly six times higher than that of healthy adolescents [73], and one study on children with chronic pain presenting for tertiary pain care found distorted sleep in 74% [76]. Sleep disturbances have also, in a number of studies on children with chronic pain, been associated with functional disability in terms of interference with daily-life activities such as school-functioning [27, 77, 78]. In a recent study [79] on a tertiary pain care sample of children with chronic pain in the ages 10-17, poor sleep was also found to mediate the relationship between PTSD symptoms on the one hand, and pain interference and pain intensity on the other. The authors concluded that sleep may be a potentially important treatment target, especially for children with chronic pain that do not respond well to standard pain treatments [79].

Whether chronic pain on an overall level causes sleep disorder or vice versa does not seem to be easily answered. Instead, there seems to be a reciprocal relationship between these

disorders, with one influencing the other over time due to biological as well as psychological and social circumstances [37]. Thus, adequate sleep could be an important factor of strength in responding to the challenges in pediatric chronic pain, which is supported by studies illustrating that good sleep is a factor of longitudinal resilience in other pediatric populations [80].

2.1.8 Neurobiological processes

In the following section, some of the main neurobiological processes that have been implicated in chronic pain are discussed; the coverage, however, does not attempt to be exhaustive.

There is emerging evidence that neural plasticity, that is, the brain's ability to change and adapt to new circumstances throughout the lifespan of a person, may provide an integral part as a mechanism involved in development of persistent pain even without the presence of acute pathophysiology [81]. One form of dysfunctional neuroplasticity is central sensitization where, due to maladaptive neural learning processes, the sensitivity to pain signaling is increased in the central nervous system (CNS), with or without the (continued) presence of input from peripheral neurons (e.g. tissue damage) [82]. Central sensitization is present in several chronic pain conditions, including fibromyalgia and musculoskeletal pain [83]. Central sensitization furthermore appears to be associated with emotional state [84], e.g. in adolescents with fibromyalgia [85], and may involve a form of continuous neural self-reinforcement where pain eventually gets stuck within the CNS [82, 86].

Neuroinflammatory processes (brain- and spinal cord glial cell-induced release of proinflammatory cytokines) has been implicated as one of the driving forces behind central sensitization [87]. In recent studies, central cytokines have been found to function as neuromodulators (through the secretion of molecules that affect e.g. the neuron's regulation of pain) in both the CNS and the peripheral nervous system [87, 88]. In either system, cytokines may hence activate heightened pain sensitivity (allodynia) or pain insensitivity after having been released into the CNS [87]. If this process of cytokine release is sustained in the CNS, it may promote multi-site chronic pain [87, 88].

In the CNS, a stress response is handled by the autonomic nervous system and the hypothalamic-pituitary adrenal (HPA) axis in concert. Activation of the HPA-axis results in secretion of cortisol, and activation of the sympathetic branch of the autonomous system results in secretion of epinephrine and norepinephrine [89]. These systems have complementary functions in the body, and work jointly to make energy available and to increase blood pressure. In the face of challenges, the adaptive response of these systems is to promote stress-adaptive behavior and to reinstate homeostasis. Regulation of the HPA axis in healthy states rely e.g. on negative feedback and sensitivity to increased levels of e.g. cortisol [89]. HPA-dysregulation in chronic pain has been indicated in several studies where this process of cortisol back-signaling was indicated to be disrupted along with non-normal (both higher and lower than normal) levels of cortisol [55, 90-93].

Dopamine is a neurotransmitter that affects a number of functions including, but not limited to, cognition, sleep, and pain processing in terms of e.g. involvement in endogenous pain

modulation, according to preliminary evidence [94]. Chronic pain (e.g. fibromyalgia) has been associated with impaired dopamine function (hypodopaminergic state) in a number of clinical- and preclinical studies [86, 95-98] which in individuals with chronic pain has been associated with increased pain sensitivity and reductions in reward-driven behavior, i.e. performing behaviors that under normal-state circumstances would be positively reinforced [86, 98].

Based on the above findings it may be concluded that several neurobiological processes are involved in the experience of chronic pain, and, tentatively, findings could indicate that, much like on the behavioral level, also on a neuronal level, maladaptive learning processes and (neural) "rigidity" (as the opposite of high neural plasticity) appear to be associated with chronic pain.

2.1.9 Summary notes on risk and resilience factors in relation to impaired functioning in pediatric chronic pain

In the previous sections, some of the social, psychological, and biological factors that are associated with the presentation and experience of pain and functioning in pediatric chronic pain have been presented. On a summary note on functioning, research shows that pediatric chronic pain conditions may lead to severe impairment and disability in subsamples of affected individuals in both community and clinical samples [25, 27, 99]. Lower school attendance, less social engagement and peer-interaction, restrictions in physical activities, and sleep disturbances are functional impairments frequently associated with chronic pain in children [42], confirming the notion of chronic pain as a significant health problem [99, 100]. Moreover, in research on health-related quality of life (HRQoL) in chronic pediatric pain, children report significantly lower HRQoL than children with other chronic conditions and healthy children [101].

As mentioned in the above sections, several factors contribute to an increased risk for functional impairment in pediatric chronic pain [102]. Factors related to the individual, such as gender and biology (stress and pain response), pain catastrophizing, mental state, pain intensity and location, and poor sleep have been consistently related to higher levels of disability, along with factors related to the larger context of the individual, such as low family cohesion, parental anxiety, and depression [25, 31, 42, 57, 103].

In general, the body of research on resilience factors in pediatric chronic pain is small and it has been suggested that an increased focus on factors of strength could contribute in moving the field forward [104]. On an overall level, high self-respect, meaningful and supportive relationships with peers, a sense of family bond, and social competence, are factors that have been associated with better functioning in pediatric chronic pain [42, 105-107].

Finally, on a note on methodology; in some epidemiological studies conducted among community- and school samples, the portion of severely impaired individuals (e.g. with daily pain episodes and related disability) may de facto be very small [21, 108]. This may

further reduce the ability to generalize such findings on e.g. pain disability to more severely impaired groups [15].

2.2 TREATMENTS FOR PEDIATRIC CHRONIC PAIN

2.2.1 Pharmacological treatment

There is a lack of randomized controlled trials for the use of pharmacological therapies in pediatric chronic pain [109]. While usually very effective in the treatment of acute pain, pharmacological treatments in isolation, however, have been reported to have a limited effect on pediatric chronic pain, and appear, on occasion, to be used by pediatric chronic pain patients without indication [15]. There are furthermore large differences among children in terms of who will respond to a certain pharmacological treatment and, overall, the use of such treatments are nowadays mostly recommended solely within the frame of multimodal treatment, in combination with e.g. psychological treatment interventions [110].

2.2.2 Psychological interventions

2.2.2.1 Cognitive behavioral therapy (CBT)

CBT is comprised of a number of behavior-psychological interventions with strong empirical support in a large number of therapeutic areas [111]. With a foundation in learning theory, the goal of CBT is to improve functioning through behavior change and change of thinking patterns that are not adaptive [112].

In chronic pediatric pain management, psychological interventions are common, usually incorporated within a multidisciplinary treatment approach [17], and frequently based on CBT [113]. Although many studies on psychological interventions (CBT), exist, the evidence of efficacy does not match the amount of studies [113]. A number of systematic reviews [114-117] on psychological interventions in pediatric chronic pain, including both in person- and remotely delivered formats, show that psychological interventions deliver promising results but merely in the short term [113, 114]. Furthermore, CBT-treatments seem to lack in specificity in terms of treatment content, reducing the possibility for replication as well as the understanding of effective components [114]. In terms of evidence for outcomes other than pain, such as anxiety, depression, and sleep, such factors have often not been included [113].

In line with research on the importance of parental factors, parents are also frequently included in psychological treatments for pediatric chronic pain; however, the relation between parental involvement and child functional outcomes has not been satisfactorily established [115], and efficacy of interventions in terms of parent outcomes is either lacking or has generally not been maintained over the long term [118]. Studies on CBT for chronic pain that e.g. evaluate sleep as well as parental mood factors, are however emerging [119, 120]; in one study, parental anxiety, depression and pain catastrophizing was found to predict child disability [120], providing further evidence regarding the importance of assessing and treating parental factors in pediatric chronic pain.

2.2.2.2 *Acceptance and Commitment Therapy (ACT)*

ACT is a psychological therapy developed within CBT that integrates processes of acceptance and mindfulness with behavioral change. As an extension of learning theory, the theoretical underpinning of ACT is Relational frame theory (RFT), a theory of language and thinking [121]. RFT aims to apply learning theory to verbal behaviors, to better understand how the process of using language, like any behavior, is shaped through reinforcement and thus may introduce a rigidity (*or* flexibility) in thinking depending on the individual circumstances. Words and thinking thus constitute stimuli that; first, are activated in the presence of certain circumstances (e.g. pain); and second, like any stimuli, may activate reinforced behavioral "protocols", with the function of e.g. avoidance [121]. The goal of ACT is increased psychological flexibility, which is conceptualized as the ability to act according to long term values and goals also in the presence of aversive interfering stimuli such as pain or distress [122]. Psychological flexibility has also been described as a "fundamental aspect of health", with presumably high relevance to other constructs such as executive function [123].

In ACT-treatment for pediatric chronic pain, the objective is to promote a more values-consistent behavioral repertoire in the presence of pain; e.g. attending school and meeting friends both when pain is low and high. Exposure, to actively engage in behaviors that increase pain or distress but are valued, is encouraged, and combined with acceptance strategies to enhance psychological flexibility [124]. Acceptance and level of functioning has been strongly associated in research on pediatric chronic pain [125], and ACT-based psychological treatments for pediatric chronic pain are gaining increasing and promising evidence [107, 126-128]. However, the need for larger studies with longitudinal designs, stringent methodology, and the inclusion of parents in treatment protocols has also been emphasized [124, 129].

Research has also examined psychological flexibility among parents of children with chronic pain. Parental psychological flexibility is conceptualized as the parent's willingness to experience own distress for the purpose of pursuing long-term values and related goals, such as effectively assisting the child to manage his/her pain and distress in pursuing valued behaviors although this may cause own distress [130, 131]. Two studies have validated the Parental Psychological Flexibility Questionnaire (PPFQ) in samples of parents of adolescents with chronic pain. Results from both studies showed a positive relationship between the level of psychological flexibility in parents and the level of functioning in adolescents. Authors thus concluded that increasing psychological flexibility in parents of children with chronic pain could, in itself, be a potentially important treatment target with the potential of improving treatment effects for the child with chronic pain [130, 131].

2.3 PEDIATRIC CHRONIC PAIN AND NEURODEVELOPMENTAL COMORBIDITY

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, or set of disorders (hence "spectrum"), characterized by deficits in communication and social interaction and restricted, repetitive behavior patterns and interests that cause impairment [132, 133]. The estimated prevalence of ASD in children in the normal population is 1.47% [134-137], and

ASD is more than twice as prevalent in boys [138]. Children within the ASD-spectrum may present with a high variability in difficulties, including intellectual disability (with or without), language impairment (with or without), and varying levels of sensory modulation difficulties [133, 139].

The abnormal experience of sensory symptoms in ASD has in recent years been included as a diagnostic criterion of the disorder [133], appears to be common [140-142], and overall is gaining increasing interest in research [143]. Sensory symptoms in ASD frequently manifest in sensory modulation disorders (SMD) such as sensory under- and sensory over-responsivity (SOR) [143]. SOR is generally described as an intense or exaggerated response to stimuli that are neutral [144], and has been strongly associated with anxiety [145], gastro-intestinal problems [146], and behavioral difficulties in children with ASD [147].

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by a pattern of developmentally-inappropriate and impairing inattention, hyperactivity, and impulsivity [148]. The pooled estimated prevalence of ADHD in children in the normal population is 5.29% [149], and the disorder, like ASD, has a male-biased incidence, being twice as common in boys [150]. In children with ADHD, SOR is also highly prevalent and has shown strong associations with anxiety [151].

Children with ASD or ADHD share several comorbid difficulties, including sleep disorders [152], executive function deficits [153], and mental health disorders [154], that are all highly prevalent in both disorders [155]. Moreover, ADHD and ASD frequently present together [156], and it has been suggested that ASD and ADHD, despite different clinical characteristics, may share brain pathology, including abnormalities in dopamine signaling affecting reward-driven behavior [155, 157-159]. Alexithymia, and the associated dysfunctions in emotional processing, is furthermore substantially elevated in children with ASD [160, 161], and has been tentatively associated with symptoms of hyperactivity and impulsivity in children with ADHD [162]. Finally, children with ASD or ADHD often present with immunological, neurological, and gastroenterological comorbidity [163, 164].

2.3.1.1 Chronic pain and neurodevelopmental comorbidity

Despite a large number of clinical observations, the prevalence of comorbid ADHD and ASD in pediatric chronic pain is yet unclear. Studies in patients with abdominal pain [146, 165], a study on migraine [166], a study on neuropsychological function in pediatric chronic pain [167], and a number of case reports [1, 168-170], suggest a potential incidence of ASD and ADHD in pediatric chronic pain that may be larger than the normal prevalence of these neurodevelopmental disorders. Moreover, observations of children presenting with chronic medical conditions, indicate a possibly higher than normal incidence of neurodevelopmental comorbidity in these groups [163, 171, 172]. In summary, clinical observations, recent studies, and to some extent also similarities across clinical correlates, call for more research on the co-occurrence of pediatric chronic pain and neurodevelopmental disorders.

2.4 PHENOTYPING AND IMPLICATIONS FOR PRECISION-MEDICINE

Clinical phenotyping is receiving increased attention in pediatric chronic pain research [173, 174]. Evaluating factors of relevance for the experience of chronic pain and disability as potential risk or resilience factors as they manifest in individuals, or groups of individuals, is implicated as essential to achieve better treatment effects and to refine theories, thus moving the field forward [86, 113]. The focus on phenotyping illustrates a transition from a broader focus on pain intensity and functioning, to potential treatment targets in more or less individually tailored interventions, also known as precision medicine [173].

3 PURPOSE AND AIMS OF THE THESIS

The purpose of this research project was to identify and assess parental and child factors of importance for functioning and treatment effects in pediatric chronic pain. The overall aim was twofold; to investigate a) the role of parental psychological flexibility, including the effects of a brief parental ACT-intervention; and b) the prevalence of traits and symptoms of neurodevelopmental disorders in children and implications for functioning. The specific study aims are described below in detail.

3.1 STUDY I

The aim of Study I was to validate the Swedish version of the Parent Psychological Flexibility Questionnaire (PPFQ) in a sample of parents of children and adolescents with chronic pain, by evaluating the factor structure, reliability, and concurrent criteria validity.

3.2 STUDY II

The aim of Study II was to preliminary evaluate the treatment effects of an ACT intervention delivered in group or individually, including a brief parent support program, in a sample of adolescents with chronic debilitating pain and their parents.

3.3 STUDY III

The aims of Study III were 1) to investigate the prevalence of clinically significant ASD-traits and ADHD-symptoms in children; and 2) to evaluate differences in parent/child demographic- and pain variables between children with and without clinically significant ASD-traits and ADHD-symptoms, in a sample of children and adolescents with chronic pain and their parents.

3.4 STUDY IV

The aims of Study IV were, in a sample of children and adolescents with chronic pain and their parents (same sample as Study III) 1) to examine the relationships between ASD-traits and ADHD-symptoms, functioning (depression and pain interference), and HRQoL; and 2) to assess the mediating function of insomnia and psychological inflexibility on the relationships between ASD-traits or ADHD-symptoms as predictor-, and HRQoL, depression, and pain interference as dependent variables.

4 METHODS

4.1 OVERVIEW OF STUDY METHODS

This thesis contains four studies conducted on clinical samples of children and adolescents with chronic pain and their parents, using three different data sets. One study used a randomized uncontrolled pilot design, where participants were randomized to individual or group treatment and assessed longitudinally pre-, mid- and post-treatment (Study II). The remaining three studies utilized a cross-sectional design, including a psychometric evaluation (Study I), a prevalence study (Study III), and a correlational study (Study IV). Studies III and IV are based on the same dataset. A summary of the study methods is provided in Table 1.

Table 1. Summary of designs, participants, data collection, and statistical analyses for the studies included in the thesis.

Study	Design	Participants	Data collection	Statistical analyses
I	Cross-sectional	Parents of children and adolescents with chronic pain ($n=263$)	Self-report assessments (paper, first visit to clinic)	Descriptive statistics, factor analysis (PCA), Cronbach's alpha, correlation and regression analyses
II	Randomized uncontrolled pilot	Adolescents with debilitating chronic pain ($n=48$ at pre) Parents ($n=28$ at pre)	Semi-structured interviews, self-, and proxy-report assessments (paper, pre, mid, and post treatment)	Mean-based statistics (Jacobson-Truax ^a), Mann Whitney <i>U</i> -test, Wilcoxon signed rank's test, effect size calculations
III	Cross-sectional	Children and adolescents with chronic pain ($n=146$) Parents ($n=146$)	Self- and proxy-report assessments (paper, first visit to clinic)	Descriptive statistics, independent <i>t</i> -test, Mann Whitney <i>U</i> -test, χ^2 -test, Fisher's exact test, effect size calculations
IV	Cross-sectional	Children and adolescents with chronic pain ($n=146$) Parents ($n=146$)	Self- and proxy-report assessments (paper, first visit to clinic)	Descriptive statistics, independent <i>t</i> -test, correlation and regression analyses, effect size calculations, analyses of indirect effects/mediation

Note. ^a Method using mean-based statistics to calculate clinically significant changes; PCA, Principal Component Analysis.

4.2 ETHICAL CONSIDERATIONS

The research on which this thesis is based was conducted in accordance with the 1975 Helsinki Declaration of Ethical Principles and subsequent revisions [175].

4.2.1 Ethical permits and consent

The four studies were approved by the Regional ethical review board in Stockholm (Regionala etikprovningarnamnden i Stockholm, FE 289, 171 77, Stockholm, Sweden). The ethical permits are 2009/470-31/3, and amendment 2011/1734-32 (Study I); 2009/815-31/4 (Study II); and 2013/231-31-4 (Study III and Study IV). Participating children, adolescents, and parents in the four studies were presented with age-appropriate study information in writing. Concerning the study information in the two studies III and IV, where children between the ages 8-12 years were also included, particular care was taken to explain why the research was conducted and the implications of participation in an easy-to-understand wording. All participants were required to provide written informed consent to participate in the research before study inclusion. In the information it was clearly stated that any study participation was voluntary, that study participation could be interrupted by the participant at any time without explanation, and that declining participation would not affect subsequent care in any way. In study II, for instance, patients that chose not to participate in the study, but were still eligible for treatment according to standard clinic requirements, were offered the treatment program provided within the ordinary care at the tertiary clinic.

4.2.2 Risks and benefits

Regarding the cross-sectional studies (Studies I, III, and IV), with no treatment intervention, potential violation of integrity was seen as the most serious ethical concern, followed by the burden of assessment, i.e. time and effort spent on completing questionnaires. All self-report questionnaires were coded for anonymity and stored in locked facilities, and files were encrypted and stored on a secure computer to minimize the risk of integrity violation. The included self-report instruments were thoroughly evaluated for relevance (validity) vis-à-vis the research questions, which has been suggested as more important than time spent on completion [176]. Regarding the intervention study (Study II), ethical concerns, besides the burden of assessment as described above, included the possible risks of adverse events from participating in a psychological intervention that could possibly entail increased levels of distress and pain. Thorough information regarding treatment objectives and the possibility for increased negative symptoms were therefore provided to participants. Adverse events were also analyzed in terms of clinically significant deterioration and were subsequently reported, as recommended but not always done according to the literature [177].

All studies in the thesis are conducted on clinical samples of children and adolescents with chronic pain and their parents. Pediatric chronic pain is seen as an important area of research, being a current major health concern that often persists into adulthood. Achieving a deeper understanding of the child with chronic pain, including contextual factors of relevance to functioning, such as neurodevelopmental comorbidity and parental coping, was considered important as it could pave way for better screening methods to detect factors that may go unnoticed, as well as novel and tailored interventions to more effectively address these factors. Through developing a shorter instrument, with satisfactory validity, the patient burden of assessment could ultimately be reduced. Specifically, concerning the **participating children**, it was assessed that increased knowledge about chronic pain and neurodevelopmental comorbidity eventually could lead to more effective care for the group as a whole, and possibly fewer unnecessary assessments. New promising

psychological treatments could also constitute valuable additions and provide insight on overall terms of functioning in pediatric chronic pain. In terms of **the participating parents** or **next-of-kin**, increased knowledge about factors influencing pediatric chronic pain and disability, and how to address own worry, could lead to less concern (or more adequate concern) in parents and other relatives, potentially resulting in an improved ability to coach the child in pain. In the long term, informing effective treatments and better assessments will probably also mean less time spent in hospitals or clinics. In terms of **healthcare**, effective assessment and treatment of patients with pediatric chronic pain probably entails improved management of resources e.g. through fewer health care contacts and more satisfied patients. Finally, in terms of **community**, savings in terms of reduced school- and work absences could come as a result of improved assessment and treatment. In summary, it was concluded that the benefits would outweigh the risks associated with the research included in the current thesis.

4.3 RESEARCH SETTING

The samples of children and adolescents and their accompanying parents included in the four studies in this thesis were all recruited from a tertiary pain clinic at the Karolinska university hospital in Stockholm. The clinic employs pain physicians, psychologists, and physiotherapists and provides specialized expertise in assessment and treatment of pediatric chronic pain in an outpatient care setting with an interdisciplinary focus. Referrals are received from mainly secondary care but also from tertiary care facilities in a number of therapeutic areas. Healthcare in Sweden, including tertiary care, is largely tax-funded and all non-acute healthcare for children under the age of 18 is completely free of charge, which means that access to care at the tertiary pain clinic did not require a private health insurance or other specific fees.

4.4 PARTICIPANTS AND PROCEDURES

All child- and adolescent participants included in the current studies were referred to the tertiary pain clinic because of chronic pain.

4.4.1 Study I

The first study included 263 parents (213 women) of children and adolescents with chronic pain who were referred to the tertiary care pain clinic during a period of four consecutive years. At the child's first visit to the clinic, accompanying parents were invited to participate in the study, and participants provided data before the child's initial assessment through self-report questionnaires. Non-Swedish speakers were excluded from the study. The mean parental age was 44.4 years ($SD = 6.5$) and 53% of parents reported their education to be at university level. Child data were also collected and reported elsewhere [26, 178]. In brief, 72% were girls and the mean age was 14 years ($SD = 2.64$). The mean pain duration was four years and most children reported pain from multiple body sites (76%).

4.4.2 Study II

The second study initially included 48 adolescents (ages 12-18 years), with continuous chronic pain since more than six months not fully explained by a pathophysiological process, with substantial ongoing disability due to mainly pain (e.g. not a psychiatric

condition), and poor effects of previous treatments for pain without other on-going or planned treatments. Adolescents with an imminent suicide risk, severe cognitive dysfunction or reduced proficiency in Swedish were furthermore not eligible to participate in the study. The 48 eligible participants were randomized to a group ($n = 24$) or individual ($n = 24$) condition for treatment with an outpatient 18-session interdisciplinary ACT-based treatment, that included four parental sessions, of which one was a joint adolescent-parent session. The accompanying parents were offered to participate in the parent program with the same treatment condition (group or individual) as their adolescent. However, only one parent per adolescent was asked to provide data for the study. Data collection on pain- and demographic variables, in order to determine eligibility for participation in the study, was performed at the initial assessment at the clinic through a semi-structured clinical interview. Data on child- and parent outcome measures was collected by means of self-report assessments at three time points: pre-, mid-, and post-treatment. Following attrition and a change in age criteria to 14-18 years, the final sample consisted of 30 adolescents (24 girls) with a mean age of 16 years ($SD = 1.6$), and 28 parents (24 women) with a mean age of 47.3 years ($SD = 4.8$). Of parents, 57.7 % reported having chronic pain themselves. Six parents were subsequently excluded because data was not provided by the same parent at all time points, leaving 30 adolescents (12 in group- and 18 in individual condition) and 22 parents (11 in group- and 11 in individual condition) to be included in the analysis.

4.4.2.1 *The parental intervention*

Within the 18-session treatment program, the four parental sessions were number 3, 6, 11, and 12 (joint session), and they were thus intertwined with the 15 adolescent sessions (including the joint session). Parental home assignments were also given at one point (session 6). The purpose of the parent program was to enhance the ability of parents to support increased functioning in their adolescent through pain education, contingency management, including clarification of own values (conceptualized as long-term reinforcers), and the use of acceptance-skills to manage own distress due to their child's pain.

4.4.3 **Study III and Study IV**

The third and fourth studies were conducted on the same set of participants and included 146 children and adolescents with chronic pain (102 girls) with a mean age of 14.55 years ($SD = 2.40$), and their parents (one parent per child; 111 women) with a mean age of 45.67 years ($SD = 5.74$). Own chronic pain conditions were reported by 32.8 % of parents. Of children, 93.8% reported pain since longer than 6 months and 69.2% experienced daily pain episodes, with an additional 24% experiencing pain several times a week. Multiple pain sites were reported by 74% of children with an average pain intensity for the primary pain of 59.02 (max 100, $SD = 13.55$). Furthermore, 61.7% of children reported not knowing (including not having received) any diagnosis for their pain, and 35.4% reported not knowing any reason for initial pain onset. Participants were consecutively referred to the tertiary pain clinic during a period of three years.

The parent-child dyads were invited to participate in the studies before the child's initial assessment at the clinic, and consenting individuals provided data through two individual

sets (parent and child) of self-report questionnaires that were returned in person before the first clinical assessment. Non-Swedish speakers were excluded, as were implicitly also children who were unable to answer the questionnaires by themselves.

4.5 ASSESSMENTS

4.5.1 Overview of instruments and assessed variables

As noted in Table 1, the results from the studies within this thesis were mainly based on self-reports from both children and their accompanying parents. An overview of the self-report instruments used and the assessed variables is provided in Table 2.

Table 2. Instruments and assessed variables for each study included in the thesis by type of participant (child/parent) and excluding demographics and other background variables.

Study	Child instruments	Child assessed variables	Parent instruments	Parent assessed variables
I	N/A	N/A	HADS, PPFQ	Parental distress (anxiety and depression), parental psychological flexibility in the context of child's pain
II	NRS 0-6, PIPS, PII, PRS, CES-DC	Pain intensity, psychological inflexibility in context of pain, influence of pain on functioning/behaviors, worry/emotional reactivity to pain, depressive symptoms	HADS, PPFQ, PRS-P, FDI-P ^a	Parental distress (anxiety and depression), parental psychological flexibility in the context of child's pain, parental emotional reactivity to child's pain, child functioning
II	LPQ	Pain variables: Pain duration, pain frequency, pain site/s, perceived trigger/s of pain, perceived reason/s for first pain onset, pain diagnoses, co-occurrence of other chronic disease	SRS, Conners 3	Autistic traits in child, ADHD-symptoms in child
IV	LPQ, CES-DC, PII, PedsQL, ISI, PIPS	Pain variables (as above), depressive symptoms, influence of pain on functioning/behaviors, HRQoL, insomnia, psychological inflexibility in context of pain	SRS, Conners 3	Autistic traits in child, ADHD-symptoms in child

Note. ^aChild outcome; N/A, not applicable; HADS, The Hospital Anxiety and Depression Scale; PPFQ, The Parent Psychological Flexibility Questionnaire; NRS, Numerical Rating Scale; ISI, Insomnia Severity Index; PIPS, Psychological Inflexibility in Pain Scale; PII, Pain Interference Index; PRS, Pain Reactivity Scale; PRS-P, Pain Reactivity Scale-Parents; FDI-P, Functional Disability Inventory-Parent; CES-DC, Center for Epidemiological Studies Depression Scale; LPQ, Lübeck Pain Questionnaire; SRS, Social Responsiveness Scale; HRQoL, Health-related quality of life; PedsQL, Pediatric Quality of Life Inventory.

4.5.2 Study I

4.5.2.1 Demographic- and variables for adjustment/control (self-report)

Parental background information and demographics were assessed by means of self-report and included parental age (years), gender, and educational status (basic education/high school or university studies).

4.5.2.2 Factor structure and internal consistency (self-report)

The instrument subject to validation, the Parental Psychological Flexibility Questionnaire (PPFQ) [130, 131], was used in a version containing the 17 items and four subscales/factor structure: VBA (values-based action); EA (emotional acceptance); (pain acceptance); and PW (pain willingness), as proposed by Wallace et al. [130]. The PPFQ measures parental psychological flexibility within the context of the child's pain, and is defined as the parent's willingness to experience distress related to the child's pain in the service of long-term values and related behavioral goals for both parent and child [179]. The PPFQ was translated from English to Swedish based on standards for self-report translation and cross-cultural adaption [180].

4.5.2.3 Relationship with distress: PPFQ-concurrent criterion validation (self-report)

Parental distress (anxiety and depression) was assessed using the Hospital Anxiety and Depression Scale (HADS) [181, 182]. The HADS includes two subscales measuring the respective aspects of distress: anxiety (HADS-a) and depression (HADS-d).

4.5.3 Study II

4.5.3.1 Demographic-, background-, and screening variables (self- and proxy-report, semi-structured interview)

Semi-structured screening interviews were used to collect information concerning adolescent demographic-, school, and pain characteristics (pain frequency and duration, pain location, and pain medication). Parental background information and demographics were assessed by means of self-report and included age, gender, educational- and work status, marital status, and own chronic pain conditions.

4.5.3.2 Adolescent outcome measures (self- and proxy reports)

Six variables were assessed as child outcomes. A numerical rating scale was used to assess pain intensity on a scale from 0 (no pain at all) to 6 (extreme pain). The Pain Interference Index (PII) was used to assess the impact of pain on everyday functioning/behaviors [26]. Emotional reactivity to pain and worry was assessed with the Pain Reactivity Scale (PRS) [10]. The Center for Epidemiological Studies Depression Scale Children (CES-DC) was used to assess depressive symptoms [183]. Psychological inflexibility in the chronic pain context, defined as an inability to pursue valued behaviors in the presence of pain and distress, was evaluated using the Psychological Inflexibility in Pain Scale (PIPS) [106]. Finally, The Functional Disability Index (FDI) [184] in a parent version, and completed by parents, was used to assess adolescent functioning.

4.5.3.3 Parent outcome measures (self-reports)

Three variables were assessed as parent outcomes. Parental distress (anxiety and depression) was assessed using the Hospital Anxiety and Depression Scale (HADS) [181, 182]. For the assessment of parental emotional reactivity to the child's pain, the Pain Reactivity Scale was used in a parent version (PRS-P). Finally, for the assessment of parental psychological flexibility within the context of the child's pain, the Parent Psychological Flexibility Questionnaire (PPFQ) was used in the 10-item version developed through the psychometric evaluation and factor analysis performed in Study I [185].

4.5.4 Study III

4.5.4.1 Demographic- and background information (self- and proxy-reports)

Parental background information and demographics were assessed through self-report and included parental age (years), gender, health, rated from 1 (poor) to 5 (excellent), parental chronic pain (yes/no), and educational status (basic education/high school or university studies). Child demographic and background variables were also collected by means of (child) self-report and included gender, age (years, months), and chronic disease other than pain, and parents provided information on confirmed diagnoses of ADHD and/or ASD in their children.

4.5.4.2 Pain characteristics (child self-report)

The Lübeck Pain Questionnaire (LPQ) [20, 108] was used to assess pain characteristics in children. The LPQ is a structured self-report questionnaire containing predefined single-item, and multi-item scales (yes/no) evaluating pain duration and pain frequency during the preceding 3 months, pain site/s, perceived trigger/s of pain, and perceived reason/s for first pain onset.

4.5.4.3 Symptoms and traits of ASD and ADHD (parent proxy-reports)

For the assessment of autistic traits in children, parents completed the Swedish version of the parent report form of the Social Responsiveness Scale (SRS), and the original American norms were used for comparison [186, 187]. Clinically significant ASD-traits have been associated with T-scores ≥ 60 , and T-scores ≥ 75 are associated with an ASD diagnosis in the severe range [188]. Established cutoffs reliably distinguish children with ASD from non-affected children and children with other child psychiatric conditions [186]. In order to assess symptoms of ADHD in children, the Swedish version of the Conners 3 parent report form was used, along with Swedish norms [189, 190]. The Conners 3 generates an ADHD Index that accurately differentiates children with ADHD from children without a clinical diagnosis [191]. T-scores ≥ 60 indicate an elevated score and T-scores ≥ 65 are associated with clinically significant ADHD symptoms.

4.5.5 Study IV

4.5.5.1 Variables for adjustment/control (child self-report)

Child demographic- and pain variables were collected as in Study III. In Study IV, however, only data concerning gender and age was used and assessed as control/adjustment

variables along with pain intensity from the LPQ. In the LPQ pain intensity was assessed with a visual analog scale (VAS; 0-100 mm, six faces from laughter to crying) following the question: “How intense is your main pain usually?”.

4.5.5.2 Dependent variables (child self-report)

Three variables related to child functioning and HRQoL were assessed as dependent variables. The PII was used to assess the impact of pain on everyday functioning/behaviors, and the CES-DC was used to assess depressive symptoms. HRQoL was assessed using the Pediatric Quality of Life Inventory 4.0 core scales (PedsQL) [192]. The PedsQL has been used in several studies, in healthy children, in children with chronic conditions [101, 193-195], and in children with chronic pain [101, 196, 197].

4.5.5.3 Predictor variables (parent proxy-reports)

Two variables assessing traits and symptoms of neurodevelopmental disorders in children were used as the predictor variables. ASD-traits were assessed and collected as in Study III using the SRS and data on ADHD-symptoms were likewise assessed and collected using the Conners 3.

4.5.5.4 Variables for analyses of indirect effects/mediators (child self-reports)

Two variables, insomnia and psychological inflexibility in the context of pain, were analyzed for indirect effects on the relationships between predictor- and dependent variables. Insomnia (perceived sleep difficulties) was assessed using the Insomnia Severity Index (ISI) [178, 198]. Relating to the past two weeks, ISI evaluates sleep patterns, satisfaction with the current sleep pattern, problems with daily functioning due to insomnia, sleep worry, and noticeability by others. Psychological inflexibility in the chronic pain context was evaluated using PIPS.

4.5.6 Benefits and limitations of self-report

The specific limitations concerning the use of self-report assessments pertaining to the studies in this thesis are addressed in the limitations section below (6.6). In a general context, self-report data has been suggested as essential to behavioral and clinical research, as well as to medical practice, as a valuable and unique source of information that should not be seen as a mere substitute for other methods of verification [199]. However, caution regarding self-report should also be taken. In one study on pediatric chronic pain patients, results e.g. suggested that higher scores for self-reported social desirability were associated with lower scores for self-reported psychological distress, interpreted as indicative of social desirability response bias [200]. Overall, however, research that span a number of fields and study designs, including pediatric chronic pain [14, 201], cognition, psychometric-, and longitudinal studies, point to the value of self-report instruments and that children, from the age of 6 years and with certainty from the age of 8 years, can reliably complete age-appropriate self-report questionnaires and supply valuable information concerning their own health-status, with a predictive value [202]. In terms of assessing behavioral dimensions and medical history, parent proxy-reports also constitute an important contribution [22]. In summary, self-report can be a valuable and unique source of information but the use of self-report, like any method of measurement, should include a

thorough assessment of aspects related to instrument validity and reliability, research setting, the type of respondent (age, cognition) [203], response bias, and ethical concerns [199].

4.6 STATISTICAL ANALYSES

All analyses in the studies included in this thesis were performed using SPSS in version 22 (Study I), version 23 (Study II), and version 25 (Studies III and IV) [204]. Analyses of indirect effects (Study IV) were performed using PROCESS for SPSS [205]. In every study, descriptive statistics were used to examine the data, including checking for missing values and ascertaining valuable distributions. Missing data were in all samples found to be missing completely at random (Little's MCAR =ns.) [206]. The percentages of missing data points for included participants per variable are reported in detail in each article, but overall missing data points were below 1% across all data sets. Imputation of missing data was largely handled using the expectation maximization algorithm (EM) [207] (Study I, III, and IV), and in Study II through person mean imputation. The choice of statistical analyses was made based on the research question at hand, the type of variable (numerical, categorical), the number of groups studied, and variable distributions (normal, non-normal) [208]. Table 3 provides an overview of the statistical analyses used in relation to each study and research question.

Table 3. Overview of the statistical analyses used in the four studies in the thesis by study and research question.

Study	Research questions	Statistical Analyses
I	Exploration of PPFQ-factor structure and loadings	Principal Component Analysis (PCA)
I	Determination of PPFQ-internal consistency and item contribution	Cronbach's alpha
I	Assessment of PPFQ-concurrent criterion validity: strength (and function) of relationship with HADS	Correlation and hierarchical multiple regression analyses
II	Assessment of differences in measures between groups: treatment format (group/individual)	Mann–Whitney <i>U</i> -tests (non-normal)
II	Assessment of temporal changes in outcomes following ACT-intervention (pre, mid, post)	Wilcoxon signed-rank tests (non-normal)
II	Assessment of clinically significant changes in outcomes following ACT-intervention	Mean-based statistics (Jacobson–Truax method)
III	Assessment of prevalence/occurrence of clinically significant traits/symptoms of ASD/ADHD	Descriptive statistics (T-score means, <i>SD</i> , percentages)
III, IV	Assessment of differences between groups (group status: clinically significant traits/symptoms of ASD/ADHD) for numerical variables	Independent <i>t</i> -tests (normal), Mann–Whitney <i>U</i> -tests (non-normal)
III	Assessment of equality of proportions by group status (clinically significant traits/symptoms of ASD/ADHD) for categorical variables (yes/no)	χ^2 -tests, Fisher's exact tests
II, III, IV	Analysis of effect sizes	<i>r</i> , Cohen's <i>d</i> , Hedge's <i>g</i>
IV	Examination of variable relationships: strength	Correlation analyses
IV	Examination of variable relationships: function/predictive value	Hierarchical multiple regression analyses
IV	Analysis of indirect effects (mediation)	Bootstrapping (resampling)

Note. PPFQ, The Parent Psychological Flexibility Questionnaire; HADS, The Hospital Anxiety and Depression Scale; ACT, Acceptance and Commitment Therapy; ASD, Autism spectrum disorder; ADHD, Attention-deficit hyperactivity disorder; *SD*, Standard deviation.

Throughout the studies, a correlation of $r = \pm .00 - .29$ was considered weak, $r = \pm .30 - .49$, moderate, $r = \pm .50 - .89$, strong, and, $r \geq \pm .90$, very strong [209]. Effects sizes (Study II, III, and IV) were considered small ($d = 0.3$; $g = 0.3$; $r = > 0.10$), medium ($d = 0.5$; $g = 0.5$; $r = > 0.30$) and large ($d = 0.8$; $g = 0.8$; $r = > 0.50$) [210, 211]. In Study IV, clinically significant change was defined according to the Jacobson and Truax method [212], as a change from the mean of the study population of two standard deviations (*SD*) in the direction of better or worse functioning. *P*-value in Study I, III, and IV was set at $p < .05$, and in Study IV at $p < .01$.

5 RESULTS

5.1 STUDY I

The assumptions for using a PCA were met. The exploratory factor analysis of the PPFQ containing 17 items (PPFQ-17) and four subscales with PCA supported a three-factor solution with eigenvalues >1 (6.68, 2.23, and 1.38). The sequential elimination of items due to significant loadings on several factors, poorer extraction within the factor structure, or negative contributions to overall scale reliability (alpha) resulted in a final PPFQ-version of 10 items (PPFQ-10) and three factors that explained 69.5% of the item-variance. The three factors matched the factor/subscale labels: values-based action (VBA), pain willingness (PW), and emotional acceptance (EA) proposed by the authors of the original PPFQ in Wallace et al. [130], and were retained (Table 4). One of the original subscales/factors, pain acceptance (PA), was eliminated in the process of item reduction. Full scale internal consistency was good ($\alpha = 0.86$) and for subscales fair (PW, $\alpha = .73$), moderate (VBA $\alpha = .76$) and excellent (EA $\alpha = .87$), accounting for the number of items [213], and satisfactory levels of skewness and kurtosis for a normal distribution were observed.

Table 4. Factor loadings and communalities based on a principle components analysis with oblimin rotation for 10 items from the 17-item version of the PPFQ ($n = 263$).

Item No. ^a	Item ^a	Factor loadings (PCA) ^b			Communality (extraction)
		Emotional Acceptance (EA)	Pain Willingness (PW)	Values Based Action (VBA)	
7	Despite my child's pain, we are able to pursue activities that are important to our family		.157	.820	.721
8	When my child has pain episodes I am able to remain aware of our goals and other things that are important to us as a family.	.271	-.113	.715	.696
11	It is possible to live a normal life while my child suffers with pain.			.814	.652
9 _r	I avoid situations where my child will have pain.		.756	.124	.607
13 _r	Pain control must come first whenever my child does activities.		.780	-.138	.698
24 _r	My child must avoid activities that lead to pain.		.826		.683
22 _r	I suffer terribly from my child's pain and need to make this suffering stop.	.830			.744
26 _r	My child's pain makes it impossible to focus on anything else.	.683		.243	.717
28 _r	I am overwhelmed by worry over my child's pain.	.845			.753
31 _r	I struggle with my own thoughts and feelings about my child's pain.	.853			.681

Note. ^aFrom the original PPFQ by McCracken et al.; *r* = reversed scored item. Values are reported from the pattern matrix, sorted by subscale; total variance explained = 69.5%; Factor loadings < 0.1 are suppressed; ^b Extraction method: PCA, with oblimin as the rotation method (kaiser normalized; rotation converged in five iterations); EA, emotional acceptance; PW, pain willingness; VBA, values-based action.

In total, 35% and 21% of parents scored at or above the clinical cutoff of 8 for anxiety (HADS-a) and depression (HADS-d) respectively [182]. Psychological flexibility (PPFQ-10) had a strong and negative relationship with anxiety ($p < .001$), and with depression ($p <$

.001). Lower psychological flexibility was associated with higher distress. The PPFQ-10 further significantly contributed to the prediction of anxiety ($p < .001$) and depression ($p < .001$), and accounted for 29% of the variation in HADS-a and for 35.6% of the variation in HADS-d, with adjustment for age, gender, and education.

5.2 STUDY II

Comparing the results on pre-treatment assessments between the adolescents ($n=30$) and parents ($n=22$) that completed the study, and those who were excluded or dropped out, no significant differences were found.

No significant differences were found between treatment conditions (group and individual), using the statistical significance level of $p < .01$. Significant improvements ($p = .001$ and $p = .004$) post-treatment, with medium to large effects, were seen among adolescents for pain reactivity (PRS), psychological inflexibility (PIPS), pain interference (PII), and depression (CES-DC). Parent FDI-ratings of functional disability concerning their adolescents did not show a significant improvement ($p = .032$). Significant improvements in adolescent variables were mainly seen from pre- to post, and from mid- to post treatment.

Concerning parental variables, parents reported a pre-treatment median anxiety score of 9 on the HADS-a, and a pre-treatment median depression score of 5.5 on the HADS-d. In terms of parental outcomes, significant ($p = .001$) improvements post treatment, with large effects, were seen in parent pain reactivity (PRS-P), and parent psychological flexibility (PPFQ). Significant improvements in these variables were seen from pre- to post, and from mid- to post treatment. Of parents, 76% (PRS-P) and 54% (PPFQ) also showed *clinically* significant improvements. Changes in parent anxiety or depression were not significant.

5.3 STUDY III

Of all children, 20 (13.7% in total; 17.6% of girls; 4.5% of boys) received scores equivalent to clinically significant ASD (SRS) and 29 children (19.9% in total; 19.6% of girls; 20.5% of boys) received scores equivalent to clinically significant ADHD (Conners 3). In combination, the total sample prevalence of clinically significant ASD-traits and ADHD-symptoms was 26% (38 children, including 11 children receiving scores above clinical cutoff on both instruments). Of all children, 4.8% of had an indicated previous diagnose of either ADHD, ASD or both (one child; 0.7% in total).

Concerning demographic- and background variables, girls were more likely to have clinically significant ASD-traits ($p = .035$), and parents of children with scores below the cutoff for clinically significant ASD-traits reported significantly better health than parents of children above cutoff ($p = .020$). Also, parents of children with clinically significant ADHD-symptoms were less likely to report a university education ($p = .034$). No other significant differences regarding demographic or background variables were found.

In terms of pain characteristics, results for pain duration, pain frequency, or pain sites did not show any significant differences between children with and without clinically significant ASD-traits or ADHD-symptoms. Concerning pain triggers, in children with clinically significant ASD-traits, pain was more likely triggered by being in school (p

=.007), while pain in children with clinically significant ADHD-symptoms was more likely triggered by “New situations” ($p = .006$) and by the “Family situation” ($p = .008$). Finally, children with clinically significant ASD-traits were more likely to not know of any reason for initial pain onset ($p = .003$).

5.4 STUDY IV

Of all children, 58% reported a HRQoL (full PedsQL scale) below or equal to at-risk (for poor HRQoL) [194, 214]. Also, 35% reported significant depressive symptoms (CES-DC) [183] and 43% reported clinically significant insomnia (ISI) [215].

Children above cutoff for clinically significant ASD-traits (SRS) and ADHD-symptoms (Conners 3) (combined; $n = 38$) reported significantly lower HRQoL than children ($n = 108$) below cutoff ($p < .001$) on the PedsQL full scale and all four subscales, with large effects for emotional-, social-, and school functioning. Children above cutoff also reported significantly ($p < .001$) higher levels of pain interference (PII), and significantly ($p < .001$) more depressive symptoms than children below cutoff. These effects were large.

With reference to at-risk cutoff scores for the PedsQL and CES-DC, 79% of children above cutoff for clinically significant ASD/ADHD-traits and symptoms reported a HRQoL equal to or below at-risk (children below ASD/ADHD cutoff, 50%), 58% reported significant depressive symptoms (children below ASD/ADHD cutoff, 28%), and 63% reported clinically significant insomnia (children below ASD/ADHD cutoff, 36%).

Both higher levels of ASD-traits, and higher levels of ADHD-symptoms were, to a moderate degree, associated with higher levels of depressive symptoms and pain interference respectively ($p < .001$), and with lower levels of HRQoL ($p < .001$). ADHD-symptoms and ASD-traits further contributed significantly to the prediction of HRQoL ($p < .001$), depressive symptoms ($p < .001$), and pain interference ($p < .001$), and in combination accounted for 14.3% of the variation in PedsQL, 15.2% of the variation in CES-DC, and 11.3% of the variation in PII, with adjustment for age, gender, and pain intensity. In terms of their individual contributions, both C3 and SRS obtained significant beta coefficients for all dependent variables, with the largest unstandardized beta coefficients for HRQoL.

Analyses of indirect effects showed significant ($p \leq .01$) indirect effects of insomnia (ISI) in each of the relationships between ADHD-symptoms and the dependent variables (depressive symptoms, pain interference, and HRQoL), with adjustment for the covariates age, gender, and pain intensity. In contrast, no significant indirect effects were seen for insomnia in any of the relationships between ASD-traits and the dependent variables. In similar analyses of indirect effects, significant ($p \leq .01$) indirect effects of psychological inflexibility (PIPS) in all of the respective relationships between ADHD-symptoms and ASD-traits and the dependent variables were found. In three models (Conners 3 - PII; SRS - PII; SRS - PedsQL) with PIPS as the mediator, the direct effects (c') between the predictor and the dependent variables were non-significant, indicating a strong mediating effect of psychological inflexibility on these relationships.

6 DISCUSSION

The purpose of this research project was to identify and assess parental and child factors of importance for functioning and treatment effects in pediatric chronic pain. More specifically, the project aims were to validate an instrument for parental psychological flexibility (**Study I**), to assess the effects of a brief parental ACT-intervention on parent outcomes (**Study II**), to assess the prevalence of traits and symptoms of ASD and ADHD in children (**Study III**), and to explore the relationships between traits and symptoms of ASD and ADHD, functioning, and HRQoL (**Study IV**).

6.1 MAIN FINDINGS

In **Study I**, the construct validity and reliability of the Swedish translation of the PPFQ was confirmed. Also, the psychometric analyses resulted in a shortened instrument with a total of 10 items and three (instead of four) [130] factors (i.e. PPFQ-10). PPFQ-10 explained a significant amount of variance in both criteria variables, i.e. parental anxiety and depression. In **Study II**, parents of adolescents with chronic pain showed significant improvements in psychological flexibility and pain reactivity following a brief ACT-based parental intervention, with clinically significant increases in functioning for a majority of parents. **Study III** showed that the total prevalence of clinically significant ASD-traits and ADHD-symptoms in this sample of children presenting with chronic pain in tertiary care was 26% (ASD-traits 13.7%; ADHD-symptoms 19.9%). Clinically significant ASD-traits were more prevalent in girls than boys, but no gender differences were seen in clinically significant ADHD-symptoms. In **Study IV**, ASD-traits and ADHD-symptoms significantly predicted pain interference and depression, as well as reduced HRQoL in children with chronic pain. Children with clinically significant ASD-traits or ADHD-symptoms had significantly higher levels of depressive symptoms and pain interference, and significantly lower HRQoL, compared to the rest of the sample. When exploring the nature of these relationships, psychological inflexibility was shown mediate the influence of ADHD-symptoms as well as ASD-traits on the dependent variables (depression, pain interference, and HRQoL). Also, insomnia mediated the relation between ADHD-symptoms and dependent variables.

6.2 CHILD CHARACTERISTICS

The samples of children included in this research project were comparable on demographic variables and clinical correlates, such as pain, depression, and insomnia, to existing studies on pediatric chronic pain. The samples e.g. included a large majority of girls, having a mean pain duration exceeding six months, and daily pain episodes when presenting for tertiary care [18, 21, 23, 26, 27]. In all three samples, a majority of children (56 - 76%) also reported pain from multiple body sites, which concurs with research showing that many children with chronic pain report multi-site pain [24, 25], particularly girls [24]. Also, children in the included samples (**Study II, III and IV**) reported headache and abdominal pain as the most common pain sites, which is consistent with existing studies [18, 24], which have also shown a higher risk of experiencing pain from additional locations when presenting with headache or abdominal pain [24]. A considerable number of children in the included samples further presented with clinically significant levels of depressive

symptoms (**Study II, III and IV**), i.e. at or above 24 on the CES-DC [183]. In Study IV, 58% of children reported a level of HRQoL that was below or equal to the cut-off for poor HRQoL [194, 214]. Furthermore, 43% reported clinically significant insomnia (ISI) [215]. These results are also in line with other studies on pediatric chronic pain showing that sleep disorders [75] and comorbid mental health conditions [8, 52] are common, and that children with chronic pain report significantly lower HRQoL than children with other chronic conditions and healthy children [101]. In summary, the typical child with chronic pain included in the current project was a teenage girl experiencing multi-site pain, mainly from the head and stomach, with comorbid depressive symptoms, insomnia, and poor HRQoL, and results provide additional support for the relationships between pediatric chronic pain, insomnia, and poor HRQoL [74, 75, 99, 101, 178, 214, 216].

6.3 PARENTAL FACTORS

Of the accompanying parents in the current studies, a majority were mothers and 33 - 58% reported having own pain conditions. Chronic pain conditions have been found to be common among parents of children with chronic pain [47], and parental own chronic pain has, as noted earlier, been associated with an increased risk for anxiety and depression in children [48] as well as poorer outcomes than for other children with non-afflicted parents [49]. Notably, the level of own pain in parents was considerably higher in **Study II** (58%), that only included adolescents with debilitating chronic pain, than in **Studies III and IV** (33% own pain). The mean and median parental anxiety and depression scores on the HADS in **Study I and II** were also at or above the clinical cutoffs [182, 217], with particularly elevated scores for anxiety among parents in **Study II**. Anxiety is frequently reported among parents of children with chronic pain along with depressive symptoms [218], and has been shown to predict child depression and functioning in longitudinal studies [46]. Overall, parental sample characteristics and clinical correlates are consistent with previous research in pediatric chronic pain and emphasize the relationships between parent and child clinical profiles in pediatric chronic pain [42].

The construct of parental psychological flexibility was shown to display consistency also in a Swedish sample of parents in **Study I**. This points to the instrument's clinical utility in assessment of parental flexibility in handling distressing situations vis-à-vis their child's pain. The strong associations between PPFQ and parental anxiety and depression may indicate that lower psychological flexibility, as an indication of behavioral rigidity/rule governed behavior, potentially increases the risk for less adaptive and avoidance driven behavior, which may eventually lead to a feeling of helplessness and distress. Studies on parent's distress in pediatric chronic confirms this pattern between behavior and distress, including feelings of helplessness and child age-inappropriate parenting [42].

The inclusion of parents in the treatment of pediatric chronic pain is encouraged but significant treatment effects have typically been lacking, particularly in the long term [118]. Recent studies, however, show that parental distress over time predicts child disability, stressing the importance of parental factors. [119, 120]. In **Study II** the parental levels of psychological flexibility and pain reactivity were significantly improved, while levels of parental distress were not. This corresponds well with the conceptualization provided by learning theory and RFT [121]. Notably, psychological flexibility may result in more

activity engagement and thus more exposure to distress [121], which further implies the relevance of analyzing the temporal aspect of changes in the proposed mechanisms (psychological flexibility) and outcome variables. In summary, effects from studies on parental interventions in pediatric chronic pain are emerging, and the results from Study II provides tentative additional support for the involvement of parents. A majority of parents reported improvements that were also clinically significant with regard to managing the pain of their child. This indicates that psychological flexibility may constitute an important treatment target in order to increase effective parenting and improve resilience to parental distress.

6.4 NEURODEVELOPMENTAL COMORBIDITY (ASD-TRAITS AND ADHD-SYMPTOMS)

In **Study III** the prevalence of clinically significant ASD-traits was 13.7% and of clinically significant ADHD-symptoms, 19.9%. These numbers are clearly elevated as compared to a large, population-based longitudinal case-control study (SRS) [219], and in terms of mean T-scores, in comparison to overall instrument norms (Conners 3) [189, 220]. Using tentative comparisons between the results from the present study and the normal prevalence of ASD and ADHD, the levels of traits and symptoms indicative of neurodevelopmental disorders are also substantially higher [134, 135, 138], especially in girls that were found to show more clinically significant ASD-traits than boys. Research shows that both girls with ASD [221] and girls with ADHD [222] tend to be missed or disregarded in clinical practice and, although tentative, these findings may indicate that children with chronic pain are at risk for presenting with a comorbid neurodevelopmental disorder. Moreover, of all children, only 4.8% had a previously indicated diagnosis of ASD or ADHD, which may further indicate that neurodevelopmental disorders could go unrecognized in many children with chronic pain [163]. The lack of differences in pain variables (intensity, duration, frequency, and site) is interesting, and one reason may be that the current study did not include children with more severe neurodevelopmental deficits (e.g. to allow for self-report questionnaires). Thus, it is possible that children with clinically significant ASD-traits or ADHD-symptoms in the current study represent a subsample within the ASD- or ADHD spectrum with a comparatively higher level of functioning in this domain.

The children with chronic pain and clinically significant traits of ASD or ADHD symptoms reported significantly higher levels of depressive symptoms and insomnia, more pain interference, and significantly lower HRQoL, than did the other children in the sample in **Study IV**. The causal direction of these relationships cannot be inferred. Tentatively, however, it is possible that deficits in executive function associated with ASD and ADHD [153], may cause difficulties in social and academic situations, which may thus function as a chronic stressor for these children [167]. This in turn may elevate the risk for various health problems [167], which is supported by research showing that medical comorbidities are common in ASD and ADHD [163, 164]. Research has also indicated shared neuropathophysiological processes between chronic pain and neurodevelopmental disorders. For example, hypodopaminergic state (low dopamine function) and sensory abnormalities have been documented in chronic pain conditions [86, 96, 98] as well as in ASD and ADHD [146, 223, 224], and may be linked to reward-driven behavior [98]. Also,

it has been suggested that children with ASD and high levels of anxiety and sensory over-responsivity may be at risk for developing chronic pain [146].

The mediating role of insomnia on the relationships between ADHD-symptoms and HRQoL, depression, and pain interference is interesting in the light of recent research suggesting a very close connection between ADHD and sleep disturbances, which may contribute to some of the core ADHD symptoms [225]. Insomnia has also recently been suggested as a mediator in the relationships between PTSD-symptoms and pain interference in pediatric chronic pain [79], indicating the importance of addressing insomnia in pediatric chronic pain treatment. The mediating role of psychological inflexibility in the relationships between both ASD-traits and ADHD-symptoms and HRQoL, depression, and pain interference is particularly interesting because of the potential implications of psychological flexibility for e.g. goal orientation and resilience [123]. Maintaining focus on values and goals in the face of interfering stimuli may require attention and capacity for complex decision-making under stress. These behaviors appear closely associated with aspects of executive function [226], and impairments in executive function constitute central deficits in ADHD and ASD [153].

6.5 CLINICAL IMPLICATIONS

Although tentative, the results support the utility of assessing and targeting parental psychological flexibility in the treatment of children with chronic pain. Results further suggest that neurodevelopmental disorders should be assessed more frequently in children and adolescents presenting at pain clinics due to chronic pain. Screening is not equivalent to the extensive assessment required for diagnosis. However, the present research project shows that a relatively brief screening process facilitated detection of potentially critical factors in a group of children with severe impairments in a number of domains. Thus, screening for ASD and ADHD in pediatric chronic pain may help to identify at-risk groups. The mediating roles of insomnia and psychological inflexibility further suggest that insomnia and psychological flexibility may be potential treatment targets for children with comorbid chronic pain and clinically significant traits of neurodevelopmental disorders, particularly when these factors are high and related to functioning and HRQoL. Clinical interventions for these patients may further benefit from complementary strategies to improve attentional control skills, given how attention is both linked to executive function and psychological flexibility.

6.6 LIMITATIONS

The studies included in this thesis have a number of limitations of which some are inherent to their design. First, the cross-sectional design in **Study I, III, and IV** does not allow for causal or temporal inferences [227], which means that any discussions concerning possible reasons for results are to be regarded as merely tentative. Second, the sole use of self-assessments for the children in **Study IV** may have increased the risk of common method bias, which potentially influences the likelihood of finding significant relationships among included variables. For all studies, the inclusion of objective measures of functioning, e.g. psychiatric diagnoses in parents (**Study I and II**), and e.g. school absence in children (**Study II and IV**) could have increased the validity of the findings. Third, using only HADS as the criteria variable in the validation of the PPFQ in **Study I** represents a

limitation, as it may not be generalizable to other criteria variables. Fourth, in **Study II**, the lack of a robust design with e.g. randomization to waitlist condition limits the internal validity of the results. Also, the sample of parents was relatively small, and the design did not allow for examination of change processes. Furthermore, follow-up assessments were not included, which prevents analyses of the long-term stability of treatment effects. Finally, although **Study III** was adequately powered for assessing the main research questions, a larger sample size would have benefitted sub-group analyses of e.g. pain sites and triggers further.

7 CONCLUSIONS AND FUTURE DIRECTIONS

The present research project contributes to the field by providing more knowledge about the assessment and possible utility of addressing parental psychological flexibility in pediatric chronic pain treatment, however, more research is warranted. Future studies should e.g. evaluate the predictive utility of the PPFQ for child treatment outcomes, and evaluate if parental support programs increasing parental psychological flexibility also have positive effects on the children. The research also contributes with increased knowledge about comorbid ADHD-symptoms and ASD-traits in pediatric chronic pain, and illustrate significant relationships between such traits and symptoms and overall functioning in children. Children with debilitating chronic pain, and in particular girls, may be at risk for having a comorbid, and possibly undetected high-functioning neurodevelopmental disorder. Results suggest the utility of screening for neurodevelopmental disorders in children with chronic pain, and may indicate insomnia, and skills related to psychological flexibility, such as attentional control and coping with demanding situations, as potential treatment targets to improve functioning and HRQoL. The results also suggest further research, to e.g. validate these findings in larger studies, evaluate the utility of tailored interventions, and examine a possibly shared neuropathophysiology of chronic pain and neurodevelopmental disorders, including dopamine function and sensory abnormalities. Furthermore, results call for studies that examine the relation between e.g. pain, insomnia, psychological inflexibility, and executive function in pediatric chronic pain.

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