From DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

PSYCHOLOGICAL FACTORS, SICKNESS BEHAVIOR AND INFLAMMATORY BIOMARKERS IN LONGSTANDING PAIN

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Stockholm 2022

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THESIS FOR DOCTORAL DEGREE (Ph.D)

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The thesis will be defended in public at the Karolinska University Hospital, Stockholm, June 16th

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"If we knew what it was we were doing, it would not be called research, would it?"

  - Albert Einstein

POPULAR SCIENCE SUMMARY OF THE THESIS

One in five of us has pain that does not go away, making it harder to go about in everyday life. For some, the pain can be accompanied by depression, anxiety, and difficulties sleeping. Why does the pain, which is a signal to protect us, stay for years when it is not helping us any longer? We do not fully know this yet, and when the pain is longstanding, medicines seldom help to ease symptoms or increase functioning. Several patients have less symptoms, better functioning, and higher quality of life after behavioral treatment, however, there is variation in outcome. Some patients experiencing longstanding pain report several symptoms, some of which also can be described as sickness behavior. A good measure of sickness symptoms is important to facilitate further studying of these phenomena in longstanding pain. Also, several studies have found elevated levels of low-grade inflammatory biomarkers in patients with longstanding pain and for example depression. Sickness behavior and inflammatory biomarkers could be factors that influence the effect of the behavioral treatment. The purpose of this thesis was to explore the relationship between psychological factors, sickness behavior, and inflammatory biomarkers in patients experiencing longstanding pain. This research may improve knowledge of symptoms experienced by patients with longstanding pain and a better understanding of factors possibly underlying the variability in treatment outcome.

In the first study, we wanted to test if the questionnaire SicknessQ was a good measure of perceived sickness behavior among persons with longstanding pain, and we found that it was. In study two, we wanted to investigate how sickness behavior in patients with chronic conditions differed from that in individuals with experimental acute sickness, primary care patients, the general population, and healthy controls. In addition, we wanted to explore how sickness behavior was related to self-rated health and health-related functioning. We found that patients with chronic pain and Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/CFS) reported similarly high levels of sickness behavior – higher than primary care patients, and comparable to levels in experimental inflammation.

In studies three and four, levels of low-grade inflammatory biomarkers were measured, and questionnaires were used before and after the participants underwent Acceptance and Commitment Therapy (ACT). The treatment is an exposure-oriented behavioral intervention that promotes the ability to engage in valued activities also in the presence of pain and distress – psychological (or behavioral) flexibility. In study three, we wanted to investigate if levels of depression, anxiety, insomnia, self-rated health, pain intensity as well as sickness behavior were related to low-grade inflammatory biomarkers in patients with chronic pain. These symptoms had weak associations with the included

inflammatory biomarkers. In study four we wanted to investigate if low-grade inflammatory biomarkers affected pain interference (the influence of pain on a person's everyday life), pain intensity, and psychological inflexibility after ACT-treatment. We found that participants with higher levels of two inflammatory biomarkers at the start of treatment had less improvement in psychological inflexibility.

ABSTRACT

Background: Longstanding pain affects a large number of adults worldwide. In addition to pain, several factors like depression, anxiety, and insomnia can also affect disability and quality of life. Some patients improve following psychological treatment with regards to symptoms, functioning, and quality of life, but there is considerable variation in outcome. Furthermore, it is not fully known for whom or why treatment is effective. Sickness behavior and inflammation are possible factors to consider in the maintenance of longstanding pain, and these factors may influence treatment outcome.

Aims: The specific aims of this thesis were to: Evaluate aspects of construct validity and reliability of the SicknessQ in patients with longstanding pain (Study I); Investigate how sickness behavior in patients with chronic conditions (chronic pain and ME/CFS) differed from that in participants with experimental acute sickness, primary care patients, the general population and healthy controls. In addition, to explore how sickness behavior was related to self-rated health and health-related functioning (Study II); Investigate if levels of depression, anxiety, insomnia, pain intensity, self-rated health, and sickness behavior were related to low-grade inflammatory biomarkers (Study III); Investigate if low-grade inflammation affected the outcome of ACT concerning maximum pain intensity, psychological inflexibility as well as pain interference and whether there were changes in ongoing inflammatory activity following ACT (Study IV).

Methods: Study I: Construct validity of the SicknessQ was evaluated by performing a confirmatory factor analysis (CFA) and by hypothesis-driven analyzes. Reliability was evaluated by analyzing the internal consistency of items. Study II: Correlations and linear regression analyzes were used to investigate associations between sickness behavior, self-rated health, and health-related functioning. Study III: Associations between the factors described in the aims were analyzed using bivariate Spearman rank correlation coefficients and regression analyzes. ANOVA was performed to investigate potential differences between subgroups. Study IV: The treatment effects and moderating effects of IL-6 and TNF-α on alterations in outcomes were analyzed using linear mixed models.

Results: Study I: In the final CFA, the Chi-Square test was not significant (χ^2 [32, $N = 190$] $= 42.95$, $p = 0.094$), indicating a perfect model fit for the one-factor model. Internal consistency was adequate, as indicated by a Cronbach's α value of 0.82 for the entire questionnaire. Study II: Patients with chronic pain ($M = 16.1$), patients with ME/CFS ($M = 16.1$), LPS-injected individuals ($M = 16.3$), and primary care patients ($M = 10.7$) reported significantly higher SicknessQ scores than individuals from the general population ($M = 5.4$) and healthy controls ($M = 3.6$), all p's < 0.001. Higher levels of sickness behavior were significantly associated

with poorer self-rated health and health-related functioning (p's < 0.01) in the general population and chronic pain sample, but not significantly in the ME/CFS sample. Study III: There were significant correlations between insomnia and hsCRP ($p < 0.05$); sex and ESR ($p < 0.05$); age and IL-6 ($p < 0.05$) and IL-8 ($p < 0.05$); BMI and IL-6 ($p < 0.001$), hsCRP ($p < 0.001$) and ESR ($p < 0.001$). Sickness behavior and anxiety ($p < 0.05$ and $p < 0.001$, respectively) contributed significantly, explaining 49% of the total variance in depression. Similarly, sickness behavior ($p < 0.05$) contributed significantly, explaining 34 % of the total variance in insomnia. Inflammatory biomarkers, however, did not contribute significantly to the models. There were significant differences between subgroups of depression regarding age, self-rated health, anxiety, insomnia, and sickness behavior ($p < 0.001$, respectively) as well as hsCRP ($p < 0.05$). In subgroups of insomnia, there was a significant difference in BMI, pain intensity, self-rated health, anxiety, and IL-6 ($p < 0.05$, respectively) as well as depression and sickness behavior ($p < 0.001$, respectively). Study IV: Mean baseline levels of IL-6 and TNF-α tentatively moderated improvement in psychological inflexibility during treatment ($p = 0.044$), but not in pain interference ($p = 0.205$) or pain intensity ($p = 0.536$). Cytokine levels did not change over the course of the treatment (IL-6/TNF-α $p = 0.086/0.672$).

Conclusion: The results indicated that the SicknessQ is a brief questionnaire with reliable and valid statistical properties to assess sickness behavior in adults with longstanding pain. Patients with chronic pain and ME/CFS reported similarly high levels of sickness behavior, higher than primary care patients, and comparable to levels in experimental inflammation. Participants rated a relatively high symptom burden, but the included symptom variables had weak associations with the included inflammatory biomarkers. Higher levels of baseline inflammatory biomarkers (IL-6 and TNF-α) were related to less improvement in psychological inflexibility.

LIST OF SCIENTIFIC PAPERS

I. Åström J, Holmström L, Karshikoff B, Andreasson A, Kemani MK. Evaluating the construct validity and internal consistency of the Sickness Questionnaire in a Swedish sample of adults with longstanding pain. Scand J Pain 2022;22:88–96. doi:10.1515/sjpain-2021-0070.

II. Jonsjö MA, Åström J, Jones MP, Karshikoff B, Lodin K, Holmström L, et al. Patients with ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) and chronic pain report similar level of sickness behavior as individuals injected with bacterial endotoxin at peak inflammation. Brain, Behav Immun - Heal 2020;2:100028. doi:10.1016/j.bbih.2019.100028.

III. Åström J, Karshikoff B, Holmström L, Lekander M, Kemani M, Wicksell RK. The relationship between psychological factors and markers of low-grade inflammation in patients with chronic pain (manuscript in preparation).

IV. Karshikoff B, Åström J, Holmström L, Lekander M, Kemani M, Wicksell RK. Baseline pro-inflammatory cytokine levels moderate psychological inflexibility in behavioral treatment for chronic pain. J Clin Med 2022;11:2285. doi:10.3390/ jcm11092285.

Scientific paper not included in the thesis:
Åström J, Lidén Y, Wicksell RK, Wincent A, Sjölund KF. An observational study on risk factors for prolonged opioid prescription after severe trauma. Scand J Pain 2020;20:345-351. doi: 10.1515/sjpain-2019-0095.

CONTENTS

LIST OF ABBREVIATIONS

IASP	International Association for the Study of Pain
ICD-11	International Classification of Diseases 11th Revision
CRPS	Complex Regional Pain Syndrome
SQRP	Swedish Quality Registry for Pain Rehabilitation
CNS	Central Nervous System
LPS	Lipopolysaccharide
hsCRP	high-sensitivity C-Reactive Protein
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-4	Interleukin-4
IL-17A	Interleukin-17A
TNF-α	Tumor Necrosis Factor-alpha
CSF	Cerebrospinal Fluid
IL-1Ra	Interleukin-1 Receptor Antagonist
NsLBP	Non-specific Low Back Pain
TGF-β	Transforming Growth Factor β
NS	Neutral Stimulus
UCS	Unconditioned Stimulus
UCR	Unconditioned Response
CR	Conditioned Response
CS	Conditioned Stimulus
RFT	Relational Frame Theory
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
SicknessQ	Sickness Questionnaire
SBI-R	Sickness Behavior Inventory-Revised
IL-1β	Interleukin-1β
IL-1R	Interleukin-1 Receptor
ESR	Erythrocyte Sedimentation Rate

CBT	Cognitive Behavioral Therapy
ACT	Acceptance and Commitment Therapy
RCT	Randomized Controlled Trial
MBSR	Mindfulness-Based Stress Reduction
HADS	Hospital Anxiety and Depression Scale
ISI	Insomnia Severity Index
PDI	Pain Disability Index
SF-12	12-item Short Form Survey
NRS	Numeric Rating Scale
PIPS	Psychological Inflexibility in Pain Scale
SF-36	RAND SF-36 Short Form Health Survey
PHQ-9	The Patient Health Questionnaire-9
GAD-7	General Anxiety Disorder-7
SRH-5	Self-Rated Health
PII	Pain Interference Index
KUH	Karolinska University Hospital
CFA	Confirmatory Factor Analysis
ANOVA	Analysis Of Variance
PEA	The Proximity Extension Assay
NPX	Normalized Protein eXpression
IBQ	The Illness Behavior Questionnaire
SAIB	Scale for the Assessment of Illness Behaviour
BRIQ	Behavioural Responses to Illness Questionnaire
IPQ-R	The Revised Illness Perception Questionnaire
TLR	Toll-Like Receptor

1 INTRODUCTION

Pain urges us to take action to protect ourselves from injury and external threats to our bodies. Pain can therefore be seen as a motivational state that initiates defending responses, to diminish damage, followed by recuperative behaviors for recovery from injury. In this way, pain is important for our survival. The pain experience, however, depends on the brain's evaluation of danger and the expected benefit of protective behavior, not on the true danger level and the actual benefit of our protective behavior. When pain persists, it can be hindering in a way that affects our everyday life.

Several patients with longstanding pain improve after psychological treatment and experience that they are less hindered by symptoms, but there is considerable variation in outcomes. Working as a clinical psychologist at the Karolinska University Hospital, I thought about how we could adapt our exposure therapy to have a better effect for the patients currently not benefitting adequately from the regular treatment. I noticed that several patients with longstanding pain described many other symptoms such as fatigue, concentration issues, low mood, and "a feeling of sickness". I wondered if these symptoms, resembling sickness behavior, could be one of the many possible factors that influenced treatment outcome, as at least for some patients the symptoms seemed to be of much hindrance. I was also intrigued when a previous study conducted at our clinic showed that baseline inflammatory biomarkers tentatively moderated the behavioral treatment effect, and that also one inflammatory biomarker was lower after treatment. I was interested to see if these results would be displayed with a larger study sample. I hoped that this thesis could give more knowledge about symptoms and the role of inflammatory biomarkers in longstanding pain, as this may generate new hypotheses regarding future treatment.

Stockholm, May 2022

2 LITERATURE REVIEW

2.1 Definitions of pain

The definition of pain has recently been updated by the International Association for the Study of Pain (IASP) to highlight that pain is an experience that can be associated with tissue damage but does not have to be: *An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage* [1]. Chronic pain is also denoted as longstanding or persistent pain.

The definitions of chronic pain have been revised in the classification system ICD-11 [2][3]. In cases with a persistent injury or disease in the body, with pain lasting for more than three months, the pain is labeled as chronic secondary pain. Examples of chronic secondary pain are cancer-related pain, pain in long-term inflammatory diseases, or persistent pain after a nerve injury. In these types of pain, medication may sometimes be necessary to treat the underlying disease. A much more common type of long-term pain is called chronic primary pain, which is defined as pain in one or more parts of the body that has lasted for more than three months and is associated with significant disability and/or emotional suffering and is not better explained by another diagnosis. The subgroups of chronic primary pain are chronic primary musculoskeletal pain (such as long-term low back pain), complex regional pain syndrome (CRPS), chronic primary visceral (internal) pain (such as IBS), chronic primary headache, or orofacial pain, and chronic widespread pain. Chronic primary pain is not clearly linked to any single factor, but it can be said that the pain system reacts more strongly than necessary and that the warning system is overactive [2][3].

2.2 Longstanding pain – epidemiology

Longstanding pain affects about 20% [4] of the population and has a higher prevalence in women and with increasing age in the adult population [5]. Several experimental studies have demonstrated that women are more sensitive to pain than men [6]. A large study including 22 406 patients with chronic pain from the Swedish Quality Registry for Pain Rehabilitation (SQRP) showed that the mean age was 42.4, 11.8 % were born outside of Europe and 23.7 % had an university education [7]. Also, pain complaints are common in obese individuals, and obesity is common in chronic pain conditions [8].

Pain conditions seem to contribute the most to disability around the world and have an extensive negative impact on quality of life compared with other health problems [9]. About one-quarter to one-third of children experience longstanding pain, with about 1 in 20 experiencing moderate to high levels of pain-related disability [10]. Functional abdominal pain in childhood and adolescence has been

shown to increase the risk for chronic pain later on [11]. Pain has been shown to affect daily functioning and quality of life but is also associated with substantial societal costs. The estimated yearly cost in Sweden has amounted to 87.5 billion SEK, including medicines, health-care utilization, sick leave, and production losses [12]. In the United States, the estimates of the national cost of pain range from 560 to 635 billion dollars [13]. In primary health care, four out of ten visits to doctors are shown to be due to pain [14]. Thus, longstanding pain can have a severely negative effect on the individual who experiences it, as well as on society at large.

Acute pain is commonly successfully treated with pharmacological therapy [15]. However, in longstanding pain, pharmacological treatment approaches are often ineffective or insufficient to alleviate symptoms and increase functioning [16]. Opioid treatment for longstanding pain is associated with increased health risks, such as opioid abuse, overdose, fractures, sexual dysfunction, and myocardial infarction [17] as well as financial costs [18]. Opioid-dependent patients are more likely to engage in healthcare utilization from new providers and less likely to return to work [19]. Psychological treatments that address longstanding pain will be covered later in this literature review.

2.3 The experience of pain, physiology, and etiology of longstanding pain

The common definition of pain entails that pain is subjective, and is affected by several different factors [1]. In conjunction with specific signaling via the nervous system, the pain experience consists of three components: sensory discriminative (intensity, location, character, and duration of pain); affective (discomfort associated with the pain); and cognitive (the effect of pain on thoughts and actions) [20][21]. Thoughts, perceptions, and feelings can both intensify and alleviate the pain experience. Experimental studies have shown that attention to pain, depressive mood, and anxiety toward pain amplify pain perception [22][23]. On the other hand, being asked about more positive aspects of the situation and how one manages the pain has instead been shown to increase pain tolerance [24]. Pain has been described as not only a sensation but a motivation, similarly to itch, thirst, and hunger, a certain emotion that reflects homeostatic behavioral drive [25].

In addition to our feelings and experiences, the place we are at and the people who are present at the moment can also affect the pain experience. If the context is perceived as threatening, the pain experience can become more unpleasant – and if the context is perceived as important or even pleasurable, the pain experience is affected in the other direction. The American researcher and anesthesiologist Henry K. Beecher reported as early as 1946 that pain and tissue damage does not have to correspond particularly well. Only one-quarter of the soldiers included in his observational study said that the pain from their severe wounds was enough to cause them to want morphine. Beecher suggested that this may be because the

injuries prevented the soldiers from fighting and escaping a life full of discomfort, anxiety, fear, and the real risk of death [26].

There are many potential factors involved in the transition from acute to longstanding pain. Nociceptor inputs can spark a prolonged increase in the excitability and synaptic effectiveness of neurons in central nociceptive pathways, described as central sensitization [27]. In this case, the pain system becomes generally overprotective by amplifying warning signals in our central nervous system and alerting us to things even if it is not a dangerous situation anymore. It can be likened to a fire alarm which is supposed to detect fire smoke but instead can be triggered by only water vapor. Greater functional connectivity of the nucleus accumbens with the prefrontal cortex has been shown to predict pain persistence, suggesting that the corticostriatal circuitry is causally involved in the transition from acute to longstanding pain [28]. Also, elevated levels of inflammatory biomarkers have been found in patients with longstanding pain [29] and may be another factor potentially affecting the transition from acute to long-term pain. This will be explored in the following chapter.

2.4 Pain and inflammatory biomarkers

2.4.1 Parts of the immune system involved in pain

Research emphasizes the importance of the immune system in long-term pain problems, in relation to the onset and maintenance of pain. Different factors are suggested to be involved; classical neurotransmitters, as well as immune mediators, both released centrally from the central nervous system(CNS)-resident microglia and astrocytes, and from infiltrating cells such as T-cells. Microglia, the central nervous system's immune cells, are activated during both pain and inflammation and are suggested to be key players in the transition from acute to chronic pain [30]. Cytokines are small proteins, signaling molecules, which are coordinating the immune system. One could say that they are the immune system's language. Certain cytokines seem to be involved in the initiation as well as the persistence of pain by directly activating nociceptive sensory neurons [31].

2.4.2 Experimental studies with inflammation and pain

As causality cannot be inferred by observational clinical studies, experimental studies are used to study the mechanisms by which the immune system influences the pain system. The most common immunological trigger in humans is ultralow doses of the bacterial endotoxin lipopolysaccharide (LPS), which is an established model to measure immune-to-brain communication and behavioral features of inflammation [32]. Pain sensitivity (hyperalgesia) has been shown to increase during experimental immune activation [33], causing a central effect in the pain circuitry. Also, subclinical inflammation is related to increased pain sensitivity, with

higher levels of high-sensitivity C-reactive protein (hsCRP) negatively related to cold-pressor tolerance [34]. Healthy participants injected with LPS have shown decreased activity in brain areas involved in descending pain regulation as well as increased activation of areas involved in pain and interoception [35].

2.4.3 Cytokines in patients with longstanding pain
Elevated levels of inflammatory cytokines have been found in patients with longstanding pain [29]. Higher levels of pro-inflammatory markers have also been associated with greater pain [36][37], e.g. concentrations of both Interleukin-6 (IL-6) and Interleukin-8 (IL-8) have been found to be correlated with the severity of clinical symptoms [38]. However, there are also studies finding no differences in cytokines between patients with fibromyalgia and controls [39], nor between patients with pelvic pain and controls [40].

As studies show conflicting results, this overview will discuss the aggregated findings from meta-analyses. There are to my knowledge three meta-analyses that study inflammatory biomarkers and fibromyalgia: A meta-analysis from 2011 including 25 articles illustrated that patients had higher serum levels of Interleukin-1 receptor antagonist (IL-1 Ra), IL-6, and IL-8, and higher plasma levels of IL-8. Importantly though, the majority of investigated cytokines were not different between patients and controls [41]. A meta-analysis from 2020 included 29 studies, showing that IL-6, Interleukin-4 (IL-4), and Interleukin-17A (IL-17A) were significantly higher in fibromyalgia compared to healthy controls [42]. The most recent meta-analysis consisting of 22 studies showed significantly increased Tumor Necrosis Factor-alpha (TNF-α), IL-6, IL-8, and Interleukin-10 (IL-10) in fibromyalgia patients compared with healthy controls [43]. There are also reviews of non-specific low back pain (NsLBP) [44][45][46]. Two systematic reviews, one with seven studies [44] and one with ten studies [45], showed elevated TNF-α in patients with NsLBP. Further, another systemic review with 13 studies found a positive association between the level of TNF-α, CRP as well as IL-6, and nsLBP symptoms [46]. A literature review on neuropathic pain highlighted TNF-α as the most studied cytokine in the studies of biomarkers and neuropathic pain, but IL-1β, IL-6, and IL-17 as well as IL-4, IL-10, and transforming growth factor-beta (TGF-β) were also often studied [47]. Studies that investigate the differences in proteins between groups with chronic pain and controls using broad panels of inflammation-related proteins have demonstrated a clear difference in system inflammation patterns in both plasma and CNS [48][49][50][51][52]. However, the proteins detected varied in the different studies and the sample sizes were quite small, with risk for possible e.g. inflated false discovery rate.

In summary, there are several recent attempts in the literature aiming at mapping the expression patterns of biomarkers in different pain states, and the

pain peptide network is yet to be understood and described as a whole. The literature is contradictory when it comes to altered protein patterns and pain, both peripherally, as assessed in blood and tissue samples, and in the CNS, as assessed in CSF. The inflammatory biomarkers vary in the direction and level of expression. This may be explained by disease state and duration as well as variations in symptom severity, and differences in assays and design, such as the timing of measurements. Furthermore, even if an association is found, causality cannot be established. It is still unknown if a subgroup of patients has pain due to inflammation or vice versa, or due to other factors such as insomnia or lack of physical activity, which may, in turn, affect inflammatory markers. Most studies mentioned above, include homogenous groups of patients and general conclusions about other pain populations can thus not be made.

2.5 Psychological perspective on pain

Longstanding pain is commonly viewed from a bio-psycho-social perspective. This model was developed as a response to the biomedical perspective in which illness is regarded as caused by only biological mechanisms. The bio-psycho-social perspective instead suggests that biological (e.g. nociception), psychological (e.g. mood and catastrophizing), and social factors (e.g. cultural factors and social support) all play a role in the development and course of illness [53].

A range of psychological factors is related to the maintenance of pain and pain-related disability. In the 1970s, Fordyce took an important step in understanding the psychology of pain when he proposed the notion that pain could be analyzed as behaviors [54], such as resting or taking medication as well as seeking care. Thoughts and emotions, and other internal events, are also seen as forms of behavior. One learns to handle pain by thinking in a certain way or taking different actions. This may reinforce the action and make the behavior more probable in the future if these behaviors lead to less pain or associated discomfort [55].

Learning theory posits that all behavior is learned in interaction with the context mainly via different modes of conditioning. *Operant conditioning* relates to learning based on consequences that follow a specific behavior occurring in conjunction with a given antecedent situation. These consequences either increase (via reinforcement) or reduce (via punishers) the likelihood that these behaviors occur in similar future situations. Learning the consequences of our actions (e.g. operant conditioning) offers a degree of control over our environment. Described briefly, *respondent conditioning* occurs when an environmental stimulus - neutral stimulus (NS) is paired in direct temporal proximity with an unconditioned stimulus (UCS) that is associated with an unconditioned response (UCR). For example, conditioning may occur if a certain dental procedure (NS) evokes pain

(UCR) due to unforeseen nerve provocation (UCS) during the procedure, and future visits to the dentist may after this experience evoke strong fear. The fear is then a conditioned response (CR) to the now conditioned stimulus dental procedure(CS) [56]. Stimuli are also found on the inside of the person, such as emotional sensations and various bodily sensations. Interoceptive stimuli deliver afferent communication from receptors that monitor the internal state of the body such as stiff joints or a feeling of discomfort [57]. These will also be able to function as conditioned stimuli, then we talk about interoceptive conditioning. Some bodily sensations have become a conditioned stimulus for fear (conditioned response) [56]. The immediate detection of physical symptoms that represent a potential threat, such as pain or dyspnea, may be a crucial evolutionary advantage, as it makes our often shifting environment more predictable [58].

Finally, *derived conditioning* (Relational Frame Theory; RFT) refers to a learning process aiming to provide a behavioristic account of language and cognition that occurs in everyday language practices, and interplays with both respondent and operant learning processes. In short, key features include the relating of stimuli with other stimuli; behavior occurring in line with these relations; and those stimuli receiving their functions (e.g., fear) indirectly via (transformation in accordance with) their specific relations to other stimuli. This means that conditioning can take place, within language, without directly contacting the specific stimulus or situation, which is a prerequisite for operant and respondent conditioning. For example, this may occur if the person in the previous example asks about a certain medical procedure and learns that *it is like* the previously experienced dental procedure, and then subsequently equates these procedures in some relevant aspects, and the medical procedure from there on is associated with fear and potentially avoided [56].

Another important perspective, based on learning theory, is the fear-avoidance model, in which fear-avoidance beliefs are suggested to be an important factor in explaining the transition from acute to longstanding conditions [59]. According to Lethem who introduced an early version of the model, pain is interpreted as either fearful or harmless. The fear-avoidance model has recently been updated, now including either priority to valued life goals leading to approach and on to recovery, or priority to pain control leading to fear and then avoidance, interference, negative affect, and then on to more pain [60]. Fear has been shown to aggravate pain as the nervous system increases its sensitivity to an upcoming threat and the body becomes more hypervigilant, increasing the risk of transition to long-term pain. *Vigilance* is an abnormal focus on potential signals of pain or injury that can be part of the reason why an outwardly small injury can result in intense pain [61]. In longstanding pain, avoidant behavior can work together with the fear of pain and vigilance to symptoms and therefore maintain pain and

disability. E.g. people with a higher baseline in anxiety-avoidance are two times as likely to have back pain and have a 1.7 times higher risk of reduced physical function a year after baseline [62]. In sum, for patients with chronic pain, extreme avoidance behavior has been shown to aggravate pain [61] and the degree of avoidance behavior is a predictor of pain-related disability [63]. Meanwhile, interestingly, fear has been shown to induce discomfort but not necessarily disability [64].

2.5.1 Avoidance

Rene Descartes (1596-1650) had an early outlook of pain as a reflex, that a nociceptive stimulus in the body elicits pain which in turn leads to a reactive withdrawal reflex [65]. But the reflex is not occurring after the injury has happened. Pain is a strong driver for learning, aiming at predicting to preventing harm. Charles Darwin coined "Great pain urges all animals… to make the most violent and diversified efforts to escape from the cause of suffering" (1897), highlighting that emotion is driving action [66]. The theory of pain has developed from re-action to pro-action [67].

There are many theories for the transition from acute to longstanding pain. A fair amount of research has focused on the classical conditioning of pain previously described, that a neutral movement can elicit fear and avoidance response. Far less research has been focused on avoidance itself, and from a clinical perspective, one could argue that avoidance behaviors are even more important. I recommend the review of Meulders [64], which gives an excellent overview of different forms of learning and avoidance. Pain-related avoidance is any behavior aiming to prevent an anticipated painful situation or stimulus or to avoid the aversive anticipatory state associated with it, from occurring. Pain prioritizes the identification of signals that precede the occasion of pain and bodily damage and enables us to protect ourselves to limit or avoid the harmful impact [64]. Experiential avoidance, which is an attempt to suppress unwanted internal experiences, has been indicated to explain individual differences in the pain experience. Pain acceptance or the ability to engage in valued activities despite pain is negatively associated with negative mood, functional impairment, and pain intensity [68]. However, it should be noted, that the associations point to risk factors and not causal pathways.

From a clinical view, it is important to note that although avoidance can prevent patients from facing the feared outcome such as pain or associated discomfort, it can paradoxically lead to amplified fear in the long-term [61], and increase the threat of pain and lead to interference in daily life [63]. On this note, even when the aversive outcome is avoided, fear-related activation in the insula and amygdala seems to continue [69], suggesting that avoidance maintains rather

than removes fear. Unfavorably, avoidance behavior diminishes the occasions to learn that the feared stimulus no longer is connected with pain, and this makes avoidance especially hardy to extinction. Avoidance may have a rewarding element that could elucidate its continuation, even if it is connected with high costs [70]. Thus, a person's perceived wish to avoid unpleasant experiences, such as pain, could prevent one from activities that are important and rewarding, which in turn could lead to pain disability or pain interference.

2.6 Sickness behavior
Hart defined sickness behavior as 'a coordinated set of adaptive behavioral changes that develop in ill individuals during the course of an infection' [71]. Sickness behavior includes symptoms such as increased pain sensitivity, pain, malaise, fever, loss of appetite, anxious as well as depressive behavior, and anhedonia [72]. These symptoms represent very common problems in health care [73][74]. Exposure to pro-inflammatory cytokines or endotoxins produces sickness behavior that is similar to flu-like symptoms [75]. These changes were first described in laboratory animals that were infected experimentally, and that is how the term 'sickness behavior' was coined, but they are now studied in human models as well. In the body, cytokines communicate to the brain that an infection has happened in the periphery, and cytokines can do this via the route via the blood and the blood-brain-barrier interface [76] or by direct neural transmission via the afferent vagus nerve [77].

Sickness behavior is a multi-faceted construct and can be seen as an umbrella term that includes the illness response to endotoxins, behavioral changes and symptoms (which can be observed by others), and one's own experience of feeling sick. Sickness behavior has evolved to enable recovery from an acute illness, but when the recovery process is delayed it may contribute to prolonged sickness [72]. The sickness behaviors can be activated without the involvement of an infectious agent, through administration of LPS [32] as described, by conditioning [78], or by stress [79]. Sickness behavior is therefore relevant in situations besides the classical situation where the organism fights an actual infection [32][78][79]. Sickness behavior that is prolonged and has become dysfunctional is implicated in the development and maintenance of persistent pain [80]. Longstanding pain, depression, and fatigue have been suggested to be partly a consequence of maladaptive sickness behavior [81]. In Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), patients can besides fatigue also present with widespread pain and headache, general malaise, cognitive difficulties, and tender lymph nodes [82].

People's perception also seems to matter with regards to levels of sickness behavior, shaped by top-down expectations. In an experimental study with

participants experiencing overall sickness behavior following LPS, low expectations of becoming sick before injection resulted in more emotional distress. Helping patients to achieve more realistic expectations of symptoms is possibly something that could be done in clinical work [83]. Perceived sickness behavior closely resembles determinants of poor self-rated health [84], which is a strong predictor of long-term health, and poorer subjective health is shown to be associated with higher levels of inflammatory cytokines. Self-rated health is shown to be a more robust predictor of cytokine levels than physician-rated health [85].

A reliable and valid measure of generalized sickness symptoms is important to facilitate further studying of this topic and to investigate the prevalence and validity of this construct for patients with longstanding pain. It may have a clinical value to explore perceived sickness behavior due to correlations with e.g., sleep problems, depression, and pain, and could perhaps be used as a global measurement for the symptoms and co-morbidity seen in patients with longstanding pain. For both research and clinical purposes, a validated and reliable global instrument that is easy to distribute, easy to interpret, has adequate psychometric properties, and is in line with sickness behavior theory is of importance. To our knowledge, no measurement of sickness behavior had been validated in persons with longstanding pain when we planned Study I, and we saw a knowledge gap. We, therefore, decided to conduct a psychometric evaluation of the Sickness Questionnaire (SicknessQ) in a pain sample from our clinic, to explore the construct of perceived sickness behavior and test aspects of validity as well as reliability. We were interested in how perceived sickness behavior may affect patients with longstanding pain and how we could improve treatment for patients with these symptoms.

Because there was not an instrument specifically capturing sickness behavior in humans, The Sickness Questionnaire (SicknessQ) was developed to assess perceived sickness behavior, symptoms, and experiences in relation to sickness (such as the desire to be still, alone and inactive), symptoms of soreness, shakiness, nausea, headache as well as the experience of feeling depressed and drained. SicknessQ is developed in Swedish and designed to capture core aspects of sickness behavior and current symptoms in a more acute illness phase as well in more longstanding conditions, for example in longstanding pain. A previous study has shown that the SicknessQ has adequate internal consistency and is adequately and significantly associated with depression, anxiety, self-rated health, and a single item of feeling sick [86]. The questionnaire has been evaluated twice after the first study [87][88], in addition to the study conducted as part of this thesis. Recently, another instrument aiming at capturing sickness behavior has been developed, the Sickness Behavior Inventory-Revised (SBI-R), demonstrating adequate reliability

and construct validity in a sample of patients with metastatic lung cancer [89]. It has yet to be evaluated in patients with longstanding pain.

2.7 Longstanding pain and psychiatric co-morbidity

Longstanding pain is associated with psychiatric co-morbidity (depression and anxiety) [90][91], fatigue, sleep problems, functional disability, and reduced quality of life [4]. A study from a Swedish specialized inpatient pain clinic showed that fatigue, as well as difficulties concentrating, were experienced by over 80% of participants [92]. Panic disorder, social phobia, and posttraumatic stress disorder also have noticeably higher prevalence rates in the pain population in comparison to the general population [93][94][95]. It has been shown that a majority of patients with longstanding pain describe that the pain severely affects sleep, the ability to exercise, walk, do household chores, participate in social activities, and the ability to have a sexual relationship [4]. For children with longstanding pain, especially girls, a recent study suggests there is an elevated risk of having a neurodevelopmental disorder [96].

The sequential relationship between psychiatric co-morbidities and longstanding pain is unclear and most likely bidirectional. The onset of affective and anxiety disorders came before longstanding pain in adolescents in one study, proposing that psychiatric disorders in childhood may be a risk factor for developing chronic pain [97]. In musculoskeletal pain, it has been shown that depression promotes pain, but that pain promotes depression as well [98]. The occurrence of multiple psychiatric disorders in patients with chronic pain has been shown to significantly increase disability [99].

2.8 Psychiatric co-morbidity and inflammatory biomarkers

The prolonged activation of the innate immune system may be involved in several disturbances in the brain, ranging from Alzheimer's disease to stroke, depression [77], and schizophrenia [100]. Inflammatory mechanisms have been proposed as an underlying factor for longstanding pain and depression due to overlapping neuroimmune mechanisms [80], e.g. the kynurenine and tetrahydrobiopterin pathways [101][102]. Several meta-analyses of cross-sectional associations have found elevated inflammatory markers in depressed patients compared to healthy controls [103][104][105]. Another meta-analysis found aberrant cytokine levels in the blood, cerebrospinal fluid, and postmortem brain samples of patients with suicidality in comparison to healthy controls [106].

The DSM criteria for depression are broad and it has been suggested that persistent low-grade inflammation may be associated with a subtype of major depression, inflammatory cytokine-associated depression [107]. Higher CRP levels have been associated with depressive symptom severity among women, suggesting

a possible subgroup of depressed patients with elevated inflammatory markers [108] and minor increases in inflammation have been shown to correspond with increases in features of depression [109]. Dysregulation of the inflammatory response system may be linked with a more severe form of depression more probable to re-occur, as a longitudinal study showed that higher levels of IL-6 and CRP predicted depressive symptoms at follow up five years later [110]. It has been suggested that repeated mild infections play a role in the etiology of major depression [111] since repeated low-grade infection has been associated with a higher likelihood of difficult-to-treat responses [109].

Anti-inflammatory treatment has been tested for depressed patients, and common antidepressants seem to affect inflammatory levels. IL-6 levels have decreased with SSRI treatment in patients with major depression [112]. Patients who received SSRI before and during interferon therapy were significantly more likely to remain free of depression [113]. TNF antagonists have no general efficacy in treatment-resistant depression, but for patients with high baseline inflammatory biomarkers, the treatment may improve depressive symptoms [114].

Also, anxiety and insomnia are common co-morbid problems for patients with longstanding pain. When it comes to anxiety, two recent meta-analyses found inflammatory markers to be elevated in people with post-traumatic stress disorder [115][116], while results for other anxiety disorders are mixed [117][118][119]. There is support for insufficient sleep contributing to increased inflammatory activity in a meta-analysis [120] and one other study with patients with chronic fatigue [121]. Persistent but not intermittent insomnia is associated with a sharper increase in serum CRP level [122]. Furthermore, sleep disturbance seems to increase the vulnerability to depression by amplifying affective sensitivity to cytokines in females [123]. Although, another other study found no relationship between measures of self-reported sleep duration and CRP [124].

Poor self-rated health is associated with higher levels of inflammatory cytokines in women, specifically Interleukin-1 beta (IL-1β), Interleukin-1 receptor (IL-1R), and TNF-α, but not IL-6 [85]. Later, a study has shown a significant association between erythrocyte sedimentation rate (ESR) and self-rated health in adolescent men [125]. Subjective ratings of health have been shown to offer vital clinical data about inflammatory status, outside usual objective risk factors, also amongst generally healthy individuals [126].

The relationship between cytokines and psychiatric symptoms above does not state causality. For example, depressive symptoms have been found to predict later changes in inflammatory markers[127], while one meta-analysis of longitudinal studies found small but significant associations between inflammatory markers and succeeding depressive symptoms [128]. Further studies are required to establish

the relationship between psychiatric co-morbidity and inflammatory biomarkers, especially in patients with longstanding pain, where there is a large knowledge gap.

2.9 Behavioral treatment for patients with longstanding pain

As described previously, pharmacological treatment is often insufficient in alleviating symptoms and increasing functioning for persons with longstanding pain [16]. Since pain is a subjective experience [1] and a close link between pain and emotions has been documented, the pain might be modulated by emotions [23], attention, expectation, and learning [22]. Psychological treatment for longstanding pain has the potential to address the symptoms and co-morbidity described earlier in this review (e.g., depression, insomnia, perceived sickness behavior, and avoidance behaviors) – and not only pain or functional ability. Broadly, cognitive behavioral therapy (CBT) aims at reducing symptoms and disability and improving mood. Exposure is an important part of CBT and comprises a guided systematic approach toward the fear-provoking stimuli, for example, an object or a situation [129].

Part of the CBT family is Acceptance and Commitment Therapy (ACT), which is a therapy model based on a contextual behavior science approach [130], focusing on increasing behavioral flexibility, also named psychological flexibility, as a means to achieve improvements in clinical outcomes, such as functioning and quality of life. In ACT, experiential avoidance refers to behavior that aims at reducing the intensity, frequency, and duration of unwanted experiences such as pain and sickness symptoms. While avoidant behavior is adaptive in the acute phase of illness, the outcome of such strategies seldom leads to positive outcomes in the long run. The overall aim of ACT is to identify such behavior as unhelpful and to shift the perspective, from behaviors aiming at short term alleviation from unwanted symptoms, towards behavior in line with personal values and short- and long-term goals, also in the presence of unpleasant subjective experiences such as pain and fear that cannot be affected directly – this is behavioral flexibility [130]. Additionally, both CBT and ACT include more educative sessions that aim to provide a more helpful framework for understanding longstanding pain and psychological factors, and for achieving more long-term effectiveness in regaining functioning and higher quality of life.

ACT for longstanding pain has been evaluated in several trials. In general, results show increased function and behavioral flexibility, reduced disability, depressive symptoms and anxiety, but results are mixed with small to large effect sizes [131][132][133][134][135][136][137][138][139][140][141]. One study showed that 20 % were clinically improved on functional disability after treatment [140]. A recent systematic Cochrane review states that CBT has very small to small beneficial effects for reducing pain, distress, and disability in chronic pain. The

review further states that the trials were of moderate to very low quality, which makes the results uncertain [129]. Also, there is uncertainty about the duration of effects [142].

CBT delivered via internet or mobile phone interface is becoming more common and internet-delivered treatments are supported for a number of conditions [143] and there is also evidence that internet treatments can be cost-effective [144][143][145], as well as having similar effect sizes as group treatment [144] for a number of different conditions. Several clinical trials show promising results for internet-delivered CBT for longstanding pain, regarding decreased pain intensity, disability, anxiety, depression, and increased functioning, however, effect sizes are modest and uncertain due to relatively few studies and some low-quality studies [146]. At large, internet-delivered ACT have been efficacious as to decrease pain interference, but results are mixed [147][148][149][150][151]. In a recent review including five randomized controlled trials (RCTs), small effects for psychological flexibility, depression, and mindfulness were found post-treatment, and medium effects were seen for pain interference and pain acceptance [152]. A meta-analysis from this year with 36 studies found small effect sizes for interference and disability, depression, anxiety, pain intensity, self-efficacy, and pain catastrophizing [153].

Even though predictor or moderator analyses in relation to treatment outcomes have not been conclusive so far, patients with initially high behavioral flexibility tended to decrease their pain interference following treatment [154]. When it comes to mediation, increased behavioral flexibility mediated reduced mental and physical health, pain interference, pain intensity, depression, and anxiety [155][156]. Although, it should be stated that there are a limited number of large-quality RCTs, and psychological flexibility measures rely on retrospective recall that is not context-dependent which direct measurements via mobile phone could be.

In conclusion, although CBT is an evidence-based treatment for maintaining or increasing functioning and quality of life for patients with longstanding pain, treatment efficacy varies between individuals. In order to help more people suffering from longstanding pain and its associated symptoms, there is a need to address the large individual variability in the outcome as well as to clarify predictors of treatment outcomes. The investigation of these variables, predictors, moderators, and mediators is central to generating new knowledge with the purpose of further refining and developing treatment methods [157].

2.10 Behavioral treatment and inflammatory biomarkers
There are a number of possible factors at the start of treatment that could play a role in the outcome of treatment. Inflammation is one possible candidate for

influencing behavioral treatment effects, as inflammation may increase pain sensitivity directly and amplify cognitive and emotional disturbances, thus hindering the effect of the treatment. Experimental immune activation can increase anxiety and depressed mood, decrease cognitive abilities [80], affect motivation [158] and induce pain in humans [33] as well as malaise [81]. Thus, some routes react to inflammatory cues, affecting pain processing, mood, and cognition [80]. Below is an overview of investigations of the role of inflammation and its potential role as a predictor or moderator of treatment effect.

Several studies have explored psychological treatments' effect on inflammatory biomarkers with mixed results [159][160][161][162][163][164]. Out of five studies focused on depressive disorder, IL-6 was significantly decreased after CBT [161][162] in two. TNF-α was decreased significantly after CBT for depressed patients in the study including this marker [162]. CBT with exercise for depressed patients was associated with increased anti-inflammatory IL-10 at weeks 8 and 16 compared to the active control condition and waiting list [160]. The reduction of pro-inflammatory markers during CBT was associated with better clinical improvement for depressed patients [159]. Another study investigated inflammatory markers in depression and anxiety [164], and none of the markers were reduced following treatment. For insomnia, one study showed that CBT reduced CRP [163]. Thus, the potential effect of behavioral treatment on inflammatory biomarkers is indecisive. A recent meta-analysis showed that the overall combined effect size from pre to post psychological intervention on levels of pro-inflammatory biomarkers levels was statistically significant, although of a small magnitude. Only CRP was found to significantly decrease following psychological intervention when looking at the individual biomarkers [165]. Another meta-analysis described that there are inconsistencies between studies, but that at least one inflammatory marker was reduced following CBT in 14 of 23 studies [166].

In patients with longstanding pain, two studies before this thesis indicated the possible role of inflammation as a moderator of treatment effects in behavioral therapy [167][168]. Higher pre-treatment levels of cytokines were significantly related to lesser treatment response of pain intensity, psychological inflexibility, and mental health-related quality of life after ACT and applied relaxation. Interestingly, the levels of peripheral TNF-α also decreased from pre- to post-treatment [167]. In a study with patients with fibromyalgia, IL6/IL-10, as well as IL-8/IL-10, were associated with less improvement in psychological inflexibility after Mindfulness-Based Stress Reduction (MBSR)-treatment [168]. Two other Swedish studies also found decreasing cytokine levels among the patients with longstanding pain after multimodal rehabilitation programs including pain education, physical exercise, and interventions based on cognitive-behavioral

16

therapy [169][170]. In addition, another fairly small study [171] found that IL-8 decreased after treatment. In sum, inflammatory biomarkers might affect treatment outcome, and symptomatic improvement following behavioral treatment might involve changes in inflammatory biomarkers. However, given the large variability in outcome following treatment, it is very plausible that the possible effect of inflammatory biomarkers on treatment outcome also varies greatly between subgroups of patients.

2.11 Summary of the literature review

Longstanding pain and its associated symptoms can have a large and negative impact on the individual and for society at large. Associations between psychiatric co-morbidity and inflammation, as well as longstanding pain, have been reported in several studies, but the association is unclear. Furthermore, inflammatory biomarkers and sickness behavior may be possible predictors of treatment outcome. A good measure of sickness symptoms is important to facilitate further studying of these phenomena. The research conducted within the frame of the present thesis may be a further step toward improving knowledge of what affects interference in patients with longstanding pain and generate new hypotheses regarding what factors can be of importance for treatment outcome.

3 RESEARCH AIMS

The specific aims of this thesis were to:

1. a) Evaluate aspects of construct validity (structural validity) by performing confirmatory factor analysis and; b) by testing the hypothesis that ratings of sickness behavior in combination with other factors e.g. depression and anxiety would be significantly related to ratings of avoidance.
c) Evaluate reliability by analyzing the internal consistency of items. (Study I).

2. a) Investigate the level of sickness behavior in patients with chronic pain and patients with ME/CFS as compared to four reference groups.
b) Determine whether there were differences in the sickness behavior profile between patients with chronic pain, ME/CFS, and healthy subjects injected with LPS.
c) Investigate the relationship between sickness behavior and health-related functioning as well as self-rated health, along with if the strength of the associations differed between patients with chronic pain, ME/CFS, and individuals from the general population. (Study II).

3. a) Investigate the interrelationships between levels of depression, anxiety, insomnia, pain intensity, self-rated health, and sickness behavior as well as levels of low-grade inflammatory biomarkers (TNF-α, IL-6, IL-8, IL-10, hsCRP, and ESR).
b) Investigate potential differences in relation to age, BMI, pain intensity, anxiety, sickness behavior, and levels of low-grade inflammatory biomarkers (TNF-α, IL-6, IL-8, IL-10, hsCRP, and ESR) between subgroups reporting no, low, or medium to severe ratings of insomnia and depression. (Study III).

4. a) Investigate if baseline low-grade inflammatory biomarkers affect the outcomes pain intensity, psychological inflexibility, and pain interference following ACT-treatment.
b) Investigate whether any ongoing inflammatory activity is altered following ACT-treatment. (Study IV).

4 MATERIALS AND METHODS

Table 1. Overview of studies I-IV.

Study	Design	Participants (n)	Variables	Statistical analyzes
I	Cross-sectional validation study	190	SicknessQ, HADS, ISI, PDI, SF-12 item one, NRS, the avoidance subscale in PIPS	Confirmatory Factor Analysis, Pearson correlations, regression analyzes, Cronbach's alpha
II	Cross-sectional	623*	SicknessQ, SF-36/SF-12	Pearson correlations, regression analyzes
III	Cross-sectional	83	PHQ-9, GAD-7, NRS, ISI, SRH-5, SicknessQ, blood samples of TNF-α, IL-6, IL-8, IL-10, hsCRP, ESR	Bivariate Spearman rank correlations, regression analyzes, ANOVA
IV	Pre-post	78	Maximum NRS, PHQ-9, GAD-7, PIPS, PII & blood samples of TNF-α and IL-6	Linear mixed model

Note: SicknessQ (Sickness Questionnaire), HADS (Hospital Anxiety and Depression Scale), ISI (Insomnia Severity Index), PDI (Pain Disability Index), SF-12 - item one (12-item Short Form Survey (SF-12)), NRS (Numeric Rating Scale), avoidance subscale in PIPS (Psychological Inflexibility in Pain Scale), SF-36/SF-12 (RAND Short Form Health Survey), PHQ-9 (The Patient Health Questionnaire-9), GAD-7 (General Anxiety Disorder-7), SRH-5 (Self-Rated Health), TNF-α (Tumor Necrosis Factor-alpha), IL-6 (Interleukin-6), IL-8 (Interleukin-8), IL-10 (Interleukin-10), hsCRP (high sensitivity C-Reactive Protein), ESR (Erythrocyte Sedimentation Rate), PII (Pain Interference Index)

* Out of the 48 healthy subjects, 29 received an injection with LPS, and are therefore part of two samples.

4.1 Study I

In this cross-sectional study, patients were referred from primary and tertiary care units in Stockholm County, Sweden, to the Behavioral Medicine Pain Treatment Unit at the Karolinska University Hospital (KUH) from 2009 to 2013. Patients were eligible for study inclusion if they were ≥ 18 years of age, presented with a pain duration ≥ six months, and could fill out the questionnaires independently in Swedish. The participants were assessed by a psychologist and a pain physician. Data on age, gender, medication (pain, psychiatric and anti-inflammatory drugs), and pain duration were collected by a pain physician at the first visit. Level of sickness behavior (SicknessQ), depression and anxiety (HADS), insomnia (ISI), functional disability (PDI), self-rated health (SF-12 - item one), pain intensity (NRS), avoidance (subscale Avoidance in PIPS) were investigated with validated questionnaires (see Study I for more details). Construct validity was analyzed by performing a Confirmatory Factor Analysis (CFA). To further address construct validity, a number of hypothesis-driven correlational analyzes, described in Mokkink et al. [172], were performed. To investigate aspects of reliability the internal consistency was evaluated by analyzing Cronbach's α, and an α value ≥ 0.80 was considered adequate.

4.2 Study II

This cross-sectional study included six samples; patients with chronic pain (n = 190), patients with ME/CFS (n = 38), patients with primary care patients (n = 163), healthy subjects with lipopolysaccharide-induced(LPS) inflammation (n = 29), individuals from the general population (n = 155) and healthy subjects (n = 48). Out of the 48 healthy subjects, 29 of them received an intravenous injection with 0.6 ng/kg LPS (E. Coli, Lot nr: G3E0609, United States Pharmacopeia Rockville, MD. The participants with chronic pain in Study II are the same as in Study I. The recruitment process and patient characteristics in the different groups are reported in more detail in Study II, as well as in prior studies referred to in Study II. Sickness behavior was measured using SicknessQ. In the chronic pain, ME/CFS, and general population groups, SF-36/SF-12 (RAND Short Form Health Survey) was used to assess health-related functioning and self-rated health. See Study II for psychometric details of the questionnaires included. Levels of sickness behavior in patients with chronic pain and patients with ME/CFS were compared to primary care patients, individuals from the general population, and healthy subjects. Correlations and regression analyzes were used to investigate associations between sickness behavior and self-rated health as well as health-related functioning in patients with chronic pain, patients with ME/CFS, and the general population.

The hypotheses were that patients with chronic pain and patients with ME/CFS would report higher levels of sickness behavior in comparison to healthy subjects, primary care patients, and individuals from the general population but lower than healthy subjects injected with LPS. Furthermore, the hypotheses were a) that patients with chronic pain and ME/CFS would report similar levels of sickness behavior, including items on fatigue and pain given the high co-morbidity, b) as well as report lower levels on items not relating to core symptoms in their respective condition, than LPS-injected healthy subjects. Moreover, the hypotheses were that the strength of the associations between self-rated health and sickness behavior, and physical and mental health-related functioning would be similar in patients with chronic pain, ME/CFS, and individuals from the general population.

4.3 Study III

In this cross-sectional design, self-report questionnaires and blood plasma levels of inflammatory biomarkers were collected from adult patients with chronic pain at baseline as a part of Study IV. See the methods summary of study IV below for a description of recruitment, screening, inclusion as well as exclusion criteria. Depression (PHQ-9), anxiety (GAD-7), pain intensity (NRS), insomnia (ISI), subjective health (SRH-5) and sickness behavior (SicknessQ) were measured with validated questionnaires (see Study III for more details). Data on age, gender, demographics, medications, pain duration, pain localization, and co-occurring symptoms were collected at the study start. The Olink Inflammation Panel (Olink, Uppsala, Sweden; https://www.olink.com/products/inflammation/) was used for analysis. The cytokines were standardized using Z-score standardization, i.e. a mean $= 0$ and a standard deviation $= 1$. Associations between psychological factors (depression, insomnia, anxiety, self-rated health, sickness behavior), pain intensity, and inflammatory biomarkers (TNF-α, IL-6, IL-8, IL-10, hsCRP, ESR) as well as sex, age, BMI, pain duration and recruitment type, were analyzed using bivariate Spearman rank correlation coefficients.

Two multiple linear regression analyzes, with insomnia and depression as dependent variables, were conducted to further evaluate the contribution of the included independent variables, as well as the explained variance. To further illustrate potential differences between subgroups of participants, with regard to demographic and background variables, self-ratings of pain intensity, pain duration, self-rated health, anxiety, and sickness behavior as well as BMI and inflammatory markers, analysis of variance (ANOVA) was performed. Established clinical cut-offs for insomnia (ISI) and depression (PHQ-9) were used to categorize participants. The scores on ISI were categorized as follows[173]: "No insomnia" (0-7); "Mild insomnia" (8-14); and "Moderate to severe insomnia" (15-28). The scores on PHQ-9 were categorized as follows[174]: "No or mild depression" (0-

9); "Moderate depression" (10-14); and "Moderate to severe depression" (15-27). To identify possible significant differences between subgroups, Tukey's HSD post hoc analysis was performed, with adjustment for multiple comparisons.

The hypotheses were that there would be a positive correlation between pain intensity, co-morbid symptomatology, and low-grade inflammatory biomarkers. Secondly, the hypotheses were that these interrelationships would be stronger in subgroups of patients with high levels of co-morbidity.

4.4 Study IV

Participants with chronic pain were consecutively recruited between 2016 and 2018, either via referrals from primary and tertiary care units in Stockholm County to be included in a face-to-face ACT-treatment, or via an advertisement in local newspapers to be included in an internet-delivered ACT-treatment. Inclusion criteria were: ≥ 18 years of age; pain duration > six consecutive months, with a negative impact on daily functioning; pain not estimated to be alleviated by medical intervention; were able to communicate in Swedish; stable medication for the last two months. Exclusion criteria were: participated in a simultaneous treatment based on CBT; severe psychiatric co-morbidity that required acute assessment or treatment (e.g., psychotic symptoms, suicidal ideation); a spontaneous improvement could be expected. Further exclusion criteria for phlebotomy were pregnancy, having given birth within the last year, breastfeeding, and hemophilia. Participants included in the face-to-face treatment were assessed with semi-structured interviews by a pain physician and a psychologist. Patients recruited for internet-delivered treatment were instead assessed by either a psychologist or candidate psychology student under supervision via telephone interview. In this latter setting, a physician was consulted based on the further need to assess pain symptoms in more depth. Psychiatric conditions were evaluated using a somewhat modified version of the Mini International Neuropsychiatric Interview version 5 [175].

The participants completed surveys in conjunction with the blood sampling and before and after the ACT-treatment. The included validated questionnaires were maximum pain intensity (NRS), depression (PHQ-9), anxiety (GAD-7), psychological inflexibility (PIPS), and pain interference (PII). See Study IV for psychometric details of the questionnaires included. Blood plasma of IL-6 and TNF-α levels was analyzed with the Olink Inflammation Panel (Olink, Uppsala, Sweden; https://www.olink.com/products/inflammation/). A composite score based on the mean values of IL-6 and TNF-α levels at baseline was used as a measure of ongoing low-grade systemic inflammation, similar to Lasselin et al. [167]. Linear mixed models were used to analyze the treatment effects and moderating effects of low-grade inflammation on alterations in outcomes.

The hypotheses were that 1) Pain interference and psychological inflexibility would improve following treatment, and pain intensity decrease; (2) Levels of low-grade inflammatory biomarkers would decrease during treatment; and (3) Baseline inflammatory levels would moderate the effect of treatment on pain interference, pain intensity, and psychological inflexibility.

4.5 The treatment: Acceptance and Commitment Therapy

In studies III and IV participants could be enrolled in three different treatment schedules: ACT face-to-face treatment, internet-delivered treatment (iACT), or treatment via a mobile application interface (ACTSmart). The ACT-treatment face-to-face followed the standard treatment at the Behavioral Medicine Pain Treatment Unit, KUH, which has been evaluated before [136]. iACT has been evaluated previously with good effect [176], as has ACTSmart [177]. The different treatment schedules have different formats, but the theoretical foundation and content were similar – to diminish avoidance behaviors and increase value-based behaviors. The interventions included present-moment-awareness, acceptance, and defusion (distancing to thoughts) to enable participants to engage in value-oriented exposure. iACT and ACTSmart were arranged in a microlearning format, with experiential exercises and value-oriented exposure [176]. Participants had access to the next level in treatment when the prior level was finished. The face-to-face treatment included weekly 45 minutes-long sessions and the digital treatment program in iACT and ACTSmart was eight weeks and included contact with the psychologist and feedback via messages at least weekly within the treatment platform. All treatment schedules included working with assignments for the next session or module. The treatment was conducted by licensed psychologists or intern psychologists who had training in ACT and treatment for adults with longstanding pain. These psychologists received supervision by a clinician with extensive experience in ACT-treatment for patients with longstanding pain.

4.6 Methodological discussion
4.6.1 Statistics

In all four studies, statistical methods such as linear regression or Pearson correlation have been used for ordinal data, analyzes commonly used for the interval or continuous data. It has been argued that if the data is ordinal non-parametric tests should be used, but if the data can justly be classified as interval, sample size and the distribution are important to evaluate [178]. I am aware of the issues and decided to use these analyzes in the articles, even though the output is an approximation rather than a precise estimate, and the findings remain tentative.

Furthermore, Study IV was not a replication of the study by Lasselin et al. [167], as we did not include IL-8 or the self-report questionnaire, the Pain

Disability Index (PDI), in the analysis. Rather, we focused on the significant findings and evaluated if similar findings could be demonstrated in a larger sample. Pain Interference Index was included for all participants in the study since it is a common outcome measure in behavioral treatment, whereas the participants who were part of the first iACT-group did not have the questionnaire Pain Disability Index, which made it difficult to use since we would have to exclude several participants' data from analysis.

4.6.2 Analysis of inflammatory biomarkers

Since the literature on the role of blood proteins in longstanding pain does not show conclusive results, we found it important to choose proteins based on larger scale reviews such as meta-analysis, experimental studies as well as our previously stated hypotheses. When we chose inflammatory biomarkers to include in Study III we chose TNF- α, IL-6, IL-8, IL-10, hsCRP, and ESR based on the literature and the prior hypotheses. We also chose inflammatory biomarkers common in hospital settings (hsCRP and ESR) since they are clinically relevant. In our ethics application, we also included the biomarkers IL-1β and IL-1ra, which would also have been of relevance to include, but they were not included in the Olink inflammatory panel. However, it may be other cytokines than the ones included in our studies that are relevant in our sample with mixed pain.

There are different types of analyzes of biomarkers and in studies III-IV we chose the Olink Inflammation Panel (Olink, Uppsala, Sweden; https://www.olink.com/products/inflammation/). Since studies III-IV focused on low-grade inflammatory biomarkers it was important to have an analysis with high sensitivity and Olink's detection technique has been described by the company as having good sensitivity and specificity, using antibodies that have been labeled with DNA oligonucleotides to bind target analytes in solution. The Proximity Extension Assay (PEA), is a multiplexable assay that can measure proteins simultaneously, and hopefully, reduce confounding variables by investigating analytes within the same assay environment. Data from Olink are in the Log2 scale in Olink's arbitrary unit called Normalized Protein eXpression (NPX), which is not an absolute quantification and instead expresses relative quantification between samples. This means that values can be compared only for the same protein across the samples analyzed and not be compared across projects run at separate time points.

Lastly, an important question is what we are looking at when we study inflammatory biomarkers in patients with longstanding pain? As has been discussed by Hysing et al. [170], oftentimes the signs of tumor, calor and rubor are missing and the systemic inflammation measures are in the normal range. Perhaps the biomarker pattern detected in the studies of patients with longstanding pain

and controls is not capturing an association with pain but rather a biomarker pattern associated with restricted activity, psychiatric disorders, or stress [170].

4.7 Ethical considerations
All four studies have been approved by the Regional Ethical Review Board in Stockholm or Uppsala, Sweden.

4.7.1 Consent and autonomy
The studies followed the requirements of the Nürnberg Code with voluntarily well-informed consent, including a clear description of the patient's right to withdraw. The participant had the opportunity to read through the written information regarding the studies, which contained information about what the study participation meant for the participants and how the data was communicated and handled. After reflection time, the participant could sign approval of participation in the studies. Informed consent was obtained from all individual participants included in the studies.

According to the Helsinki Declaration (2013), item 27, the practitioner or the researcher must be aware of whether the research person is in a position of dependence or perhaps consents in compulsion. In studies III and IV we tried to minimize that risk by having a clinician ask if the patients wanted more information from a researcher. We clearly informed them that the care would not be affected if they decided to participate in the study or not. One of the exclusion criteria was insufficient ability to understand and speak Swedish (assessed inability to assimilate the treatment or questionnaires due to linguistic difficulties). Some who were not able to understand fluent Swedish were excluded, to secure that the participants have been able to access the information for the consent.

4.7.2 Participant benefit and risk
Another requirement was that there should be no unnecessary physical or mental suffering, or injury. Patients in the studies spent more time filling in questionnaires than other patients at the clinics. The forms took about 30 minutes to complete in studies I, III, and IV, and some were administered via paper form. We chose the questionnaires we decided were needed to answer our research questions and tried to make sure no unnecessary items were included, to reduce the assessment burden for the patient. The questionnaires were similar to information obtained in regular treatment, which is why these were considered to not be of an integrity-abusive character. Blood tests in studies II, III, and IV could lead to minor discomfort with the risk of bruises and present minimal risks for the patient.

For Study II, the most important ethical aspect concerned if it was safe and justifiable to expose subjects to endotoxin injection. Endotoxin injection is an

established model for experimental immune activation in humans. The experiment was carried out in the hospital area (KUS) under the physician's observation, and the injection was handled by hospital staff with previous experience in similar studies. Some discomfort may have been experienced during the insertion of the vein catheter, and to alleviate this an anesthetic cream was applied in the arm crease 10 minutes in advance.

The ACT-treatment was an evidence-based treatment and followed standard treatment at the Behavioral Medicine clinic, KUH. The ACT-treatment consisted of about 10 sessions of 45 minutes individually each week face-to-face or via the internet or smartphone interface. The treatment was provided via different formats, and the internet-delivered and smartphone-based versions were not at well tested as face-to-face. However, the different formats were based on the same treatment model. The treatment aimed to ensure that the participants return to an active life, which could mean an increased level of activity. This involved performing activities that had been avoided due to symptoms and other discomfort. However, no major treatment risks of adverse effects of the treatment were considered to exist. Adverse events, such as increased depressive symptoms or increased pain were monitored weekly.

4.7.3 Integrity and security

As part of personal integrity, privacy is respected with good handling of sensitive data. The results were compiled, processed, and stored, manually or computerized, considering the confidentiality protection according to the applicable data law. All questionnaire paper data as well as consent in the project were stored in accordance with guidelines.

For studies III and IV, the iACT platform stores participant responses from the treatment, and all quantitative data are encrypted on secure servers, located at Karolinska Institutet. Psychologists and participants used double authentication to log in, in accordance with regulations by the National Board of Health and Welfare. For integrity reasons, psychologists could only access data and responses for the participants they had in treatment. The system platform is designed to immediately discover security breaches. The risks for the participants are therefore assessed as minor. We wrote an addition to the ethical approval to recruit participants from advertisements in a newspaper, which we later did. We used Kivra for consent for the participants who preferred that over paper consent (in studies III and IV for the participants recruited from advertisement) which is a safe platform that uses Mobile BankID. Lastly, a Material Transfer Agreement (MTA) was signed between Stockholms medicinska biobank and the receiver of samples for analysis Clinical Biomarkers Facility in Uppsala, as in accordance with *Biobankslagen.*

4.7.4 Transparency and replicability

To enable transparency, we registered studies III and IV at Clinicaltrials.org. The digital platform iACT also made it possible to follow interactions between patients and psychologists throughout treatment, to enhance transparency and replicability.

4.7.5 Conclusion of ethical considerations

In conclusion, I believe that the expected benefit should exceed the risks or the extra work required by the participants. Through their participation in the treatments, the patients got access to proven strategies to deal with pain and other symptoms and hopefully a more active life with increased quality of life. There was no other immediate benefit for the individual patient in this study, but the results could affect future processing and thus be of benefit to pain patients as a group. Participants can eventually benefit from the increased knowledge of pain and symptoms that can lead to better care of patients. Improved patient care can probably increase the quality of life also for family and friends. Hopefully, the studies can lead to improved care for this group, which can lead to savings in the form of reduced work absenteeism and reduced healthcare consumption.

5 RESULTS

5.1 Study I

Of the 190 included participants, the majority were female (78.4%), with mean pain duration of 10.8 (SD = 9.7) years and a mean age of 41.0 years (SD = 13.5). The validation of SicknessQ indicated that the questionnaire can be used to measure sickness behavior in adults with longstanding pain. The CFA evaluating a one-factor model resulted in a significant Chi-Square result (χ2 [35, N = 190] = 74.42, p < 0.001), which suggested a non-satisfactory fit. However, the model fit improved when accepting shared residual variance between these items: Item (1) "I want to keep still" and item (3) "I wish to be alone"; item (7) "I feel nauseous, and item (8) "I feel shaky"; as well as between item (6) "I feel drained" and item (9) "I feel tired". After this modification, the Chi-Square test resulted in non-significant p-value (χ2 [32, N = 190] = 42.95, p = 0.094), suggesting perfect model fit. The relative fit indices all improved, which further supported the model fit (CFI = 0.978; TLI = 0.969; RMSEA = 0.0430). Furthermore, the internal consistency was adequate, as suggested by a Cronbach's α value of 0.82 for the entire questionnaire.

The demographic control variables sex and age, the clinical variable pain duration as well as sickness behavior, anxiety, depression, self-rated health, and pain intensity were included in an Enter regression model, with avoidance as the response variable. Sickness behavior (p < 0.0001), depression (p < 0.05), and pain duration (p < 0.05) significantly explained a large portion (45%) of the total variance in avoidance. The study proposed that one can view these symptoms or sickness behavior as an antecedent to avoidance behaviors.

5.2 Study II

The majority of the participants in the chronic pain, ME/CFS, and primary care samples were female; 78.4%, 81.6%, and 70.1%. Sex was nearly similarly distributed in the healthy subjects with/without LPS-injection (56.3%; 58.6% women), and in the sample from the general population, sex was similarly distributed between genders (50% women). The chronic pain, ME/CFS, and primary care groups had comparable ages whilst the healthy subjects and LPS-injected subjects were significantly younger (p's < 0.001).

Study II illustrated that sickness behavior was quite common in participants with chronic pain and ME/CFS. Significantly higher SicknessQ scores were reported by patients with chronic pain (M = 16.1), patients with ME/CFS (M = 16.1), primary care patients (M = 10.7) and LPS-injected individuals (M = 16.3) than individuals from the general population (M = 5.4) and healthy controls (M =

3.6), all p's < 0.001. Moreover, patients with chronic pain, ME/CFS, and LPS-injected individuals reported significantly higher SicknessQ scores than primary care patients (p's < 0.01). Similarly, patients with chronic pain, patients with ME/CFS, and LPS-injected subjects showed similar sickness behavior profiles of individual items. Although, patients with ME/CFS reported significantly higher on fatigue, and patients with chronic pain reported significantly higher levels on depression. Furthermore, higher levels of sickness behavior were significantly associated with worse self-rated health and with lower levels of both mental and physical health-related functioning in the chronic pain and the general population sample (p's $< .01$). These associations were not statistically significant in the ME/CFS sample. In the chronic pain and ME/CFS samples, the strength of the associations between the SicknessQ and self-rated health as well as the health-related physical functioning composite score was significantly weaker in comparison to the general population.

5.3 Study III

The majority of the 83 participants included in the analyzes were women (72.3%), the mean age was 50.7 ($SD = 14.7$) years and the reported mean pain duration 16.3 ($SD = 13.2$) years. Study III indicated that the included symptom variables (depression, anxiety, insomnia, pain intensity, self-rated health, and sickness behavior) had weak associations with the included inflammatory biomarkers (TNF-α, IL-6, IL-8, IL-10, hsCRP, and ESR). There were significant correlations between insomnia and hsCRP ($r_s = 0.25$, $p = 0.03$); sex and ESR ($r_s = 0.29$, $p = 0.01$); age and IL-6 ($r_s = 0.26$, $p = 0.02$) and IL-8 ($r_s = 0.32$, $p = 0.00$); BMI and IL-6 ($r_s = 0.51$, $p < 0.001$), hsCRP ($r_s = 0.64$, $p < 0.001$) and ESR ($r_s = 0.44$, $p < 0.001$). Recruitment type, pain duration, pain intensity, self-rated health, anxiety, depression, and sickness behavior did not correlate significantly with any of the biomarkers.

The independent variables age, BMI, recruitment type, hsCRP, TNF-α, IL-6, pain intensity last week, anxiety, and sickness behavior were included in the linear regression models with the dependent variables depression and insomnia. Sickness behavior ($p < 0.05$) and anxiety ($p < 0.001$) were significantly explaining 49% of the total variance in depression. With insomnia as the dependent variable, sickness behavior ($p < 0.05$) was significant, explaining 34 % of the total variance.

Participants with a higher symptom burden of insomnia and depression reported significantly higher ratings on several clinical measures. However, the pattern of inflammatory biomarkers was more diverse. The ANOVA based on three categories of depression suggested significant differences between subgroups regarding age, self-rated health, anxiety, insomnia, and sickness behavior ($p < 0.001$, respectively) as well as hsCRP ($p < 0.05$). The mean value of hsCRP was

significantly different between no and moderate depression (p = [0.04], 95% C.I. = [0.07, 3.50]), while, in a sensitivity analysis excluding three participants with a hsCRP > 10, this difference was not significant. The ANOVA based on three categories of insomnia illustrated a significant difference between subgroups concerning BMI, pain intensity, self-rated health, anxiety, and IL-6 (p < 0.05, respectively), as well as depression, and sickness behavior (p < 0.001, respectively). The mean value of IL-6 was significantly different between no to mild insomnia (p = [0.03], 95% C.I. = [0.08, 1.55]), but in a sensitivity analysis excluding three participants with a hsCRP > 10, this difference was not significant.

5.4 Study IV

A total of 78 participants were included in the analysis. The majority were women (72.0%), the mean age was 52.0 (*SD* 15.0) years and the reported pain duration was 16.1 years (*SD* 13.4%). Of the participants, 56 received internet-based treatment (iACT), and 22 received face-to-face treatment. Fifty-seven of the included participants completed the treatment, resulting in an attrition rate of less than 25%.

Pain interference (p < 0.001) and psychological inflexibility (p < 0.001) improved significantly during ACT-treatment, but pain intensity did not (p = 0.078). Cytokine levels did not change over the course of the treatment (IL-6/TNF-α p = 0.086/0.672). Mean baseline levels of IL-6 and TNF-α tentatively moderated improvement in psychological inflexibility during the course of ACT-treatment (β = 14.624, p = 0.044) but not in pain interference (p = 0.205) or pain intensity (p = 0.536). This illustrated that higher mean baseline levels of IL-6 and TNF-α were related to higher levels of psychological inflexibility throughout the treatment. Sensitivity analyzes suggest robustness to this finding, since including only completers generated a significant relationship between baseline inflammation and changes in PIPS as well.

6 DISCUSSION

6.1 Validation of SicknessQ and discussion of sickness behavior

Study I indicated that the questionnaire SicknessQ can be used to measure perceived sickness behavior in adults with longstanding pain. To assess the prevalence of sickness symptoms, it is of importance to discuss the construct of sickness behavior, and what it is since there are similar terms and constructs such as sickness symptoms and feeling of sickness. As described in the literature review, the term sickness behavior is sprung out of experimental studies where the behavior of sickness was observed in rats. SicknessQ is the first global measurement of perceived sickness behavior in humans [86]. When symptoms are investigated in humans, it is possible to report behaviors verbally, which makes it possible to also look at inner behaviors. Looking at the items in the SicknessQ they read as symptoms, or feelings of sickness, rather than observable operant behavior. However, in a contextual behavioral science perspective, the word behavior refers to everything one does, including things that others cannot see we do, such as feeling or thinking [56].

In study I [179] we proposed from a behavioral standpoint, that the perceived sickness behavior based on items in SicknessQ, such as pain, can be described as motivational factors antecedent to a class of avoidant behaviors directed at short-term gains in relation to these antecedent factors, for example by achieving a decrease in pain by resting. These factors can also be combined with thoughts, such as 'I can't handle this pain', which are in turn connected to emotional processes such as worry and the physiological sensation of being tired, adding to the motivational state driven by the sickness response [180][181]. Antecedent factors, currently influencing factors present when someone does something, include both discriminatory stimuli and motivating operations. The aspect of the antecedent which signals the presence of a previously encountered reinforcing consequence is called a discriminatory stimulus [56]. The concept of a motivating operation includes situational factors, such as hunger, that increase the probability of a specific behavior, e.g. searching for something to eat, but also increase the valor of the signaled consequence. From a behavioral analytic view, sickness behavior (measured with the SicknessQ) could be described as an antecedent motivating operation, avoidance the behavior, and pain disability as well as possibly lower functioning the long-term consequences. The finding in Study I illustrating that sickness behavior explained a large part of the variance in avoidance, gives more depth to this theoretical perspective. Also, behavioral avoidance has been related to disability in chronic pain conditions [63].

The SicknessQ was developed to fill the gap for a questionnaire measuring self-reported sickness behavior, i.e., the symptoms that organisms show during

disease, in humans. There is a nearby construct called illness behavior. Engel's Biopsychosocial model was conceptualized in 1977, proposing a development of pain arising from a physical problem, to distress, then illness behavior, and finally the acquisition of a sick role, integrating biological, psychological, and social elements [182]. Mechanic described illness behavior as 'the manner in which individuals monitor their bodies, define and interpret their symptoms, take remedial action, and utilize sources of help as well as the more formal health care system' [183]. Rademacher et al. have in a recent editorial mentioned illness behavior as part of chronic sickness behavior, together with symptoms (such as fatigue, sleep disturbances, social anhedonia, depression, and pain) and chronic inflammation [184]. Illness behavior is covered by several questionnaires, some of which are diagnosis-specific. The Illness Behavior Questionnaire (IBQ) includes an assessment of general hypochondriasis, disease conviction, psychological versus somatic perception of illness, affective inhibition, and disturbance, as well as denial and irritability [185]. The Scale for the Assessment of Illness Behavior (SAIB) and a briefer 10-item version, focus on five factors: verification of diagnoses, the expression of symptoms, medication, the consequences of illness, and interoceptive scanning [186][187]. The Behavioral Responses to Illness Questionnaire (BRIQ) instead assesses the behaviors occurring specifically in the acute phase of illness, pertaining to all-or-nothing behavior, limiting behavior, as well as emotional and practical support seeking [188]. The Revised Illness Perception Questionnaire (IPQ-R) consists of an assessment of commonly experienced symptoms, timeline (acute/chronic), timeline cyclical, consequences, personal control, treatment control, illness coherence, and emotional representations [189]. Even though illness behavior is a similar construct to sickness behavior, the questionnaires above did not capture what we intended to explore in our studies and were not suitable for our hypotheses.

SicknessQ could further facilitate the evaluation of the role of sickness behavior in relation to avoidance as well as processes of change and efficacy with concern to behavioral treatments in longstanding pain. It is of importance to further operationalize and understand sickness behavior, to find out how it is linked to other constructs, and to know more about the various symptoms that patients with longstanding pain describe.

6.2 Are the experienced symptoms in patients with longstanding pain associated with inflammatory biomarkers?

Our hypothesis in Study III that there would be a positive correlation between low-grade inflammation, pain intensity, and co-morbid symptomatology was not supported, suggesting that the cross-sectional relationship between these factors were absent or weak in this sample. Experimental studies with endotoxin have

shown associations with higher levels of e.g. anxiety and depressive mood and inflammatory biomarkers [80], but the associations between symptoms and inflammatory biomarkers for patients with persistent symptoms may be different. The patients in Study III displayed long pain duration and multiple pain localizations, the findings could be different in a future study with another sample with longstanding pain or other persistent conditions, as the associations possibly are different between individuals.

Furthermore, as seen in Study III, participants with a higher symptom burden of insomnia or depression had significantly higher ratings on several clinical measures than participants with lower ratings on insomnia and depression. It is noteworthy that the significant difference between the inflammatory biomarkers for the participants with higher vs lower symptom burden of insomnia and depression is lost when participants with a higher hsCRP than 10 are excluded from analysis, indicating that the higher hsCRP values are driving the result. A study with a larger sample size could further explore the hypotheses in Study III and investigate whether the results would differ with more participants. This could also enable subgroup analyzes, exploring whether there is a subset of patients with symptoms that correlate with the level of cytokines, similarly to inflammation-associated depression [107].

In Study III, we only measured proteins at a one-time point, but there is a large natural variance of cytokines in peripheral blood, which could be one factor behind the lack of associations. Future studies using repeated measures may take these natural variations into more account. One could also investigate the hypotheses in Study III exploring networks of inflammatory agents instead of individual markers. The functions of different cytokines in chronic pain have also been discussed in the literature. An imbalance of pro-and anti-inflammatory cytokines has been argued to be one contributing factor to the maintenance of chronic pain, rather than the level of inflammatory biomarkers[190]. For example, a lack of anti-inflammatory and analgesic Th2 cytokine activity is associated with longstanding widespread pain [191] and some authors argue that therapeutic interventions could aim to balance and resolve, rather than suppress, inflammation [192]. The lack of associations in this study could also be due to other factors having a more important role than inflammatory markers for patients with longstanding pain. Perceived sickness behavior specifically measured with SicknessQ, explained significant variance in both depression and insomnia. This indicates that perceived sickness behavior, rather than inflammatory biomarkers is a relevant level of analysis in insomnia and depression in our sample.

The portrayal of sickness behavior entails that persons have the symptoms due to the immune system's sickness response [77]. In studies I-IV the participants have had pain and symptoms for a longer period than one would after experimental

inflammation, and it is not possible to conclude if the participants have these symptoms due to a prior sickness response. What we can conclude from studies I-III is that the participants with longstanding pain overall report high levels of SicknessQ and experience symptoms. In Study III, the participants with longstanding pain rated similar levels of sickness behavior as the group with chronic pain in studies I and II. Furthermore, almost all participants in Study III reported that they experienced other symptoms beyond pain, similar to sickness symptoms, such as being easily tired and experiencing concentration problems. In Study III, inflammatory biomarkers did not correlate with the participants' perceived sickness behavior or their self-rated health. Interestingly, in Study II, patients with chronic pain rated similar levels of sickness behavior as healthy participants during an acute inflammatory response resulting from injection with LPS [193], and even higher than primary care patients, some of them seeking consultation due to infections. Also, the chronic pain, ME/CFS, and primary care groups all rated high on pain and headache.

Regardless of whether or not the symptoms started from a prior sickness response, the patients' perceived symptoms appear to be of clinical importance as Study II [193] found that higher levels of sickness behavior were associated with poorer self-rated health and health-related functioning. These associations may reflect a vicious cycle where the perceived symptoms are interfering with daily life, resulting in a reduction of activity level and impaired functioning which in turn could further worsen health. On that note, self-rated health has been found to accurately predict mortality [85], and the perceptions or expectations of our health are a predictor of outcome in several medical conditions [194].

6.3 Why do sickness symptoms (and pain) persist?

Longstanding pain has been described as a failed state in which pain becomes stuck [195]. As described previously, the participants in studies I-III [179][193] rate quite high sickness behavior on a group level, although as seen in Study III, these symptoms were not associated with the inflammatory biomarkers studied, and the inflammatory biomarkers on a whole were in the normal span. It is unclear why some patients with longstanding pain have perceived sickness behavior and how the symptoms originate or persist. It could be several possible reasons as to why, a sickness response can be the origin which leads to symptoms that lingered on, with or without an elevated inflammatory process still present. Lifestyle factors such as high BMI, low activity level, or side-effect of medications may have impacted the symptoms of sickness.

Perceived symptoms are the result of an intricate combination between physiological bottom-up and perceptual-cognitive top-down processes [196]. Attentional bias to symptoms might impact the processing of somatic

communication and may affect the frequency and intensity of the experienced symptoms. The attentiveness of nonthreatening bodily sensations that would otherwise escape awareness may increase by this selective attention, and add more intense and frequent sensations of symptoms, which in turn could increase the number of times associative learning happens. Thus, increasingly more interoceptive and exteroceptive stimuli can become connected with symptoms [197]. Interoception, the conscious assessment of 'how we feel' and this selective attention to internal signals of symptoms such as pain, aim to make pain onset more predictable but may have unfavorable effects [198]. Perhaps similarly to chronic primary pain, the sickness behavior has had a protective function that has derailed with excessive alertness to symptoms. One could view pain, and maybe also sickness behavior, as the perceived need to protect body tissue, rather than always a marker of the state of body tissues.

Based on learning theory, there are several potential ways for symptoms to persist. Poor associative learning, like overgeneralization, diminished safety learning, and less differential learning may be a transdiagnostic vulnerability marker [199]. Recently, Moseley and Vlaeyen [200] proposed that imprecise encoding of conditioned stimulus may lead to overgeneralization of the conditioned pain response itself, turning a protective activity into disabling longstanding pain. Also, for humans, our self-rules, or instructions provided by others, can act as obstacles to discovering that certain situational contingencies have changed and that certain amplifiers or rewards no longer appear after the behavior - it can make us less sensitive to the new actual contingencies [56]. The expectancy effect, also called placebo or nocebo effect, in pain and sickness behavior is also of interest. When subjects were expecting a lower pain intensity, pain-intensity ratings showed that the same stimuli were rated as less intense [201]. This may involve reappraisal mechanisms such as perceived control over pain and making the pain less threatening. The degree of this modulatory effect varies between individuals [202].

One other possible explanation for pain or symptoms persisting could be that the immune system can learn and remember. Firstly, immunological responses can be learned by associative learning [203]. Also, increased pain behaviors, maintained in preadolescent and adult rats, have been seen after neonatal exposure to LPS in rats, suggesting structural changes in the pain system after infection [204]. The cells of the immune system will recall the particular pattern of circulating molecules that occurred at the time of the attack e.g. injection or bacteria, one can say that they have been primed. The toll-like receptors (TLR:s) learn what a dangerous event looks like, by detecting molecules that are associated with different types of dangerous events [205] and will be activated indiscriminately to anything that resembles the danger, evoking a protective response.

The role or importance of these different potential explanations as to why pain and sickness symptoms persist presumably vary between individuals. Further research could investigate this further to aid in the development of interventions targeting these underlying factors.

6.4 May inflammatory biomarkers moderate treatment effect in cognitive behavioral therapy or change during treatment?

In Study IV [206] inflammatory biomarkers IL-6 and TNF-α tentatively moderated psychological inflexibility but not pain interference or pain intensity following ACT-treatment. We did not have a control group and only one outcome measure was significant, so we are approaching the findings tentatively. In the previous similar study from our clinic [167] inflammatory biomarkers were significantly related to lesser treatment response of psychological inflexibility, as well as pain intensity, and mental health-related quality of life. Inflammatory biomarkers have also in another study been found to tentatively moderate less improvement in psychological inflexibility after behavioral treatment [168], indicating some more robustness to our finding. The questionnaire PIPS aims to measure psychological flexibility regarding pain, or rather behavioral flexibility, which is about taking steps towards not avoiding. Experimental studies have suggested that inflammation can change motivation, in such a way that sensitivity to monetary rewards is impaired, but sensitivity to punishments is enhanced [207]. This motivational reorganization may further drive pain-related avoidance in such a way that change efforts become less efficacious. People may, in the presence of induced inflammation or the experience of sickness alternatively pain, act in an avoidant way that is not efficient in the long term. It may be more difficult to do alternative behaviors instead of avoidance behaviors with an inflammatory process in the body. The patients might be tired, feel sick, not feel energized, or have thoughts that they can't manage to do the exposure part of the treatment. Some may not feel that it is safe with exposure when they experience these symptoms and may not have received information or a rationale including this experience of other symptoms than pain.

Inflammatory biomarkers are just one of many potential moderators of treatment outcome, other factors could be the degree of depression, sleeping difficulties, or BMI. In Study III, eighteen percent of the participants in the study were classified as obese, so BMI could be something to further address. There is limited knowledge on how or why inflammation or other possible moderators could hinder treatment, and more studies are warranted to expand on the findings in patients with longstanding pain.

Interestingly, in the prior study by Lasselin et al. [167] at our clinic, the levels of peripheral TNF-α decreased from pre to post-treatment. As described in the literature review, two Swedish studies also found decreasing cytokine levels among

patients with longstanding after interventions based on cognitive-behavioral therapy [169][170]. In one of the studies, biomarker changes correlated with changes in psychological distress but not with physical activity or pain. Although, there were only 25 participants and so the findings were tentative [169]. In the other study, the outcome after treatment in combination with biomarkers was not described just that certain biomarkers were decreased a year after treatment [170]. In Wang et al. [171] IL-8 decreased after a three week-treatment, but it was only 20 participants included in the study. In opposite to these studies, in Study IV we found a tendency for TNF-α to be higher after ACT-treatment, but the change was not significant. It would be interesting to evaluate in a study with more participants, if more intensive treatment or longer time for follow-up where participants would have time to change behavior, could affect the results.

6.5 Enhancement of exposure therapy for patients with longstanding pain

As I described in the literature review, the efficacy of psychological treatments for patients with longstanding pain varies [129]. If inflammatory status before treatment moderates psychological flexibility and therefore avoidance, as tentatively indicated in Study IV, how can we use that knowledge clinically? The patients' conditions are supposed to be medically satisfactory and assessed, so that the persons who could benefit from anti-inflammatory medication may have had that intervention already. However, how one deal with the symptoms is possible to address and behaviors are possible to change. Avoidance behavior is an important treatment target as avoidance has been shown to exacerbate pain [61] and impact disability [63]. Törneke et al. posit that psychological treatment should aim at multiple-exemplar training of psychological flexibility [208]. An inhibitory learning approach, presented by Craske et al. [209], could also be investigated to enhance exposure in patients with longstanding pain. Also, learning more about avoidance and variables possibly affecting it, such as perceived sickness behavior, can be important for treatment.

The persistent symptoms described in this thesis are common in health care and a major health cost. The medical model where a doctor maps symptoms, diagnoses and investigates etiology, and then initiates treatment, is considered to be the basis for success in Western emergency medicine, but this method has proven difficult in longstanding pain or diffuse symptoms [73]. The SicknessQ may be used as an assessment of which extent the patient experiences these symptoms, and as an indication of if the symptoms should be addressed in treatment. For patients where an underlying disease that rather should be treated is excluded, the core of treatment and key therapeutic strategies could be 1) help the person be aware of antecedents (e.g. discomfort such as pain, hindering thoughts and feelings but also sickness symptoms), and problematic consequences of the responding to

the antecedents, 2) view alternative behaviors and train this repertoire as an alternative functional class in presence of discomforting experiences, 3) in a way that will include appetitive functions (behaviors in valued direction) [208]. This could also include interpreting the sickness symptoms as a protective function which are not needed any longer, and a rationale for why exposure could have benefits in this case. One study found that patients with persistent pain overall found it important to have had information about that pain does not have to equal tissue damage and hear about the overprotective system which prevents recovery [210]. This could be translated to sickness behavior as well, and reconceptualize the symptoms in treatment. To have a helpful education, more knowledge of sickness behavior is needed in patients with longstanding pain. The findings of how the participants have rated sickness behavior in Study II may be of use to at least describe that these symptoms may be common in patients with longstanding pain.

6.6 Limitations

The limitations for studies I-IV can be read in the respective articles, so I will here add the limitations which are not included or elaborated on there. Regarding limitations for Study II, there were different procedures and time points in the different samples, e.g. some of the groups have filled in SF-12 whereas others have filled in SF-36. In studies I-IV the clear majority of patients with longstanding pain received medicine for their pain and this might have influenced baseline levels of inflammatory biomarkers. In studies III and IV, the pain diagnoses were not assessed by a physician and only pain localization was described. For the participants with longstanding pain in studies I and II, pain diagnoses were collected at the first visit by a pain physician. However, since the origin of the pain was not stated in the dataset, some pain diagnoses could not be categorized retrospectively. The majority of participants in studies I-IV were female and older in age, as is common in clinical pain research, but we have included sex and age as control variables. Regarding limitations specifically for studies III and IV, it would have been of interest to have a control group as a reference for the levels of inflammatory biomarkers in participants with longstanding pain. It would also have been of interest to have had more time points for blood samples, as it is known that levels of cytokines in peripheral blood can be affected by factors such as time of day, physical activity, acute stress, sleep quality, and other factors [211]. We also did not have information on participants' prior illnesses that could have affected their inflammatory status. The participants in studies III-IV were recruited in different ways, referrals to the Behavioral Medicine Pain Treatment Unit at the Karolinska University Hospital, or via recruitment advertising. Although there were some significant differences regarding age, pain duration, depression, and anxiety, analyzes showed that this did not change the results. Regarding limitations specifically for

Study IV, I want to highlight that in the absence of a control group, it is not possible to infer that baseline levels of inflammation moderate the effects of ACT, making it important to see the results tentatively.

7 POINTS OF PERSPECTIVE

7.1 Future research

Several possible avenues for further research arise from the studies in this thesis. Future studies could assess the SicknessQ's utility to predict behavior, by evaluating predictive validity. The relationship between sickness behavior, avoidance, and pain disability could be further explored, for example by investigating if high ratings of sickness behavior at the start of treatment predict pain disability, possibly mediated by avoidance. Studying these interrelationships further could be of importance for adapting treatment for patients with longstanding pain. Further research could evaluate sickness behavior as a mediator, potential moderator, or a possible outcome measure in CBT treatments. Investigating the role of different potential explanations as to why pain and sickness symptoms persist, and how this varies between individuals could be explored, to aid the development of interventions targeting these underlying factors. Regarding enhancement of psychological treatment, interventions specifically addressing sickness behavior, while aiming at behaviors in a valued direction, could be evaluated.

As we have seen in the literature review results are conflicting regarding psychiatric co-morbidity, sickness symptoms, and inflammatory biomarkers in longstanding pain. It would be of interest to investigate the hypotheses of Study III in a larger sample with a control group as a reference and investigate whether the results would differ with more participants. The larger sample could also enable subgroup analyzes, exploring whether there is a subset of patients for whom sickness behavior or psychiatric co-morbidity correlate with the level of cytokines. Also, it may be inflammatory biomarker profiles rather than specific cytokines that are of relevance for the variables which are investigated in this thesis, a level of analysis that could be further explored, optimally with more time points of measurements.

8 CONCLUSIONS

SicknessQ is a questionnaire with reliable and valid statistical properties to assess sickness behavior in adults with longstanding pain. Participants with longstanding pain and ME/CFS reported similarly high levels of sickness behavior, higher than primary care patients, and comparable to levels in experimental inflammation. Participants with longstanding pain rated a relatively high symptom burden, but the included symptom variables had weak associations with the included inflammatory biomarkers. Higher levels of baseline inflammatory markers were related to less improvement in psychological inflexibility. I hope that this thesis is a step towards improved knowledge of the symptoms of longstanding pain and the role of low-grade inflammation, as well as a step toward a better understanding of factors possibly underlying the variability in treatment effects.

9 ACKNOWLEDGMENTS

First and foremost I would like to thank all the participants who have been part of the studies. Without you, nothing in this thesis would be possible.

Linda Holmström, thank you for your encouragement and for guiding me through this doctoral journey. Thank you for making sure that the clinical relevance is coming through in these studies, it has been so valuable to have your eyes on the project.

Mike Kemani, I am so grateful that you wanted to take the time to be my supervisor, with all your knowledge, kindness, and humor. You have had a great impact on the theoretical direction of these studies, and made my years as a doctoral student more fun and engaging.

Bianka Karshikoff, thank you for your intriguing thoughts on science and the immune system, as well as for facilitating the possibility for me to choose Stanford for my lab exchange. Thank you for being present in the data collection, even though you were on the other side of the world.

Rikard Wicksell, thank you for facilitating the onset of this project and the start of my doctoral journey. Beginning as a psychologist at Behavioral Medicine, which you and Gunnar started, has introduced me to the area of pain and several of the wonderful people on these acknowledgment pages.

Thank you to all my prior colleagues at 'Smärtcentrum' and Behavior Medicine at the Karolinska Hospital – *Valeria Mattsson Benvestito, Marie Kanstrup, Barbro Ahlberg, Birgitta Hellgren, Maria Elb, Owe Landström, Jan Persson, Karl-Fredrik Sjölund, Johan Bogefeldt, Kristina Jansson, Mikael Gewers* and many more. Thank you *Niklas Törneke* for giving me a valuable theoretical framework during my clinical work. Thank you *Emma Akhondi, Emma Birkehag*, and *Urban Ekman* for being part of the recruitment to studies III and IV. Thank you *Malin Persson* for being a part of the iACT-treatment, I enjoyed our discussions.

Jenny Rickardsson and *Charlotte Gentili*, thank you for all your work with iACT, ACTSmart, and discussions about our projects. Jenny, I have great memories from sharing 'Jenny-rummet' with you.

Gunnar Olsson, thank you for everything I have learned from you, for bridging psychology and medicine, for all the songs, and for caring deeply about helping people.

Camilla Wiwe Lipsker, thanks for being my mentor. You are brilliant and I remember our time together at Smärtcentrum with a smile.

Thank you *Mats Lekander* for rich discussions about studies II-IV, and *Anna Andreasson* for your thoughts on sickness behavior in studies I-II.

Thanks to everyone involved in the *National Research School in Psychiatry*, teachers, and fellow doctoral students, for passing on your knowledge and skills. I value the time with you so much. Thank you to the *staff at the Karolinska Institutet library* for giving helpful answers to any question I have ever had to you. Thank you *Ingrid Skelton Kockum* and *Alexandre Beckman* at CNS for helping me to move forward.

Thank you, *Stuart Thomas*, professor at Monash University, for taking the time to supervise my thesis while being an exchange student in Melbourne many years ago. Your writing advice still helps me. Thank you, *Kate Stevens*, radiologist, scientist, and pilot, for giving me a warm welcome when I visited Stanford. Your guidance on the Stanford campus and dinner at your place is a dear memory to me.

Johan Holmberg, *Vendela Zetterqvist*, *Sophie Johnson*, *Sara Bartles*, *Kozma Ahacic*, and *Jenny Thorsell Cederberg* - thank you for the rich discussions. Thank you *Brjánn Ljótsson* for me being able to join some of your research group meetings, and thanks to everyone in the Ljótsson research group for interesting chats and scientific input.

Thank you to my fellow colleagues at Behavioral Medicine – *Lisa Werneman*, *Emma Kettis*, *Lovisa Farrow*, *Emily Tallroth Turner*, *Ida Högdal*, *Eva Götharson*, *Ea Wållgren*, *Anna-Carin Magnusson*, *Julia Lönnborg* and many more. I am looking forward to seeing more of you when this book is finished.

Rikard Hanafi, as I said in the speech at your wedding, to choose kind things to say about you or good memories is like when Bubba in Forrest Gump continuously describes different ways of serving shrimp – it's difficult to stop. *Martin Jonsjö*, you are unusually funny. Our conversations, gymming, and skiing have made these years much more fun. *Björn Lilieqvist*, you are kind, funny, and knowledgeable in the best combination, and I have learned so much from you. *Rebecca Grudin*, always an inspiration, thanks for lunches and discussions. *Elsa Håkansson*, thank you for reading through Study I and parts of my Kappa, but mainly for being an awesome

person and friend. *Moa Pontén*, thank you for interesting talks about life but also pain and learning theory. *Ämma Tangen*, chats with you have given me so much motivation.

Thank you all my friends. *Madeleine, Anna, Linda-Malín, Josefine, Cyrus, Louise, Peggy, Caroline, Marie, Paliz, Nathalie, Jason, Angelica, Sara, Lukas, Karl, Anna, Sara, Andreas, Sandra, Henrik, Pontus, Cecilia, Birgitta, Julian.*

Thank you, *Julie, Øyvind, Ingrid, Erik, Thomas, Ida, Peder,* and *Kristin* – and the rest of my extended family.

Mattias, Vera, Sara and *Tuva,* many thanks.
Late grandpa *John-Erik* and late grandma *Ann-Marie*, thank you for your love and support.
Grandma and dear friend *Maj-Britt*, thank you. You inspire me.
Mom and *dad*, thank you for your loving encouragement and for inspiring me with your curiosity as well as thirst for knowledge.

Christian, Ellen, and *lillasyster*, my dream team, I am deeply grateful for you every day.

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