From the Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

MAKE FRIENDS WITH YOUR PAIN MONSTER

Internet-delivered acceptance- and value-based exposure in chronic pain – model and treatment

Jenny Rickardsson

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Internet-delivered acceptance- and value-based exposure in chronic pain – model and treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Jenny Rickardsson

Principal Supervisor:
Associate professor Rikard Wicksell
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Co-supervisors:
PhD Linda Holmström
Karolinska Institutet
Department of Women's and Children's Health
Division of Paediatric Neurology

PhD Vendela Zetterqvist
Uppsala University
Department of Neuroscience
Division of Child and Adolescent Psychiatry

PhD Erik Andersson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Professor Mats Lekander
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology
and
Stockholm University
Department of Psychology
Stress Research Institute

Opponent:
Professor Madelon Peters
Maastricht University
Faculty of Psychology and Neuroscience
Department of Clinical Psychology Science

Examination Board:
Professor Katja Boersma
Örebro University
School of Law, Psychology and Social Work
Center for Health and Medical Psychology

Professor Eija Kalso
Helsinki University
Faculty of Medicine
Department of Diagnostics and Therapeutics

Associate professor Jonas Ramnerö
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology
and
Stockholm University
Department of Psychology
Division of Clinical Psychology

The trouble with avoidance
Is that it ain't no trouble at all
I just avoid my problems
And to hell if I don't mind
When I wake up tomorrow
They'll be too easy to find

Paraphrase from "The trouble with drinkin' " by Aaron Lee Tasjan

Martin, Ingrid, Sonja and Ava: You are my first, my last, my everything.

ABSTRACT

Background: Chronic pain is a complex and common condition, often affecting functioning across a wide range of outcomes as pain interferes with daily activities. The understanding of mechanisms for development and maintenance is however limited, with chronic pain syndromes being the result of a complex matrix of biopsychosocial factors reciprocally impacting each other. Medical treatments are often insufficient in reducing suffering and increasing functioning. Acceptance and Commitment Therapy (ACT) targets psychological flexibility – the ability to continue towards a valued direction in life, despite inner distress and obstacles – and is a promising treatment approach. Access to ACT treatment is limited, and internet-delivery could improve access and reach.

Aim: The purpose of this thesis was to develop a feasible and effective internet-delivered ACT intervention for adults with chronic pain, and increase our understanding of potential mechanisms in pain-related disability and treatment.

Methods: Four studies were conducted. In study I we used a cross-sectional design to evaluate validity aspects of the Valuing Questionnaire (VQ). In study II, also using a cross-sectional design, psychological flexibility was examined as a potential resilience factor for persons with chronic pain. Study III investigated the feasibility and potential efficacy of iACT – a novel internet-delivered treatment in a microlearning format – for clinical and self-referred adults with chronic pain. An open pilot design was used. In study IV a randomized controlled trial design was used to compare the efficacy of iACT to a waitlist control group. Primary outcome was pain interference, secondary outcomes were psychological inflexibility, value orientation, quality of life (QoL), pain intensity, anxiety, insomnia and depressive symptoms.

Results: VQ had adequate model fit and internal consistency, and also contributed to the variance in pain interference, depressive symptoms and QoL. In study II, PF was found to be a candidate for a modifiable resilience factor in chronic pain. In study III results indicated that the iACT treatment was feasible and preliminary efficacious for both clinical and self-referred patients. In study IV, participants in the iACT arm showed improvements compared to the WLC across all nine outcomes investigated.

Conclusions: Values can be effectively assessed with the brief self-rating questionnaire VQ. Psychological flexibility may be a modifiable resilience factor for the development and maintenance of chronic pain. A micro-learning format of ACT via the internet can be both feasible and efficacious as to increase functioning across a wide range of outcomes for chronic pain patients. The studies in this thesis provides a groundwork for future scientific investigations of some of the psychological mechanisms relevant for chronic pain.

LIST OF SCIENTIFIC PAPERS

I. Rickardsson J., Zetterqvist V., Kemani M.K., Holmström L., Andersson E., Wicksell R.K. (2019). Assessing values – Psychometric properties of the Swedish version of the Valuing Questionnaire in adults with chronic pain. *Journal of Contextual Behavioral Science*.14: 40-49.

II. Gentili C., Rickardsson J., Zetterqvist V., Simons L.E., Lekander M., Wicksell R.K. (2019). Psychological Flexibility as a Resilience Factor in Individuals With Chronic Pain. *Frontiers in Psychology*. Vol 10; article nr 2016

III. Rickardsson, J., Zetterqvist, V., Gentili, C., Andersson, E., Holmström, L., Lekander, M., Persson, M., Persson, J., Ljótsson, B., Wicksell, R. K. (2020). Internet-delivered Acceptance and Commitment Therapy (iACT) for chronic pain – feasibility and preliminary effects in clinical and self-referred patients. *mHealth*. 2020:02.

IV. Rickardsson, J., Gentili, C., Holmström, L., Zetterqvist, V., Andersson, E., Persson, J., Lekander, M., Ljótsson, B., Wicksell, R. K. iACT – internet-delivered Acceptance and Commitment Therapy as microlearning for chronic pain. A randomized controlled study with one-year follow-up. *In manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
CBT	Cognitive Behavioral Therapy
CFA	Confirmatory Factor Analysis
CP	Chronic pain
CRPS	Complex Regional Pain Syndrome
EQ-5D	European Quality of Life – five dimensions
GAD-7	Generalized Anxiety Disorder – seven items
HADS	Hospital Anxiety and Depression Scale
ISI	Insomnia Severity Index
ITT	Intention to Treat
IQR	Inter-Quartile Range
NNT	Numbers Needed to Treat
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCD	Obsessive Compulsive Disorder
OR	Odds Ratio
PF	Psychological flexibility
PHQ-9	Patient Health Questionnaire – nine items
PII	Pain Interference Index
PIPS	Psychological Inflexibility in Pain Scale
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of life
SF-12	Short Form Health Survey – twelve items
VQ	The Valuing Questionnaire
WAD	Whiplash-Associated Disorder
WHO	World Health Organization
WLC	Waitlist control group

1 INTRODUCTION

Picture yourself on one of those days when you have had a massive headache. Perhaps you have yourself to blame for some extravaganza the night before, perhaps it is due to a persistent flu. Either way, it is probably bothering you. Moving makes it worse, noise makes it worse, everything is irritating. So, you lay still on your sofa, alone. Perhaps leaning a little to the left since it hurts the least in that position. If you are lucky your headache disappears the next day and your life goes back to normal. Now, imagine the pain lingering for weeks, months and even years. What worked in the short run is no longer as appealing, you don't want to spend your life lying down. But every time you try to do something else, that pain monster hits you with its full power, and you end up back on your sofa.

It is at this stage that we see patients at the behavioral medicine unit at Karolinska University Hospital. The pitch for psychological treatment for chronic pain is not for the faint-hearted: "If your pain has been around for years, it may be around for years to come as well, no matter what medical or pharmaceutical treatments you try. We will instead try to do meaningful things in your life, and you might have even more pain. But you also have a chance to take back your life." Most of our patients take on the challenge, trying to make friends with the pain monster instead of keep fighting to avoid or defeat it. It takes bravery, time and practice, both in identifying the things that cannot be controlled, and changing what can be changed: our own behaviors.

I knew early on I wanted to make a digital version of the treatment model incubated at the behavioral medicine unit. The research my colleagues had done was impressive, and the context of learning, evaluating and developing together was amazing. But patients waited too long for care, or never accessed it all because coming to the clinic once a week for three months was too difficult. Rikard told me pursuing a digital treatment was best suited as a PhD project, so I had to register as a doctoral student to make it happen. A bit reluctantly I entered PhD studies. I realized quickly that doing research was way more exciting than I anticipated, the things I learned were useful both for me and the patients, and it actually suited me pretty well.

These four years have been awesome in many ways. I have had the privilege to spend time with amazingly talented colleagues, have worked hard to carefully design the interventions and studies in this thesis, acted as project leader, compiled and prepared data sets, analyzed data with really difficult statistic methods, written remotely understandable manuscripts, learned as much as possible and we have reached patients that otherwise would not have had access to care. After treatment one patient wrote: "I won't feed my pain monster anymore. I actually hope it will die from starving, but if not, it can come along as I do what matters to me." As for me, I won't feed my thesis monster anymore. I can hear it telling me that the number of people who read this will be limited. I notice, accept, don't give a damn, and act in accordance with my aspiration to help and trust it will be useful for many.

2 BACKGROUND

The experience of pain is universal – most humans know what it is like to have pain. The experience of pain is also unique and subjective – anyone feeling pain does so in her own personal environment. A pain experience is influenced by current events, memories of previous pain and thoughts about the future, all at the same time. Consequently, pain can only be understood in the context in which it occurs [1].

As one of our protective systems, pain functions as a motivational drive [2]. Where and why it hurts may differ, but the function of the behavioral responses is often the same: to reduce pain, avoid harm, and learn what behaviors were associated with this pain to avoid future harm [3-5]. Pain directs our attention towards what is perceived as a potential threat [4, 6], whether it is stomach-ache after eating something poisonous, pain from an ear infection or a broken bone [7]. Avoidance of activities that may trigger pain, trying to find the cause of it and searching for a solution to get rid of pain is in situations with acute pain adaptive [5]. The injury can heal, pain is reduced, and we can continue with life, having learned not to eat those poisonous berries again. But if the pain persists it is a different matter. Pain that lasts more than three months is labelled as chronic [8]. Avoidance and problem-solving behaviors tend to continue, despite not being effective in the long run [1]. This can be understood from a learning theory perspective, but before we go into that, let's start with the fundamentals.

2.1 PAIN

Pain is defined as ”an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain [9], emphasizing the subjectivity of a pain experience. A pain sensation is a complex process [4]. Up until the first half of the 20th century chronic pain was mostly considered a medical problem with a pathophysiological cause explaining intensity of symptoms [10]. This is called the specificity theory, and states in short that something is damaged, nociceptors (specialized pain receptors) in the damaged location are activated and send signals to the brain, the brain receives the nociceptive input and we feel pain [11]. At the end of the 1950's the alternative gate control theory emerged, claiming that the central nervous system was far from a passive receiver, but instead an active agent, prioritizing between different signals, amplifying some and inhibiting some [4]. In the 1960's a biopsychosocial model started dominating the field, stating that chronic pain is multifactorial; physiological processes, psychological processes and social factors all contribute to chronic pain conditions [8]. Sensed pain can thus be a trigger for pain behaviors, but a pain sensation is itself also affected by behaviors and the context; the nociceptive signaling, the transmission through the dorsal horn into the central nervous system, the verbal interpretations, memories evoked, associated fears and overt actions all contribute to a sensation of pain in all directions [3, 4, 12]. Chronic pain and disability are now understood as ”a multidimensional, dynamic interaction among physiological, psychological and social factors that reciprocally influence each other, resulting in chronic and complex pain syndromes” [13]

2.2 CLASSIFICATION OF PAIN

On many occasions, an experience of pain is a consequence of tissue damage or a symptom of sickness, as nociceptors are activated by something broken or infected and through this complex system of amplifiers or inhibitors transmit signals to the conscious parts of the brain [5, 9]. This is called a nociceptive pain mechanism. A second type of pain is called neuropathic and concerns pain that arises from damage or disease in the nervous system itself – as can be the case with amputations, diabetes or multiple sclerosis [9]. There is also a third mechanism when pain arises from altered nociception; changes in the functioning of the peripheral and/or central nervous system [9]. This type of pain has no evidence for ongoing physical damage to neither tissue nor nerves, the pain is no longer a symptom but a disease in itself. This is the case in for example fibromyalgia and complex regional pain syndrome, and this mechanism is called nociplastic [9].

The latest edition of the diagnosis handbook ICD-11 recognizes the idea that pain can be a disease on its own, with the addition of Chronic primary pain (CPP) where pain is not secondary to ongoing injury or disease [8, 14]. Diagnosis criteria include duration of pain for more than three months, functional disability and/or emotional distress [8].

2.3 EPIDEMIOLOGY AND ETIOLOGY

Chronic pain is estimated to affect around 20 percent of both adults and children throughout the world [15], even though some reports suggest that up to 40 percent of the adult population is affected [10]. Chronic pain is more prevalent with age, is more often reported by women than by men and women also report more severe pain than men [16].

Chronic pain can derive from any pain mechanism or from unclear causes. It may be associated with a number of other factors including traumatizing experiences, sexual abuse, low-grade inflammation, surgery or stress as well as peripherical and central sensitization of the nervous system [17-22]. It has been shown that large amounts of nociceptive input can alter functioning in the central nervous system, and that repeated nociceptive stimulation through learning may facilitate the transmission and reception of signals in the nociceptive/central nervous system [23]. To date, however, the role and function of these factors, and to what extent they influence the development and maintenance of chronic pain, is not clear, but there is consensus that the etiology of is multifactorial [13, 23]

2.4 PAIN INTERFERENCE AND FUNCTIONING

Chronic pain is consequently a complex syndrome. Depression, anxiety disorders, insomnia, fatigue, work/school absence, worse social relations and lowered quality of life commonly co-occurs with chronic pain [15, 24]. In a recent review Edwards et al. state that mood disorders may be interpreted as a consequence of chronic pain, but longitudinal studies show that mood disorders, and poor social relations are also risk factors for developing chronic pain [13].

Patients with chronic pain often report difficulties with maintaining attention, focusing on the task at hand, trying to remember what a friend just said, or what happened in the beginning of the film [25]. These reports are supported by both clinical and basic research, but it is not clear to what degree these problems for the chronic pain patient are best explained by pain intensity or might be better explained by other factors, such as depression and/or anxiety [25, 26].

In basic research, it is evident that pain interrupts, distracts and demands attention, and this seems to be an evolutionary advantage for survival [6, 7, 27]. Pain makes it difficult to focus on any other task, in part because turning your attention towards anything else in the presence of pain takes effort: high pain intensity seems to have priority access to the limited attentional resources available [27]. For instance, temporarily induced high intensity pain has more detrimental effects on task performance than low intensity pain or no pain in experimental studies [27]. As a consequence, other sensory input and/or goals must compete with pain as to which behavior should be initiated, continued or discontinued.

Pain commonly interferes with daily activities such as seeing friends, maintaining relationships, having sex, working, exercising, sleeping and doing household chores [15]. The extent to which pain influences behaviors and interferes with daily activities can be conceptualized as pain interference [28]. When pain is chronic, pain intensity cannot alone predict interference, disability or function to a satisfactory degree [1, 29, 30]. Some chronic pain patients who report high intensity pain, may also report low levels of interference, while other patients, who report low intensity pain, may report higher levels of interference [1, 23, 31]. Pain intensity is thus one factor among others associated with levels of interference, functioning and quality of life [30, 32, 33]. Pain interference and functioning/disability can be considered closely related concepts and pain interference is consequently an important treatment target [34-36].

2.5 ASSESSMENT IN CHRONIC PAIN

In chronic pain patient-reported outcomes are important both for research and clinical purposes. A pain experience – and also psychological constructs as anxiety or depressive symptoms – can only be fully experienced by the person going through it, and there are limitations as to what extent pain-related variables can be assessed or reported by proxy [37] or objective/physiological measures [38, 39]. The most established way to assess pain is therefore through self-report measures [40].

Variations in any proposed psychological construct measure can be due to 1) true variations in the construct; 2) the measuring method; and 3) errors in the measurement [41], and the goal for any measure or instrument would be to have the impact of the second and third factors as small as possible, and the score on the measure as closely related to the true variance of the construct as possible. We thus need to establish that an instrument is reliable and valid, in other words that the instrument consistently gives similar results, lack error and that it accurately measures what we want it to measure in order to use it. A simple example

on reliability would be that an instrument designed to measure meters is reliable if it consistently returns the same result when measuring a meter. That implies that the instrument does not react to for example heat, cold or rain yielding different lengths of the meter under different circumstances. For the instrument to also be valid the same example can be used to illustrate that it would be valid to use a reliable meter measure to measure height, but not to predict weight, as the instrument does not accurately return the true weight. A measure thus needs to be reliable to be valid, but reliability does not ensure validity.

Validity then refers to how accurate an instrument actually measures that which it is intended to measure [42]. Validation is a continuous process involving collecting evidence for different aspects of validity, for example in specific populations and in particular settings [42]. There are a few different definitions of validity terms, Kazdin suggests the following: *Construct validity* is an umbrella term meaning how well an instrument actually test the construct it is supposed to test, and *criterion validity* equals testing the relationship between the construct and other similar measures, either concurrently (at the same time point) or predictively [43]. Another aspect of construct validity is that it is theory-driven, and that "c*onstruct validation concerns the simultaneous process of measure and theory validation"* [41].

Self-report questionnaires of psychological constructs are in general as reliable and valid as clinician-rated measures, but require less time, no special training for administration and enable large-scale clinical outcome studies at low cost [44].

2.6 RESILIENCE IN CHRONIC PAIN

Some patients with chronic pain maintain physical and emotional functioning despite the significant challenge that living with pain puts on a human being. This is commonly labelled as resilience, and is defined as overcoming adversity, or functioning effectively even when facing inner distress or stressful circumstances [45]. Why some persons manage to live well with chronic pain and others do not is not yet clear [46-48]. Identified resilience factors often concern fairly stable aspects as being male, having higher education, higher socio-economic status, personality traits as optimism, high pain tolerance, high pain threshold, and high social support, that may predict or are associated with physical and emotional functioning in chronic pain [49, 50]. These factors provide limited information on modifiable resilience factors; they do not convey *how* somebody recovers or maintain functioning. Some promising attempts have been made to identify aspects of resilience that are modifiable – and thus can be addressed in treatment – such as pain acceptance, pain catastrophizing, fear of pain, pain beliefs [50, 51]. It has been proposed that discussing resilience as a dynamic, contextually sensitive process is more useful than considering it a trait [47, 52, 53]. Following this logic resilience can be viewed as a skill, and in learning theory terms an operant behavior (see section 2.7 Theoretical framework).

The definition of resilience can in this context be operationalized as recovery and sustainability. Recovery is then the ability to go back to the previous level of physiological

and psychological functioning following prolonged stress, while sustainability refers to the ability ”to move towards long-term positive outcomes in life in the presence of adversity” [47]. Defined as this, resilience as sustainability is a concept closely related to psychological flexibility: defined as the ability to act in line with values and long-term goals in the presence of inner discomfort as pain and distress [54]. Goubert and Trompetter argue that chronic pain research so far have been more interested in the recovery aspect – with research mainly concerning minimizing negative aspects of chronic pain, such as disability or depressive symptoms – and less interested in positive aspects of sustainability; helping chronic pain sufferers move towards a valued and meaningful life even when facing adversity [47].

Resilience can be contrasted with – but is not exactly the opposite to – risk factors. The absence or reduction of a negative outcome can be interpreted as the presence of its positive opposite, but this is not self-evident [55, 56]. The negative concept risk and the positive concept of resilience are related, but they are not simply each other’s opposites or ”two sides of the same coin” [47, 51]. As shown in a recent study on chronic pain patients, a positive factor – engaged living – was a more important correlate for the positive outcome flourishing, while negative factors as catastrophizing and psychological inflexibility were more important correlates for the negative outcome depression [53]. Resilience is thus not only the absence of disability or other negative outcomes – but the presence of well-being.

2.7 THEORETICAL FRAMEWORK

Pain interference can be understood as a behavioral concept; to what extent does pain influence behavior? The basics of learning theory tell us that behaviors are learned, and since they are learned, they can be modified. In the learning theory tradition, the definition of behavior includes overt observable actions, as well as covert behaviors like thoughts, feelings and bodily sensations only (possibly) observable from the inside [57]. Behaviors can only be fully understood as an action occurring within a context, as a product of the ongoing interaction between what is inside and outside the skin.

2.7.1 Learning theory

Two important sets of learning processes are described in learning theory: *respondent* and *operant* learning. Respondent learning is the process when a neutral stimulus (A) for example a subway sign, is associated with an aversive stimulus (B), such as someone bumps into you on the subway train and trigger pain and anxiety. After pairing stimuli A and B (A and B occurring in close temporal proximity) one or more times, the presence of stimulus A (the sign) alone can trigger B (anxiety).

Operant learning takes place when the consequences of a behavior influences the likelihood of that behavior occurring again in a similar context. For example, the behavior going home when seeing the subway sign results in a desired outcome: anxiety decreases and the anticipated rise in pain intensity does not happen. The behavior is reinforced by the consequence of the behavior, and the behavior is therefore likely to be repeated in similar situations.

2.7.2 Relational frame theory

In recent decades the theory of Relational Frame Theory (RFT) have emerged in an attempt to expand the scope of learning theory beyond the two traditional sets of learning. RFT adds the concept of *derived* learning to operant and respondent learning. With the evolution of language and verbal cues, humans have the possibility to let thoughts, memories, fantasies or interpretations influence behavior [12]. The human language gives us the possibility to establish associations that never have (co-)occurred anywhere but in our minds; stimuli without any apparent connection established via respondent learning, elicit behaviors that cannot be explained via reinforcement or operant learning. According to RFT behaviors are coordinated by two sets of influences: direct experience and verbal cues [12, 58].

- Direct experiences are what we hear, taste, smell, feel and see.
- Verbal or language-based cues are rules, instructions, expectations, stories, judgments, cognitive processes, appraisals or other results of a mental process.

In the subway example direct experiences would be seeing the subway sign, bumping into someone and feeling pain. According to RFT the event where stimulus A (the sign) is paired with B (the pain and anxiety when bumping) is not a necessary path to learn to avoid subway riding in order to avoid anxiety and pain. The mere thought or fantasy that someone *might* bump into you on the subway – even if you have never seen that happen – can elicit avoidance of subway riding. Verbal cues could then be ”I can never ride the subway” or ”Riding the subway must be bad for me”.

Learning theory and relational frame theory can provide a vantage point where the context for a particular behavior, behavioral patterns and possible modification(s) of context or behavior may be analyzed.

2.7.3 The fear-avoidance model of pain and disability

One way to understand the process of pain interference and reduced functioning for chronic pain patients within a learning frame, is described in the fear-avoidance model.

If pain is interpreted as highly threatening it triggers priority to pain control, fear of pain and avoidance behaviors, see Figure 1. This leads to high pain interference, and negative affect like feelings of failure or depressive symptoms.

The vicious circle continues with more pain, when increased awareness and sometimes heightened sensitivity come at play. The fear or anxiety triggered by a potentially painful situation are in this model considered respondent responses, and the avoidance behavior that follows, is under operant control. According to the fear-avoidance model interpretations of pain resulting in low threat value leads to priority to pursue valued life goals, approaching

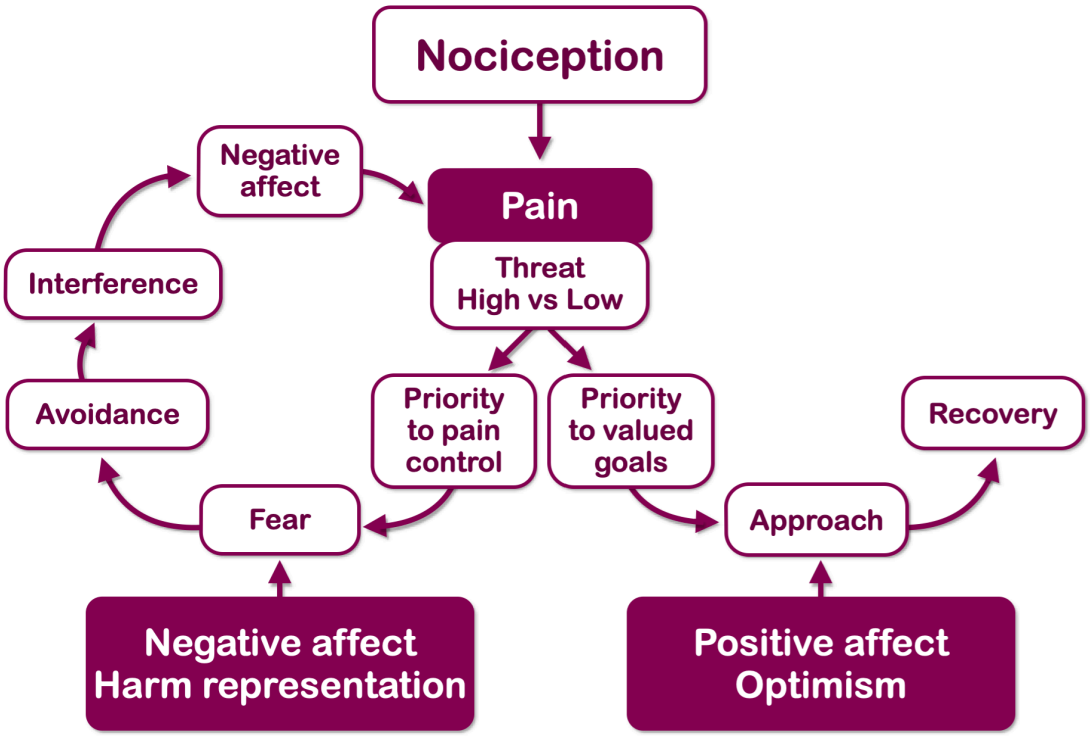

Figure 1. The fear-avoidance model of chronic pain.

behaviors and recovery [3]. Recent advancements of the theory add the notion that fear may not be a necessary ingredient in the vicious circle, as pain interference may decrease following treatment, without any decrease in feelings of fear [59].

2.7.4 The psychological flexibility model to understand reduced functioning

A related view on the process of pain interference and functioning is presented in the psychological flexibility model (PF). PF is defined as ”the ability to contact the present moment more fully as a conscious human being, and to change or persist in behavior when doing so serves valued ends” [60]. In the PF model aversive events/stimuli/responses occurs naturally over the course of life, and it is the avoidance of aversive experiences that often leads to mental health problems. When values – instead of experiential avoidance – guide human behavior we may have access to a broad range of possible behaviors and get in contact with long-term (verbal) reinforcing contingencies [60, 61].

Psychological *in*flexibility can for the chronic pain patient be gradually shaped, as negatively and positively reinforced behaviors over time may create a narrower and more inflexible behavioral repertoire. Behaviors that are different in form – such as using medication, taking a shower or decide to not pick up the phone when someone is calling – may be topographically varied, but yet serve the same operant function for a chronic pain patient: often avoidance of pain or distress, see Figure 2. Avoidance of potentially painful stimuli commonly reduces discomfort in the short perspective and is thus negatively reinforced. Behaviors that reduce discomfort (such as resting or declining a social event) are at the same time often less stimulating and active.

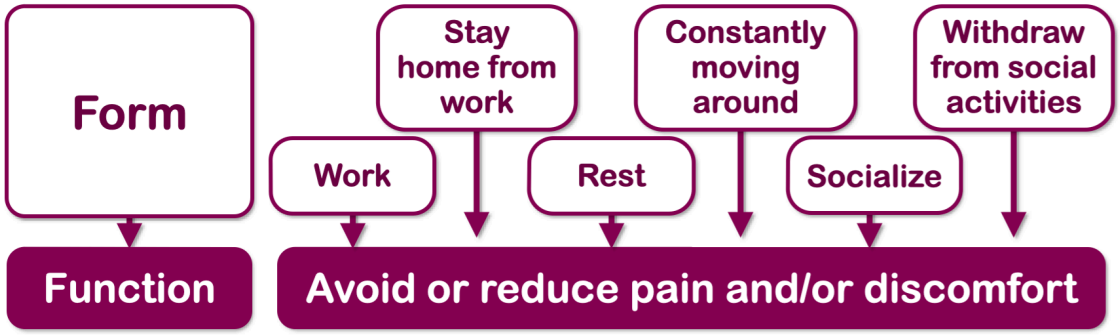

Figure 2. Form and function of behavior.

Consequently, life gets narrowed down in what can be described as a downward spiral. While the behavioral repertoire gets restricted and inflexible [60], the short-time reinforcement of pain and distress relief is for the chronic pain patient often not associated with a long-term reduction in pain. The amount of valued activities is diminished. Eventually avoidance may become an established behavior pattern [62], and over time avoidance behaviors tend to result in decreased functioning and quality of life [63, 64].

Control or avoidance behaviors may actually be counterproductive for chronic pain patients, just as avoidance can be counterproductive for patients suffering from anxiety disorders; avoiding situations that elicit anxiety/pain, may result in avoiding more and more situations, with reduced functioning without any substantial reduction in anxiety/pain as a result [65]. According to the PF model avoidance behaviors are in these cases less sensitive to the actual context, and more guided by verbal cues as thoughts, rules, and memories.

Contrasted to this experiential avoidance pattern of operant behaviors, labelled as psychological inflexibility, are a pattern of psychologically flexible behaviors that are hypothesized to promote valued living and functioning even when facing distressing circumstances – an operationalization with striking resemblance to the definition of resilience as a dynamic, contextually sensitive process [47].

2.8 CLINICAL APPROACH IN CHRONIC PAIN

Along with the earlier biomedical understanding of chronic pain, clinical treatment target was commonly reducing pain intensity until the 1960's [10, 13, 66-68]. Pharmaceutical and other medical treatments (such as surgery) often have limited effects [15, 69], compared to placebo, both on pain intensity and functioning [70]. The ground-breaking work of – among others – Fordyce promoted functioning as a feasible outcome in pain treatment, and psychological treatment modalities targeting improved self-management of pain and related distress are today widely used [10].

The most recently published Cochrane review on psychological treatments for adults with chronic pain (excluding headache) was conducted by Williams et al. in 2012. It concluded that cognitive behavioral therapy (CBT) can reduce disability and improve mood post treatment. However, the effect sizes are varied, often modest and there is uncertainty about

the duration of effects. Williams et al. also stated that there are too few studies to conclude which kind of CBT therapy content – for example coping strategies, cognitive restructuring techniques, relaxation training or acceptance – is most beneficial for chronic pain patients [71]. The Cochrane review was assessed for updating in 2016 with the decision that it was not necessary, since the additional studies made since 2012 would not change the conclusions.

2.8.1 Exposure

Functioning is thus commonly a central outcome in behavioral interventions [1, 71]. According to the theories presented above a key factor for functioning in both development and maintenance of chronic pain is avoidance (operant behavior). Exposure can be defined as a behavioral intervention where the patient is actively interacting with a feared/avoided stimulus [57, 72]. The target of exposure is traditionally extinction of the association between the stimulus and the conditioned response [73]. Exposure is usually done in a graded manner, where the patient starts with easier/less feared stimuli, stays in the situation until fear declines, and works in a hierarchy towards harder/more feared stimuli.

Recent research from Craske and colleagues show that exposure need not be graded but variability in intensity and time can be beneficial, and there can be different targets and functions of exposure, for example inhibitory learning, disconfirmation of beliefs, habituation or symptom reduction [73]. As with anxiety problems, exposure have the potential to reverse the detrimental effects of avoidance on functioning for chronic pain patients [6, 36, 74-78].

2.8.2 Acceptance and commitment therapy

Psychological flexibility as a key construct and treatment objective is most clearly operationalized in Acceptance and Commitment Therapy (ACT). In ACT for chronic pain exposure to painful and/or feared stimuli is done in both experiential exercises and in-vivo-exposures. Patients are encouraged to engage in committed action linked to chosen values. This corresponds to exposure, where the situation and activity of the exposure is chosen by the patient, guided by their values.

In therapy the patient and therapist usually work with six highly integrated processes to improve PF and promote exposure [12, 60]. All the processes are behaviors on a continuum [79], as illustrated in figure 3 on the next page.

Present moment awareness is the ability to focus on the present moment, with all it has to offer, at the other end of the continuum is a mind constantly preoccupied with the past or the future, not willing to experience what is actually going on in the present moment.

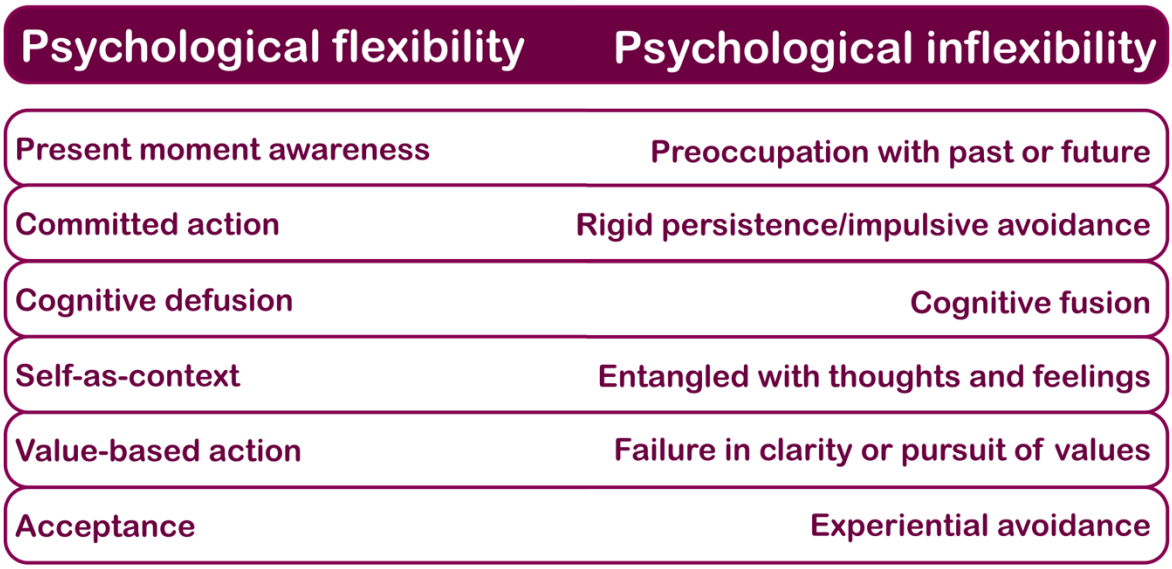

Figure 3. Psychological flexibility processes in therapy.

Committed action is the ability to pursue actions even when facing (inner) obstacles, and at the other end of the continuum rigid persistence or impulsive avoidance dominates behavior, as soon as an obstacle arises.

Cognitive defusion is the ability to separate between thoughts and the things they describe, cognitive fusion is a mind not separating thoughts and the things they describe.

Self-as-context is the ability to see oneself as someone constant, experiencing thoughts and feelings but not being defined by them. At the other end of the continuum is a self entangled with, and defined by, thoughts and experiences.

Values are freely chosen, verbally defined qualities, of who we want to be and what is important to us. Value-based action is the extent to which behaviors are guided by values, at the other end of the continuum there are no clearly defined values, or failure to pursue them in everyday life.

Acceptance is the ability to have unwanted experiences without struggling with them, experiential avoidance is unwillingness to have difficult experiences and actively trying to avoid situations where unwanted experiences may arise. [12, 17, 80-82]

The target for exposure in ACT is consequently not extinction or symptom reduction, but a broadening of the behavioral repertoire. ACT for chronic pain have been tested in several clinical and open trials, both for children [36, 83] and adults with diverse pain diagnoses [34, 63, 84, 85], and with specific diagnostic groups, such as whiplash [75] and fibromyalgia [86]. At large ACT treatments have achieved increased function and PF, reduced disability, depressive symptoms and anxiety post treatment, but results are mixed with small to large effect sizes [34, 36, 63, 75, 85-90]. Long-term effects are more uncertain, and also several clinical studies have small samples and low quality as pointed out in a recent review by Simpson et al. [91]. Predictor or moderator analyses have not been conclusive so far, but avoidance have had predictive value in some studies [30, 33].

Increased functioning following Acceptance and Commitment Therapy do not seem to require changes in pain intensity or pain-related distress [92, 93], and a decrease in pain intensity do not necessarily lead to improved functioning [92]. Psychological inflexibility have been found to mediate subsequent changes in for example disability and life satisfaction [93], in pain interference and psychological distress [94], in pain interference, anxiety, depression, pain and mental and physical health [95], in physical functioning but not satisfaction with life [32].

In open trials and cross-sectional studies, PF have been shown to predict or explain variance in disability and depression [96], depression, anxiety, avoidance and functioning [62], depression, disability and pain intensity [97]. In a review by Hayes et al. it was concluded that around 50 percent of between-group differences in post treatment outcomes in ACT was mediated by PF and related processes [98].

Acceptance has been most studied as a separate process, followed by defusion and present-moment-awareness [99]. Evaluation of committed action or values as separate mechanisms in clinical trials for chronic pain are scarce, and self-as-context as a separate process has to the best of my knowledge not been studied at all in any clinical population.

In the continuing scientific and clinical evaluation of the PF model, several processes are thus under-evaluated, and values is one of these. Several measures for values or valued action exist, most of them divide scoring into different life domains, making it difficult to quantify changes over time [100, 101]. For both research and clinical purposes, a validated and reliable global values instrument that is easy to distribute, easy to interpret, have adequate psychometric properties and are in line with ACT theory is of great importance [100, 101].

2.9 INTERNET-DELIVERED TREATMENT

One way to increase access, ensure equal geographical access and reach is to deliver treatments via internet [102, 103]. Internet-delivered treatments are supported for a number of conditions [104]. There is also evidence that internet treatments can be highly cost-effective [103, 105, 106]. Many internet treatments have some commonly used features [103]:

- Written content in chapters, called modules, each with 10 – 25 pages of text.
- One module to be completed every week during 8 – 12 weeks.
- Homework assignment to be completed every week.
- Contact with a psychologist or a psychology student via text messages.
- Worksheets to print out or complete online.

Internet treatment (mostly CBT) for mental health disorders like insomnia, social anxiety, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, depression and health anxiety have been evaluated and found to be

efficacious [107-111]. Clinical trials evaluating the effect of these programs (before implementation) show in general equal effect sizes as face to face treatments for that same disorder [103]. Internet treatments are most effective for patients fulfilling the criteria for only the targeted disorder, for patients suffering from comorbidities the pre-decided content makes it difficult to meet different needs [103]. Participants in internet-delivered treatment trials tend to be more highly educated than the general population, and there have been no conclusive results as to which patient characteristics that may predict or moderate outcome [103, 112].

Internet-delivered behavioral treatments have been evaluated for somatic conditions such as irritable bowel syndrome [76-78, 113, 114], functional gastrointestinal disorders [115-117], tinnitus [118-121], erectile dysfunction [122], chronic kidney disease [123], and diabetes with promising, albeit often smaller, effect sizes than for psychiatric/psychological disorders [112].

Several clinical trials show promising results from internet-delivered CBT for chronic pain in low back-pain, fibromyalgia and diverse chronic pain conditions, for example Carpenter et al. [124], Hedman-Lagerlöf et al. [74] and Dear et al. [125]. The latest Cochrane review by Eccleston et al. (2014) show decreased pain intensity, disability, anxiety and depression and increased functioning at post and follow-up. There is however room for improvements as estimated pooled effect sizes are small, results are uncertain due to few studies and low-quality evidence, and there is also a lack of clear effects on quality of life, no conclusive evidence on what works for whom, or through what mechanisms [126].

2.10 INTERNET-DELIVERED ACT TREATMENT FOR CHRONIC PAIN

Internet-delivered ACT for chronic pain patients has been evaluated in, to the best of my knowledge, five clinical trials so far: four in Europe [127-130] (where Scott et al., was a randomized feasibility trial without significance testing) [128], and one in Canada [131] with exclusively fibromyalgia patients. Table 1 on the next page shows an overview of these trials.

2.10.1 Summary of previous findings

2.10.1.1 Pain interference

At large, internet-delivered ACT have been efficacious as to decrease pain interference both post treatment and at follow-up, but results are mixed: from no significant effect in the Buhrman study [127] to a large effect size in the Simister study [131].

2.10.1.2 Psychological flexibility and acceptance

Four trials included pain acceptance, all showed significant increase post treatment; Cohens *d* ranged from 0.41 to 0.84 [128-131]. In two studies increase was sustained at four to six months follow-up [129, 130]. Two studies included PF, with no significant effect in the Lin study [129] and small to medium effect sizes in the Trompetter study [127].

Table 1. Randomized controlled trials with ACT for chronic pain

Author	Buhrman et al.	Trompetter et al.	Lin et al.	Scott et al.	Simister et al.
Where/when	Sweden 2013	Netherlands 2014	Germany 2017	Great Britain 2018	Canada 2018
Arms	1. ACT 2. Discussion forum	1. ACT 2. EW 3. WLC	1. Guided ACT 2. Unguided ACT 3. WLC	1. ACT + TAU 2. TAU	1. ACT 2. TAU
Patients	76 CP	238 CP	302 CP	63 CP	67 FM
Content	Willingness, mindfulness, behavior registration, goals, values, committed action, acceptance	Avoidance, values, committed action, acceptance, defusion, self-as-context.	Translated and restructured material from Buhrman et al.	Experiential exercises, behavior analysis, willingness, values.	Acceptance, values, defusion, mindfulness, self-as-context, willingness, committed action.
Format	Text, audio	Text, audio	Text, audio	Video	Text, audio, video
Scope	7 sections 8 weeks	9 modules 12 weeks	8 sections 8 weeks	8 sections 12 weeks	7 modules 8 weeks
FU (months)	6	3	4	6	3
Completion	Mean 4.2 sections	72% completers	60% guided 39% unguided	61% completers	Unclear
Pain interference (*d*)	0.56, fu + 0.32	EW: 0.33, fu 0.47 WLC: ns	0.58, fu sust.	0.2, fu 0.4	1.26, fu 1.59
Functioning (*d*)	ns	EW: ns, fu 0.4 WLC: ns	ns, fu	0.27, fu 0.42	-
QoL (*d*)	ns	-	ns	-	-
Acceptance (*d*)	0.41, fu sust.	-	0.59, fu 0.76	0.69, fu 0.13	0.84, fu 0.8
PF(*d*)	-	EW: 0.4, fu 0.47 WLC: 0.6, fu 0.54	ns	-	-
Values/Com. action (*d*)	-	ns	-	0.25, fu 0.1	- 0.19, fu - 0.46
Pain intensity (*d*)	ns	EW: 0.23, fu 0.38 WLC: ns, fu 0.28	ns	- 0.16, fu –0.11	0.84, fu 0.11
Anxiety (*d*)	0.18, fu sust.	EW: ns WL: ns	ns	-	-
Depression (*d*)	0.44, fu sust.	EW: ns, fu 0.49 WLC: ns, fu .38	ns, fu 0.50 (unguided)	0.44, fu 0.16	0.87, fu 0.56
Sleep (*d*)	-	-	-	-	ns
Other (*d*)	Catastr.: 0.51	Catastr.: 0.30 Mindfulness: fu 0.36 (WLC) Mental health: ns	-	Medication: 0.27, fu 0.1 Healthcare use: 0.5, fu 0.4	Mindfulness: ns Fusion: - 0.25, fu - 0.65 Catastr.: ns
Note	Comorbid psychiatric problems reported by 60% of participants.	Patients with depression/high psychological distress excluded. No difference in primary outcomes between ACT and WLC.	No differences guided/unguided ACT except completion rate. *d* = between guided/ WLC unless otherwise stated.	Significance testing was not done, since primary outcome was feasibility.	Negative effects on fusion and valued living for ACT. Acceptance mediated pain interference.

Note: ACT, Acceptance and Commitment Therapy; EW, expressive writing; WLC, waitlist control; TAU. Treatment as usual; CP, chronic pain; FM, fibromyalgia; FU, follow-up; *d*, Cohen's *d* (effect size); ns, not significant; QoL, quality of life; PF, psychological flexibility; Com, committed; catastr., catastrophizing.

2.10.1.3 Pain intensity

Effects on pain intensity were not significant in two studies [129, 130], negative in one [128], less than small to small in one [127]. Simister et al. used a pain measure with components beyond intensity, with large effect size post, but less than small at follow-up [131].

2.10.1.4 Mood, quality of life and sleep

All trials measured depression, with effect sizes ranging from non-significant in the Lin and Trompetter studies [127, 129] to large in the Simister study [131]. Three trials measured anxiety with no significant treatment effect in the Lin and Trompetter studies [129] and a less than small in the Buhrman study [130]. Two trials measured quality of life, with no effect of treatment [129, 130]. Simister et al. measured sleep, but with no treatment effect [131].

2.10.1.5 Values

Values were included in two studies. The Trompetter study showed no effect [127], and the Simister study showed a significant negative effect of treatment, with an additional decrease at follow-up [131]. The Scott study included committed action, with a less than small positive effect size post-treatment [128].

2.10.1.6 Mediation

In the Simister study pain acceptance mediated the effect on fibromyalgia impact, while kinesiophobia and catastrophizing did not [131]. In a follow up study, Lin et al concluded that increased PF mediated reduced disability, pain intensity, depression and anxiety and increased quality of life [95]. In the Trompetter study changes in PF as well as catastrophizing mediated changes pain interference [94].

2.10.1.7 Moderation

In the Lin study patients with initially high PF tended to decrease their pain interference following treatment, while those with low initial PF did not benefit from treatment [132]. In the Trompetter study results are related: patients with initial high levels of psychological well-being benefitted from treatment, while those with low psychological well-being did not [133].

2.10.1.8 Summary of previous findings

In short, internet-delivered ACT has been shown to be efficacious when it comes to pain interference and acceptance, with small to moderate effect sizes. The findings regarding depression, pain intensity, values and anxiety are inconclusive and there are no positive results for QoL and sleep. There is consequently vast room for improvements.

2.11 SUMMARY

Chronic pain is common and the burden on the individual, society and health-care systems is high. Pharmacological or medical treatments are often insufficient in improving functioning, and our understanding of the mechanisms in the development and maintenance of chronic pain is limited.

The burden of co-occurring problems for chronic pain patients calls for a treatment that can address dealing with pain and stress, anxiety, depression and hindering thoughts. PF seems to be an important process mediating pain interference and functioning. ACT treatment aims at increasing PF and is promising in a number of trials, but access to treatment is low and effect sizes modest.

Internet-delivered treatments can be effective, cost-effective and improve access to health care. Internet-delivered ACT trials for chronic pain are promising but there is room for improvements both regarding the size of effects and effects on co-occurring problems.

The purpose of the present work is therefore to develop a feasible and effective internet-delivered ACT for adults with chronic pain, and to increase the understanding of mechanisms in pain-related disability and treatment.

3 AIMS

3.1 STUDY I

The aim in study I was to evaluate the psychometric properties of the Swedish version of the Valuing Questionnaire in a sample of chronic pain patients.

3.2 STUDY II

In study II, the aim was to examine the role and function of psychological flexibility processes (avoidance, value obstruction and value progress) as resilience factors for chronic pain patients.

3.3 STUDY III

The aim of study III was to evaluate the feasibility and preliminary effects of a novel treatment protocol, iACT, for chronic pain in a self-referred and a clinical sample.

3.4 STUDY IV

Study IV aimed to evaluate the immediate and long-term efficacy of iACT for chronic pain, compared to a waitlist control group in a randomized controlled trial with regards to pain interference, psychological flexibility, value orientation, QoL, depressive symptoms, anxiety, insomnia and pain intensity.

4 EMPIRICAL STUDIES

Background, methods and results are presented briefly in this section, the entire papers can be found in the second half of the thesis. The four included studies are of different design and use different methodology, see Table 2 below for an overview.

Table 2. Overview of studies

Study	Design	Participants	Data Collection	Statistical analyses
I	Cross-sectional	Self-referred adults with chronic pain (n=252)	Self-report assessments in an online platform.	Descriptive statistics, confirmatory factor analysis, Cronbach's alpha, bivariate correlations, hierarchical regression.
II	Cross-sectional	Same as in Study I	Self-report assessments in an online platform.	Descriptive statistics, bivariate correlations, hierarchical regression, odds ratios, indirect effects PROCESS analyses.
III	Open pilot intervention study	Self-referred (n=24) and clinical patients (n=15) with chronic pain	Semi-structured interviews, feedback interviews, self-reported feedback, self-reported assessments, platform-generated data.	Descriptive statistics, independent T-test, Mann-Whitney U-test, Little's MCAR test, X^2-test, multilevel linear modelling, effect size calculations.
IV	Randomized controlled study	Self-referred adults with chronic pain (n=113)	Semi-structured interviews, self-reported assessments, platform-generated data.	Descriptive statistics, X^2-test, Cronbach's alpha, multilevel linear modelling, effect size calculations, numbers needed to treat-calculations.

4.1 THE INTERVENTION

The internet intervention was adapted from the evidence-based face-to-face treatment model used at the tertiary pain clinic at Karolinska University Hospital, and was designed to teach PF skills and value-based exposure in order to decrease pain interference. Content was intended to promote recurrent practice of all PF processes and was structured in a micro-learning format, with short daily episodes containing brief educational content and a practical or experiential task. In study III treatment consisted of four episodes per week for ten weeks. In study IV the treatment period was shortened to eight weeks, with five episodes a week. See Table 3 for an overview of the content as structured in study IV.

Patients were instructed to engage in treatment around 15 minutes a day, five days a week. A week's material was labelled a "level", and when completing a level, the designated therapist gave feedback and access to the next level. Therapists instructed patients that one level a week was the expected tempo, but no time restrictions were made on time spent on each level. A patient completing a level after two days gained access to the next level and a patient completing a level after 15 days, then gained access to the next level.

Table 3. Overview of treatment content (as structured in study IV)

	Weekday	Educational content	Practical/Experiential exercise	Theme[1]
Level 1	Monday	Treatment rationale	Identify dysfunctional behaviors	BA
	Tuesday	When life narrows down	What if your pain had no impact	VO
	Wednesday	Changing behaviors	Behavior analysis	BA
	Thursday	What is pain?	Behavior analysis	PE, BA
	Friday	Self-observation rationale	Observe your breathing	PMA
Level 2	Monday	In the waiting hall of life	Imagine the future	VO
	Tuesday	Chronic pain	Behavior analysis	PE, BA
	Wednesday	Perspective taking	The discomfort pie chart	D
	Thursday	The chronic pain dilemma	Evaluating pain behaviors	BA
	Friday	Self-observation rationale	Body scanning	PMA
Level 3	Monday	Pain in context	Reflect on own pain experiences	PE, D
	Tuesday	What's important in life	Define your values	VO
	Wednesday	Form and function of behavior	Do something different	BA, EXP
	Thursday	Acceptance introduction	Don't scratch the mosquito bite	A, EXP
	Friday	Outward focus	Identify elements of a song	PMA
Level 4	Monday	Walking towards values	Identify small steps	EXP, VO
	Tuesday	The pain monster	What does your monster say?	D
	Wednesday	Be skeptical towards thoughts	Name your inner radio station	D
	Thursday	Change and acceptance	Turn up your acceptance	A, EXP
	Friday	Labeling thoughts	Observe your thoughts	D, PMA
Level 5	Monday	Challenge yourself	Do something difficult	EXP
	Tuesday	The pain monster part II	Draw your monster	D
	Wednesday	Pain medication	Quiz	PE
	Thursday	Make it count	Be close to your monsters	A, D, EXP
	Friday	Self-observation rationale	Observe your discomfort	PMA, EXP
Level 6	Monday	About exposure	Do something even harder	EXP
	Tuesday	Distance to thoughts part I	The Ebbinghaus illusion	D
	Wednesday	Distance to thoughts part II	Labeling/But vs and-exercise	D
	Thursday	Recruit others to your team	Define the kind of support you want	BA, VO
	Friday	Self-observation rationale	Sit still for five minutes	PMA, EXP
Level 7	Monday	Continued exposure	Do several hard things	EXP
	Tuesday	Dealing with thoughts	Play with thoughts, keep them in your pocket	EXP, D
	Wednesday	Pro-social rationale	Do something for someone else	EXP, VO
	Thursday	Perspective taking	Take perspective on yourself	PMA
Level 8	Monday	Continued exposure	Do many hard things	EXP
	Tuesday	Self-observation rationale	Sit still for ten minutes	PMA, EXP
	Wednesday	Let discomfort be	Notice, describe, accept, turn back your attention	A, VO
	Thursday	Summary of treatment	Relapse prevention	
	Friday	New behaviors = new shoes	Design your 3-month follow-up	

Note: [1] Themes: BA, behavior analysis; VO, value orientation; PE, pain education; PMA, present-moment-awareness; D, defusion; EXP, exposure; A, acceptance.

Therapist support was provided for twelve weeks in study III and ten weeks for study IV, in both cases thereby allowing a two-week buffer for lower pace and events like journeys or sickness. Therapist support providers were three clinical and two intern psychologists at the tertiary pain treatment clinic. Supervision was provided weekly or upon request by an experienced pain psychologist. Clinical psychologists were familiar with the treatment model and had previous experience with chronic pain patients, intern psychologists had limited experience with pain and treatment model and were supervised more intensely.

Therapists were instructed to communicate with patients at least once a week regardless of patient activity, upon completion of a level, and answer messages from patients within 48

hours, except on weekends. Support was provided via text messages within the treatment platform and telephone support was available upon request. The intended functions of support were to reinforce value-based behaviors, reinforce engagement in treatment, clarify important misunderstandings and answer questions from patients.

4.2 STUDY I: Assessing values – psychometric properties of the Swedish version of the valuing questionnaire in adults with chronic pain

Values is a central component in the PF model, but psychometrically adequate measures are needed. The Valuing Questionnaire (VQ) is an Australian generic self-report questionnaire with two subscales, Progress and Obstruction, to assess values. It is not yet available in Swedish and psychometric evaluations in chronic pain samples are scarce.

The study investigated the following psychometrics for the Swedish version of VQ in a sample of chronic pain patients: 1) model fit; 2) internal consistency; 3) correlations with PF, pain interference, depressive symptoms and QoL; 4) explained variance in pain interference, depressive symptoms and QoL; and 5) explained variance in psychological flexibility.

4.2.1 Methods

A cross-sectional design was used, and 252 adults with chronic pain since at least six months were recruited via self-report. Model fit was investigated using confirmatory factor analysis (CFA). Internal consistency was investigated with Cronbach's alpha. Relations to other constructs were investigated with bivariate correlations (Pearson's and Spearman) and finally hierarchical regression analyses were used to investigate if VQ subscales added explained variance in pain interference, depressive symptoms, QoL and psychological inflexibility respectively.

4.2.2 Main findings

The majority of participants were female (81%), mean age was 47.4 years and mean pain duration was 18.2 years.

After allowing for residual correlation between three VQ items, model fit in the CFA was adequate. Internal consistencies were satisfactory with an alpha of 0.83 for the Progress subscale and 0.76 for the Obstruction subscale.

Progress correlated positively with QoL, and negatively with pain interference, depressive symptoms and psychological inflexibility while Obstruction correlated positively with pain interference, depressive symptoms and psychological inflexibility, and negatively with QoL.

Progress contributed to the variance in pain interference, QoL and depressive symptoms, both with and without control for pain and distress. Obstruction added to the explained variance in pain interference and depressive symptoms, but not QoL, when controlling for pain and distress. Both Progress and Obstruction contributed significantly to the variance in psychological inflexibility.

4.3 STUDY II: Psychological flexibility as a resilience factor in individuals with chronic pain

Some chronic pain patients continue to function well in their everyday life despite stressful circumstances and can be considered resilient. Personality traits, physiological factors, social support and past experiences have been identified as resilience factors, but more modifiable constructs such as PF have been suggested as potential resilience factors. The study aimed to 1) broadly characterize the relationship between symptoms, functioning and PF; 2) assess the amount of variance in functioning (pain interference and depression) explained by PF; 3) explore low PF as a potential risk factor for sick leave and opioid use, and; 4) examine the indirect effects of PF in the relationship between symptoms and functioning.

4.3.1 Methods

The study was cross-sectional, using the same sample as in study I: 252 self-referred adults with chronic pain. Pain intensity, pain duration, pain location and anxiety were used as symptom variables. Functioning was measured as pain interference, depression, sick leave and opioid use. PF was measured as avoidance, value progress and value obstruction.

Relationships between symptoms, functioning and PF was done with Pearson's correlation. Hierarchical linear regressions were used to investigate the amount of explained variance by PF variables. Sick leave and opioid use were analyzed with logistic regression models. Finally, a series of analyses of change processes were used to investigate the indirect effect of PF in the relation between symptoms and functioning.

4.3.2 Main findings

PF variables avoidance and progress were correlated (avoidance positively and progress negatively) with pain interference, depression and sick leave. Obstruction was positively correlated with pain interference and depression.

Avoidance contributed significantly to the variance for both pain interference (β .52) and depression (β .48), while progress contributed to the variance in depression (β .14).

The likelihood of being on sick leave was four times higher in the low value progress group compared to the high progress group (OR 0.25), and five times higher in the high avoidance group compared to the low avoidance group (OR 5.23). No significant differences in odds were found between low/high PF groups for opioid use.

The indirect effect of PF, with pain or anxiety as predictors and pain interference or depression as dependent variables, consistently showed avoidance to be of importance in the relation between symptoms and functioning.

4.4 STUDY III: Internet-delivered Acceptance and Commitment Therapy (iACT) for chronic pain – feasibility and preliminary effects in clinical and self-referred patients

ACT has been shown to elevate functioning and QoL in face-to-face treatments, but accessibility is low. Internet-delivery is one way to increase reach, but the demands on patients concerning attention, sitting still and understanding large amounts of information are tasks known to be difficult for chronic pain patients.

Study III evaluated and compared a clinical and a self-referred sample going through a novel internet treatment protocol, iACT, according to the following: 1) feasibility (acceptability, practicality and usage); 2) preliminary effects; 3) potential treatment mechanisms on the primary outcome.

4.4.1 Methods

Clinical (n=15) and self-referred adults (n=24) with chronic pain were included. Feasibility variables included comprehensiveness, workability, credibility, practicality and usage. Written feedback was collected weekly and prompted iterations in structure and content consecutively. Feasibility data are presented descriptively, comparisons were made with Chi square-, Student's T- and Mann-Whitney U-tests.

Potential effects were evaluated with pain interference as primary outcome, psychological inflexibility and value orientation as process variables, and QoL, pain intensity, anxiety, insomnia and finally depressive symptoms as secondary outcomes. Both potential effects and treatment mechanisms were analyzed with multilevel linear modeling.

4.4.2 Main findings

Feasibility results indicated that both the clinical and the self-referred sample considered the treatment acceptable, comprehensive, workable and credible. Regarding practicality, psychologists used on average 13.5 minutes per week per patient in the clinical sample, compared with eight minutes in the self-referred sample. Recruitment time differed substantially, with 15 patients in 15 months in the clinical sample and 24 patients in one month in the self-referred sample. Geographical distance between psychologist and patient was in median 40 km in the clinical sample and 426 km in the self-referred sample.

Preliminary effect analyses suggested significant moderate improvements from pre- to posttreatment on pain interference, value progress and pain intensity, small improvements on anxiety, insomnia, value obstruction, QoL and depressive symptoms, and large improvements on psychological inflexibility. There were no differences in estimates between clinical and self-referred participants. Psychological inflexibility and value progress were found to be potential mediators for primary outcome pain interference.

4.5 STUDY IV: iACT – internet-delivered Acceptance and Commitment Therapy as microlearning for chronic pain. A randomized controlled study with one-year follow-up

ACT as internet intervention has been shown to be efficacious for diverse chronic pain patients in three previous randomized controlled trials (RCT), with in general moderate improvements in pain interference and pain acceptance. But there is a need for improvements on the so far modest, mixed or non-existing effects on other outcomes, such as pain intensity, sleep, QoL, anxiety, depressive symptoms and value orientation.

Building on the learnings and the treatment developed in study III, study IV aimed to evaluate the immediate and long-term efficacy of iACT for chronic pain, compared to a waitlist control group in a randomized controlled trial. Primary outcome was pain interference, and secondary outcomes were PF, value progress, value obstruction, QoL, depressive symptoms, anxiety, insomnia and pain intensity.

4.5.1 Methods

The iACT intervention was designed to prompt daily experiential learning, teach PF skills and promote value-based exposure. 113 self-referred participants were randomized to iACT (n = 57) or WLC (n = 56). Outcome data were collected at baseline, post-treatment, and at 3-, 6- and 12-month follow-up. WLC participants were crossed-over to unguided treatment after waitlist period, hence no between-group comparisons were possible during follow-up. Intervention effects were analyzed with multi-level linear modeling with ITT.

4.5.2 Main findings

The sample was mainly female (75%), mean age was 49.5 years, and mean pain duration was 18.1 years. Co-occurring problems were common, with fatigue (79%), concentration difficulties (76%) and psychiatric conditions (67%) being the most common. Nearly two thirds (64%) did not work or study full-time at baseline. Post-treatment-assessments were completed by 100 participants (88%). Twelve-month follow-up-assessments were completed by 38 of 57 in the iACT condition (65%).

iACT participants completed on average 74 percent of the total treatment content and 58 percent (n = 33) completed the entire treatment. Psychologist time was 12.5 minutes per active treatment week per participant. Patients received on average 3.9 messages per active week from their psychologist, while participants on average sent 1.5 messages per active week.

Participants in the iACT condition had improved significantly compared to the WLC across all nine outcomes at post-treatment. Between-group effect sizes were large for pain interference, pain intensity and PF. For value progress, value obstruction, depressive symptoms and anxiety effect sizes were in the moderate range, while the effect sizes for insomnia and QoL were small. Improvements in the iACT condition were sustained during the 12-month follow-up period.

4.6 ETHICAL CONSIDERATIONS

The studies within this project include cross-sectional and interventional studies of clinical and self-referred cohorts with adults with chronic and debilitating pain. This is an important area of research since chronic pain is a major health concern today, and appears to be increasing. More efficient methods for assessment and treatment are needed, and several parties can benefit from this research.

4.6.1 Patients' benefits

Increased knowledge about treatment processes, outcomes and measures can benefit chronic pain patients in several ways. Access to treatment can potentially increase, evidence-based care may be readily available, and measures that are quick to administer lessen the burden for patients.

If the treatment developed within this project would be widely disseminated, more patients than today would have the possibility to work with taking their lives back, increasing daily functioning and reducing the negative impact pain has had on their lives so far. Also, the potential future possibility of matching patients to the right level of treatment will eventually benefit patients.

4.6.2 Healthcare benefits

Effective assessment and treatment of patients with chronic pain can be cost-saving both directly and in-directly. Treatment delivered via the internet is often cheaper to administer than regular face-to-face-treatment, and potentially patients may seek less health-care post-treatment. Resources can also be directed towards those with the most needs, if patients who benefit from an internet-delivered treatment can be handled more swiftly. On a community level there can also be possible savings in terms of reduced costs for work-absenteeism and sick leave.

4.6.3 Participant burden

All the participants are asked to complete a large number of questionnaires. In order to learn more, and collect reliable data, we need to design studies to generate as much knowledge as possible, and that sometimes results in lots of questions for each participant. We have tried hard to reduce the burden for the patient, while ensuring that the studies included in this thesis will be collecting enough data to be worthwhile.

4.6.4 Participant risks

We have identified two different risks for the participants: integrity/security risks, and risks in the treatment itself.

4.6.4.1 Integrity and security

The iACT platform stores treatment, participant responses and all quantitative data encrypted on secure servers, located at Karolinska Institutet, and we have minimized the risks for

security breaches according to existing guidelines. Both participants and psychologists used double authentication to log in. For integrity reasons, psychologists could only access data and responses for the particular participants they supported in treatment. The system platform was also designed to immediately discover and track security breaches.

4.6.4.2 Treatment risks

The treatment model aims to increase valued activities. A parallel increase in anxiety, worry and pain is expected for some, and we informed patients of this before engaging in treatment. Deteriorations as for example increased depressive symptoms or increased pain was monitored during and after treatment, and was observed for several persons. These deteriorations were in part attributed to treatment, and to some extent deteriorations were not related to the treatment itself. Over time, many chronic pain patients report fluctuating pain and functioning and it is reasonable to expect that some of the patients in the studies would have improved, deteriorated or stayed the same with or without the intervention. In the control group in study IV, the number of participants experiencing deteriorations during wait list period was twice as large as in the treatment group, making it reasonable that the treatment may have limited the number of patients that otherwise would have deteriorated. No serious adverse events were reported during any of the studies.

4.6.5 Transparency and replicability

To ensure transparency and counteract bias we registered the randomized controlled trial and pre-planned analyses at Clinicaltrials.org. The internet format facilitates replication of study results as treatment content delivery can be held constant. The format also minimizes therapist drift. The digital platform makes it possible to follow interactions between patients and psychologists throughout treatment, to further enhance transparency and replicability. At least two of the articles in the thesis were published in open access journals, to further promote access to, and transparency of scientific knowledge.

5 DISCUSSION

Chronic pain is a complex and common condition. Our understanding on how different possible mechanisms interact in both development and maintaining of chronic pain is limited. For chronic pain patients, access to evidence-based behavioral treatment is also scarce. The purpose of the studies in this thesis was to increase our understanding of factors related to chronic pain, as well as developing a feasible and effective internet-delivered ACT treatment.

5.1 THE FINDINGS IN CONTEXT

The concept and measurement of values in relation to chronic pain variables was examined in the psychometric evaluation of VQ in study I. VQ was found to have adequate psychometric properties, and contribute to the variance in pain interference, depressive symptoms and PF above and beyond pain and distress.

VQ is the first global value measure validated in Swedish, and has the strength of being comparable over time and between individuals. The findings in study I are important as they provide clinicians with a quick and easily administered value measure when working with behavioral change with patients. From a scientific perspective, the findings replicate and extend previous literature on the VQ as a valid quantifiable measurement tool of value-based behaviors [101, 134]. This is an important area of research as pre-existing value measures have had problems with inconsistent scoring and quantification of results [100, 101, 135]. The VQ is a short and easy-to-use measure and could for example be used in treatment trials to see if changes on the VQ precedes functional outcomes.

One benefit of the VQ is that it assesses a positive dimension of life. This is in contrast to the widely used paradigm of assessing negative (or absence of negative) life aspects such as pain, anxiety, obsessions, depressive symptoms or sleep difficulties [55, 56]. Assessing positive dimensions of life may provide researchers and clinicians with new opportunities to both understand and to improve the positive psychological factors, and not just “the bad ones”. The correlation between the positively valanced subscale value progress and the negatively valanced obstruction was -.39 in study I. This could illustrate that what we perceive as opposite sides of the same constructs (or two sides of the same coin), are not in fact opposites, but related constructs. A high degree of progress for value-based behaviors is not the same as the absence of obstruction for value-based behaviors, but they are related [47].

During the last two decades there has been an increased scientific interest in investigating resilience factors such as self-compassion, acceptance or present-moment-awareness [47]. In the field of chronic pain, previous studies have found that high pain intensity does not necessarily predict low daily functioning [1, 23, 31]. In study II we wanted to investigate this further and see if PF could be a resilience factor for high functioning despite chronic pain. We found that PF added explained variance in depression and pain interference, and also had an influence on the relationship between symptoms (anxiety and pain intensity) and functioning (depression and pain interference). Individuals with high degree of avoidance and

low value progress were much more likely to be on sick leave than persons with low avoidance and high value progress.

Unlike many other resilience factors for chronic pain (such as being male, younger age, have higher education or not suffering from chronic illness) PF provides opportunity for intervention and experimental manipulation [49, 136]. Identifying and measuring factors that we can exercise an impact on in treatment is important, as it may help us both understand how conditions as chronic pain develop and are maintained [47]. One suggestion for future studies would be to investigate if PF is an important resilience factor also over time. A long-term follow-up study on patients who received psychological treatment for chronic pain found that higher psychological inflexibility at post-treatment predicted higher degree of disability three years following treatment [30]. Consequently, the results from study II needs to be replicated using a longitudinal cohort design. Another suggestion for future studies could be to screen individuals at high-risk of developing chronic pain and investigate if it is possible to increase PF for these individuals, and see if this in turn has a positive effect on functioning. This would add important pieces to the puzzle in understanding how behavioral factors such as PF contribute – or not – to the development of chronic pain.

In study III internet-delivered ACT in a micro-learning format was developed, iterated and evaluated with the help of a clinical and a self-referred cohort of chronic pain patients. Participant insights and ratings indicated that working with treatment in short learning chunks several times a week was feasible. Ratings and feedback also indicated that transferring complex experiential therapeutic exercises into a comprehensive digital format was viable. Many iACT patients spent more time interacting with treatment content (more than two hours per week) than standard face-to-face therapy usually offers, while therapists in iACT spent less than 15 minutes per patient each week. This is encouraging, as the feasibility results indicates that patients can have access to qualified health care advice and treatment, with minimal load put on health care resources.

Potential efficacy of treatment was positive in study III, as participants on average improved across all nine outcomes. This is also promising, and it is, to my knowledge, the first time an internet-delivered ACT intervention for chronic pain shows preliminary evidence of positive effects across such a wide range of outcomes [127-131]. Since the intervention was built in short micro-learning episodes, it also easily allows future iterations in different contexts and into smartphone-friendly platforms. One possible extension of the iACT treatment would be to slim the intervention even more with only a few episodes and apply it in low-intensity settings, such as prevention trials. The high degree of control over the iACT intervention also enables close investigation of the incremental effect of the various components in this treatment.

The analyses from study IV, the randomized controlled trial, showed improvements in the iACT condition compared to the WLC on all outcomes. We found large between-group effects for pain interference ($d = 0.99$), psychological inflexibility ($d = 1.0$) and pain intensity ($d = 1.2$). Effect sizes for value orientation, anxiety and depressive symptoms were in the

moderate range, and for QoL and insomnia they were small. All improvements were maintained at one-year follow-up. If we use the previously mentioned Cochrane reviews for face-to-face and internet CBT versus WLC for benchmarking purposes, our results appear in some respects better than many other psychological treatments for chronic pain. Estimated effect sizes for iACT in comparison with the pooled estimates of internet CBT effect sizes are around two to three times as high. See Table 4 below for an overview.

Table 4. iACT estimates post-treatment compared to benchmark estimates

	iACT	**Face-to-face CBT[1]**		**Internet CBT[2]**		**ACT trials[3]**
	est *d*	SMD, pooled	Range	SMD, pooled	Range	Range *d*
Disability/ interference	.99	.26	-.36 – 1.24	.50	.18 – .87	ns – 1.26
Mood/depression	.52	.38	-.10 – 1.02	.19	-.14 – .65	ns – .87
Anxiety	.62	Not est		.28	-.33 – .75	ns – .18
QoL	.49	Not est		.27	.09 – .39	ns
Pain intensity	1.2	.21	-.37 – .66	.37	0.0 – 1.1	ns – .84

Note: est, estimated; CBT, cognitive behavioral therapy; SMD, standardized mean difference, ns, no significant result; QoL, quality of life. Estimations are displayed in the positive direction for improvements, and negative for deteriorations. [1] Williams et al. 2012 [71]. [2] Eccleston et al. 2014 [126]. [3] Buhrman et al. 2013 [130], Trompetter et al. 2014 [127], Lin et al. 2017 [129], Scott et al. 2018 [128], Simister et al. [131].

Importantly, iACT showed improvements in sleep, values and QoL, which extends previous findings [127-131]. The sample included in this study had suffered from pain for around 18 years on average, 63% fulfilled diagnostic criteria for at least one comorbid mental health condition and 92 percent reported additional symptom burden such as fatigue (79%), concentration difficulties (76%) and memory deficits (66%). This indicates that the results from this trial may be generalizable also to clinical patients with high degree of disability.

One possible reason for the large effect sizes in study IV could be the use of a wait-list control group, as wait-list conditions do not control for non-specific factors in therapy. Still, wait-list is currently the recommended first step control condition in the development of novel interventions [137]. Thus, the current study should not be regarded as the definitive trial, but an important first step to evaluate iACT for chronic pain. Although two previous internet-ACT studies have used active control groups [127, 130], these trials have had mixed findings and one did not control for therapist attention, module completion, treatment credibility or therapeutic alliance [130]. One suggestion for future studies is therefore to use an active comparator, for example stress-management training, where these non-specific factors are controlled for.

Another possible reason for the large effect sizes in study IV could be the micro-learning format, which is designed to promote repeated learning, a strategy proven to be more effective than binge learning [138]. The micro-learning format may be particularly well suited for chronic pain patients – known to have difficulties with for example attention, memory, sitting still [7, 26] – enabling experiential learning in short chunks. The feedback from patients in study III also trimmed structure and content to suit the expressed needs from participants with chronic pain. Additionally, the iACT treatment had a sole focus through the whole treatment to increase PF and practice exposure. This might have been easily

understood for participants, as all educational material, exercises and exposures all pointed in the same direction: increasing the behavioral repertoire, even when everything on the inside (and sometimes also the outside) tell you to narrow it.

The findings from study IV could hopefully lead to further investigations on treatment efficacy as well as mechanisms of change. Given the highly structured format of the iACT treatment, it is a promising candidate for designing dismantling studies and mechanistic trials where the proposed mechanism of change is directly manipulated. Comparisons between different structures of digital delivery could help us explore possible differences in effects between material presented in massive ways and in micro-learning format. A smartphone-friendly version of iACT has been developed – ACTsmart – and is currently under investigation (see future work by Gentili et al.). Smartphone delivery could possibly enhance effects, as it offers a therapeutic presence in patients' everyday life that is hard to achieve for face-to-face or desktop treatments [139, 140]. Additionally, smartphone technology could offer fresh possibilities to do momentary ecological assessments and even closer investigation of mechanisms of change during treatment.

The outcomes used in this thesis were all self-reports. An important venue for future research could be to also incorporate biological measures and relate these to relevant psychological processes such as PF. Many patients who received the iACT treatment said post-treatment that instead of fighting their pain monster, they try to instead focus their energy on living. It could be that PF and value-based exposure have a direct effect not only on behavior, but also on physiological systems. A subsample of iACT patients have been included in a study investigating the relationships between low-grade inflammation and PF (see Åström and Karshikoff, work in progress), and it would also be interesting to further explore if iACT treatment possibly affects central pain inhibition [141, 142], inhibitory pathways, or executive functioning [141-144].

Dissemination of iACT into regular health care is another step forward, as well as optimization studies to reduce redundant content or match treatment content to specific needs. Responder analyses would be beneficial to learn more about what works for whom, and further exploration of moderators and mediators in treatment would expand our knowledge on how potential treatment mechanisms operate over time. A potential design to investigate moderators could include several steps: 1) identifying treatment-specific moderators in, for example, face-to-face ACT and iACT; 2) randomize participants to either: a) random treatment allocation (face-to-face/iACT); or b) allocate treatment based on identified moderators.

5.2 ARE THE EFFECTS OF IACT ONLY POSITIVE?

Some of the patients in study III and IV deteriorated from pre- to post-treatment. Recent research suggest that psychological treatments also can cause negative effects [145, 146]. Importantly, as much as five to ten percent of participants who receives psychological treatments in somatic care deteriorate [147]. The most common predictors for deteriorations

are high levels of symptom distress at baseline, and chronicity [147, 148]. Contrary to this, patients that deteriorated in study IV actually reported *higher* functioning at baseline than non-deteriorating patients. Increased engagement in valued activities may increase pain intensity and at the clinic we sometimes see anxiety and/or depressive symptoms rise in the beginning of treatment. Patients who give up treatment in these early stages might never experience the beneficial effects of therapy. Future research questions could be to explore if deteriorators are less engaged in treatment or if early deteriorations are predictive for post-treatment deteriorations or attrition [149]. Qualitative interviews with deteriorating patients could increase resolution and shed more light on this important issue.

5.3 WHAT IS PSYCHOLOGICAL FLEXIBILITY REALLY ABOUT?

Theoretically, PF is often framed as a unified construct [150]. However, the clinical operationalization of PF tends to focus on the six mid-level processes of acceptance, defusion, present-moment-awareness, self-as-context, committed action and values. Although these mid-level processes are useful constructs in clinical work [151], there have been criticism that they lack both precision, scope and depth compared to traditional learning theory term definitions (such as reinforcement or stimulus function) [152]. The term defusion can for example be understood as both a procedure, a process, and an outcome [151] and this broad use of terms may blur scientific progress. To my knowledge, no systematic and empirical investigation have been able to successfully make a clinically relevant distinction between the six mid-level processes in PF [150, 153]. An alternative operationalization of PF, proposed by Törneke et al., instead suggests three behavioral classes in psychological treatment [153]:

- Identify dysfunctional behaviors and their reinforcing consequences
- Perspective-taking behaviors (practice distance to experiences, observe that you are the one observing)
- Approaching behaviors towards values

In this theoretical approach, many of the mid-level processes – acceptance, present-moment-awareness, self-as-context and defusion – could instead be merged into one single construct, in this case ”perspective-taking behaviors” [153].

Working with the development and refinement of the iACT treatment, I have become more intrigued to further empirically investigate the third behavioral class proposed by Törneke et al.; approaching behaviors. During the development of iACT content, we have thought of values as a provider of a) direction; b) appetite for exposure to aversive experiences; and c) a verbally constructed reinforcing contingency. This is in no way new thoughts, as experimental studies have shown that the addition of a value component can increase pain tolerance [154, 155], and cross-sectional data have repeatedly shown the importance of values in the chronic pain context [156, 157]. However, it still remains to be empirically investigated whether 1) values are really important to facilitate in vivo exposure in ACT and

2) if higher degree of valued direction during exposure in turn provides reinforcing contingencies (the hypothesized mechanism of change) in chronic pain treatment.

This is important issues as it could provide science and clinicians with knowledge about mechanisms to target in therapy. In order to improve our therapies and make more effective treatments, we need to pinpoint which intervention actually produces change instead of throwing a range of interventions at patients and hope that they will benefit from at least one of them [68]. One obvious way forward to continue this strive is to let theory guide advancements in clinical practice, and let empirical and clinical results be reflected in updated theories [151].

5.4 LIMITATIONS

Some limitations should be considered when interpreting the results in this thesis. As previously mentioned, all outcomes are self-reported. The addition of more objective behavioral measures would add to the validity of results. Additionally, almost all patients in the four studies were self-referred. This may affect external validity, as we cannot be sure that results are valid for clinical patients. However, study III also included a sample of clinically recruited patients and the results indicated that the observed differences between clinical and self-reported cohorts need not be crucial neither for treatment outcomes nor treatment engagement. Self-referral as recruitment method might also be considered a strength, as it may reach patients who have suffered for a long time, without getting the help they need from the regular health care system [140]. In study I and II, a cross-sectional design was used, and the continuous validation of VQ as well as PF as a resilience factor should include longitudinal data. In study III results are based on a small sample of included participants and should be interpreted with caution. Also, the preliminary investigation of treatment mediators was purely based on co-variation, without considering factors like timeline or dose-response relationships [158]. For study IV, as mentioned, the lack of an active control comparison is the most obvious limitation.

6 CONCLUSIONS

Values can be effectively assessed using a brief self-rating questionnaire. Psychological flexibility may be an important resilience factor in the development and maintenance of chronic pain. ACT delivered in a micro-learning format via internet can be both feasible and effective as to increase functioning for chronic pain patients. The studies in this thesis provides a groundwork for future scientific investigating in some of the psychological mechanisms relevant for chronic pain.

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