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EFFICACY AND PROCESSES OF CHANGE IN ACCEPTANCE AND COMMITMENT THERAPY FOR CHRONIC PAIN

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Fast i mörka tankegångar igen

Denna gång kanske inte hittar hem

Vad är det att vara fri,

när man lever inuti

Vart man föds styr vad man får bli

Vad är det att vara fri,

när monstret sitter inuti

Vad är det att vara fri,

när monstret växer inuti

Det Stora Monstret – *Manifest*

EFFICACY AND PROCESSES OF CHANGE IN ACCEPTANCE AND COMMITMENT THERAPY FOR CHRONIC PAIN

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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ABSTRACT

Background: Approximately one out of five adults in Sweden suffer from longstanding pain and many experience pain-related disability and reduced quality of life. Long-standing pain is also associated with substantial societal costs and psychological factors are central to its development and maintenance. Studies imply the efficacy of cognitive behavior therapy (CBT) and Acceptance and Commitment Therapy (ACT) for long-standing pain in adults, but there is a need for: (1) Randomized controlled trials evaluating the efficacy of ACT compared to established treatments; (2) adequate measures for use in treatment-evaluations that assess the impact of pain on behavior; (3) further evaluations of processes of change in ACT, and specifically for studies that more adequately model change over time and investigate the temporal precedence of change in the mediator in relation to the outcome; and (4) studies evaluating the cost-effectiveness of ACT.

Aims: The overarching aims of the doctoral thesis were to evaluate the efficacy and processes of change in ACT for longstanding pain. Specifically, the aims were to evaluate: (1) The efficacy of ACT delivered in a group setting (Study I and Study II); (2) the cost-effectiveness of ACT (Study II); (3) the psychometric properties of a brief measure assessing pain interference, the Pain Interference Index (PII) (Study III); and (4) if changes in psychological inflexibility mediated changes in pain disability (Study I) and pain interference (Study IV).

Methods: The efficacy of ACT was tested in two randomized controlled trials. The first trial utilized a wait-list control condition and included women with fibromyalgia (Study I). Assessments were done pre- and post-treatment and at 3-month follow-up. In Study II adults with non-specific longstanding pain were randomized to ACT or applied relaxation (AR). Data was collected pre-, mid- and post-treatment, and at 3- and 6-month follow-up. Pain disability was the primary outcome measure in both studies. Data was analyzed using hierarchical linear modeling and latent growth curve modeling. Cost-effectiveness was evaluated by calculating the quotient of the difference in average changes in costs and pain disability in ACT and AR (Study II).

The psychometric properties of the PII were evaluated using cross-sectional data from adults with non-specific longstanding pain (Study III). Analyses comprised a principal component analysis, analysis of item statistics, corrected item-total correlations

and inter-item correlations. Concurrent criteria validity was evaluated using zero-order correlations and ordinary least squares regression analyses including pain intensity, pain disability, health-related quality of life and depression. In Study I mediation analyses were based on change scores in psychological inflexibility during treatment and change scores between pre- to follow-up assessment in outcomes (e.g. pain disability). Study IV incorporated the specified timeline between mediator (e.g. psychological inflexibility) and outcome (pain interference) based on session-to-session assessments from participants in Study II and used multilevel regression analyses to model change.

Results: In Study I results showed significant improvements in the ACT-condition, in pain disability, fibromyalgia impact, mental health-related quality of life, self-efficacy, depression, anxiety and psychological inflexibility. Results in Study II illustrated significant improvements across conditions from pre-treatment to follow-up in pain disability, physical health-related quality of life, pain intensity, depression and anxiety. Also, ACT improved significantly relative to AR in pain disability during treatment, but AR improved in pain disability compared to ACT between post-assessment and 6-month follow-up. Pain acceptance increased significantly only in ACT. This increase was maintained at 6-month follow-up. In addition, results indicated that ACT was more cost-effective than AR at post-treatment and 3-month follow-up, but these results had leveled out at 6-month follow-up. The psychometric evaluation of PII (Study III) indicated the reliability and validity of the measure in assessing pain interference in adults. In Study I treatment changes in psychological inflexibility mediated pre- to follow-up improvements in pain disability and secondary outcome measures in ACT. Similarly, change in psychological inflexibility mediated change in pain interference in ACT during treatment in Study IV.

Discussion and conclusions: Results correspond with previous studies on ACT for longstanding pain and suggest the utility of ACT for fibromyalgia and non-specific longstanding pain (Study I and Study II). Also, psychological inflexibility is further established as a central treatment target and mediator of improvement in ACT (Study I and Study IV). Health economic analyses illustrated that ACT was associated with significant cost reductions and cost-effectiveness compared to AR up to 3-month follow-up (Study II). In sum, the studies add to the support for ACT for longstanding pain and specifically contribute in areas that were found to be lacking in the empirical literature.

LIST OF SCIENTIFIC PAPERS

I.   Wicksell RK, Kemani M, Jensen K, Kosek E, Sorjonen K, Ingvar M, Olsson GL. Acceptance and commitment therapy for fibromyalgia: A randomized controlled trial. *European Journal of Pain*. 2013; 17: 599–611.

II.   Kemani MK, Olsson GL, Lekander M, Hesser H, Andersson E, Wicksell RK. Efficacy and Cost-effectiveness of Acceptance and Commitment Therapy and Applied Relaxation for Longstanding Pain: A Randomized Controlled Trial. *Clinical Journal of Pain*. 2015; 00:000–000.

III.   Kemani MK, Zetterqvist V, Kanstrup M, Holmström L, Wicksell RK. A Validation of the Pain Interference Index (PII) in Adults with Long-standing Pain (manuscript submitted for publication).

IV.   Kemani MK, Hesser H, Olsson GL, Lekander M, Wicksell RK. Processes of Change in Acceptance and Commitment Therapy and Applied Relaxation for Longstanding Pain (manuscript submitted for publication).

CONTENTS

LIST OF ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
AR	Applied relaxation
CBS	Contextual behavioral science
CBT	Cognitive behavior therapy
CEA	Cost-effectiveness analysis
CNS	Central nervous system
CR	Conditioned response
CS	Conditioned stimulus
CSS	Central sensitization syndrome
CWP	Chronic widespread pain
FM	Fibromyalgia
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
NS	Neutral stimulus
PCA	Principal component analysis
PII	Pain Interference Index
RCT	Randomized controlled trial
RFT	Relational frame theory
RGB	Rule-governed behavior
UCR	Unconditioned response
UCS	Unconditioned stimulus

1 INTRODUCTION

This doctoral thesis evaluated the efficacy of a contextual behavioral therapy, Acceptance and Commitment Therapy (ACT), in improving pain-related disability, pain interference and health-related quality of life (HRQL) in persons suffering from longstanding pain and related distress. Notably, the objective was not to attain improvements in pain disability and pain interference by means of reductions in pain following treatment. Rather, we hypothesized that ACT would facilitate disengagement from, and a willingness to experience, distressing pain, related cognitions and emotions. Furthermore, we anticipated that this would create more flexible psychological or behavioral repertoires and in turn improve pain disability and pain interference. In line with these hypotheses, we evaluated if improvements in psychological flexibility were functionally related to improvements in pain disability and pain interference.

In addition, the effect of treatment on health-related costs and the cost-effectiveness of treatment were evaluated. Lastly, we evaluated the psychometric properties of a brief pain interference questionnaire that was also used as an outcome measure in the afore-mentioned analyses of processes of change. Before I present and discuss the details of the specific studies I will give a background to longstanding to pain, its prevalence, consequences and treatment challenges, and to the theoretical, clinical and empirical underpinnings of cognitive behavior therapy (CBT), and ACT in particular.

2 BACKGROUND

The ability to experience pain is of major evolutionary importance and the pain system serves facilitation of tissue integrity and tissue repair when integrity has been compromised. Pain is transmitted from nociceptive neurons via large (Aδ-fibers) and small diameter fibers (C-fibers) conveying brief sharp pain and blunt throbbing pain respectively. These fibers project to the dorsal horn of the spinal cord where nociceptive signaling is further projected to higher cortical areas (Willis and Westlund, 1997). Melzack and Wall (1965) changed the view of the spinal cord as a passive transmission station for pain, to a (metaphorical) gate where potential modulation of nociceptive input can take place. This modulation occurs by way of interaction between pain-transmitting and non-pain-transmitting neurons in the spinal cord dorsal horns, in such a way that the influence of non-pain transmitting neurons can inhibit the perception of pain (Melzack and Wall, 1965).

2.1 PAIN CLASSIFICATION

Pain is referred to as acute when it arises in direct temporal relation to e.g. tissue damage and subsides when healing has occurred (Turk and Melzack, 2011). When pain persists and exceeds a pre-defined temporal cut-off, e.g. 3 months, it is referred to as *longstanding* or *chronic pain* (Merskey and Bogduk, 1994). Longstanding pain can be an expression of ongoing *nociceptive* signaling as described above, or the consequence of a lesion or a disease in the somatosensory nervous system, i.e. *neuropathic pain* (IASP, 2012). However, pain also exists in the absence of a clear pathology and is then classified as e.g. *idiopathic* or *non-specific pain*, or, as in the case of e.g. fibromyalgia (FM), by specific descriptive criteria (Norrbrink and Lundeberg, 2010; Wolfe, 2010). FM is often referred to as a pain syndrome including tenderness, widespread pain, fatigue and disturbed sleep. The diagnosis is based on descriptive criteria comprising widespread pain and symptoms of fatigue, unrefreshed sleep, cognitive problems, and somatic symptoms, of a pre-specified severity (Wolfe, 2010). The biology involved in acute pain is well studied and relatively well understood. In contrast, the biology underlying the development and persistence of longstanding pain is less clear, but a number of biological factors have been suggested in regard to non-specific longstanding pain and FM.

2.2 BIOLOGICAL PERSPECTIVES ON LONGSTANDING PAIN

A few perspectives on the biological processes that are potentially relevant for the understanding of longstanding pain are briefly presented below. Importantly, the presentation is meant to illustrate the possibility of similar biological processes being involved in different descriptive pain classifications, but also in regard to pain-related symptoms (e.g. fatigability) and emotions. In addition, these perspectives aim to highlight the relation between the biology of pain and motivation.

2.2.1 Altered sensory processing in the central nervous system

Central sensitization is characterized by an increase in the neuronal excitability in the central nervous system (CNS) that alters certain sensory inputs (Woolf, 2011). According to Woolf (2011, p. 14), this change is initially triggered by intense activity in nociceptors that in effect strengthen the synaptic connections between the nociceptor and the spinal cord neurons. These changes in the synapses result in an amplification of inputs in such a way that stimuli that previously have been experienced as innocuous now produce pain (Woolf, 2011, p. 4). Under the above circumstances, pain may feel as

it comes from peripheral areas of the body, but in actuality it is the product of altered and irregular sensory processing in the CNS (Woolf, 2011, p. 4). For example, central sensitization may be responsible for the experience of pain following tactile stimulation, but also for causing pain and tenderness in areas adjacent to the actual area of tissue damage (Woolf, 2011, p. 8). *Temporal summation* is a phenomena that is related to central sensitization, and refers to a progressive buildup of the magnitude of neuron activity in the dorsal horn, produced by repeated activation of small diameter pain fibers, resulting in a prolonging of pain (Woolf, 2011).

2.2.1.1 The example of FM

Altered sensory processing in the CNS of the kind discussed above has been put forth as putatively central in FM, based on results from a number of studies (Gracely et al., 2002; Kuchinad et al., 2007; Mountz et al., 1995). For example, central pain processing has been implied by higher pain intensity and larger areas of referral in persons diagnosed with FM (Sorensen et al., 1998), as well as by findings showing greater temporal summation of pain in persons suffering from FM-symptoms (Staud et al., 2001). Also, previous studies imply dysfunction of endogenous pain inhibitory mechanisms (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997). In addition, based on studies showing overlap between for example FM, temporomandibular disorder (TMD) and irritable bowel syndrome (IBS) (Plesh, Wolfe, and Lane, 1996) it has been proposed that central sensitization possibly represents a unifying pathophysiological mechanism for a number of pain syndromes. In line with this, the term central sensitivity syndrome (CSS) has been suggested as a way to denote these pain syndromes (Yunus, 2007).

2.2.2 Pain as part of a sickness response

However, central sensitization may not sufficiently explain other co-occuring symptoms in for example FM, as fatigue, impaired recovery with post-exertional malaise, deficits in concentration and memory, sleep-wake cycle disturbances and emotional distress (Van Houdenhove and Luyten, 2009). Thus, the role of a severely overburdened (hypo-functioning) stress system and a pathological neuroimmune *sickness response*, facilitated by e.g. pro-inflammatory cytokines, has been suggested as a possible framework to understand these co-occuring symptoms (Fries et al., 2005; Meeus and Nijs, 2007; Van Houdenhove and Egle, 2004). This sickness response comprises both physiological and behavioral reactions related to immune activation including increased fatigability, loss of

concentration, hypersensitivity for sensory stimuli, low-grade fever and a generalized increase in pain sensitivity. Importantly, these features of the sickness response may increase motivation to withdraw from social and other daily activity (Van Houdenhove and Luyten, 2009).

2.2.3 Pain as a homeostatic emotion

In summarizing the model of pain as a homeostatic emotion, Craig (2003) describes pain as being part of the representation of the body's physiological interoceptive state. From this perspective, pain is cast a feeling and a motivation, a homeostatic emotion, like itch temperature and hunger. This system, well developed only in humans, includes an interoceptive spino-thalamo-cortical pathway providing a cortical image of the body's condition, "[…] a subjective meta-representation of the feelings from the body that are associated with emotion" (Craig, 2003, p. 4). As homeostasis is a dynamic, hierarchic process that in an ongoing time-varying manner integrates all aspects of the body's conditions, this model may also shed light on the variability of clinically presented pain (Craig, 2003, p. 23). In this view, longstanding pain can be framed as homeostatic dysfunction, a physiological imbalance causing a behavioral drive that the homeostatic systems cannot rectify automatically.

2.3 EPIDEMIOLOGY OF LONGSTANDING PAIN

2.3.1 Demographic data and prevalence

A large-scale European survey illustrated that the prevalence of longstanding pain in adults in 15 European countries ranged from 12% to 30% (Breivik et al., 2006). Results from in-depth telephone interviews with persons suffering from pain six months or longer ($n = 4839$) showed that: 56% percent of the participants were women; the mean age was 50 years; the median pain duration was 7 years; 34% reported severe pain; and that 46% suffered from constant pain. Based on interview data from approximately 197.000 persons, Pleis and Coles (2003) estimated that 28% reported lower back pain, 16% severe headache or migraine, 15% reported neck pain, and 4% facial or jaw related pain.

Results from a systematic review of prevalence studies in Demark and Sweden (including 5 studies with low bias and high representativeness for Sweden) illustrated a prevalence of longstanding regional pain, musculoskeletal and non-specific spinal pain in adults ranging from 23.9% to 56.4% (Harker et al., 2012). In these studies, 53% to 61%

percent of the participants were women and the mean age ranged from 46.5 to 50.3 years (Arvidsson et al., 2008; Bergman et al., 2001; Demmelmaier et al., 2008).

As regards FM in particular, Cöster et al. (2008) reported a prevalence of 2.5% in Sweden, a figure that falls within the prevalence range of 0.66% to 3.3% reported in five population based studies discussed by McBeth (2005), as well as the prevalence range of 1.3% to 4.8% presented by Wolfe et al. (1995). Similarly, a prevalence of 4.1% (Bergman et al., 2001) to 11.4% (Kato et al., 2006) of chronic widespread pain (CWP) has been reported in the population. Repeatedly, there is a clear overrepresentation of women fulfilling criteria for FM. In a study by Wolfe et al. (1995), 80% of participants were women. A study by Bergman et al. (2001) reported a two-fold higher prevalence of CWP in women, and in a study by Kato et al. (2006) 81.7% of persons suffering from CWP were women.

2.3.2 Prevalence of anxiety and depression in longstanding pain

Depression is frequently reported in concurrence with longstanding pain. For example, Breivik et al. (2006) illustrated that 21% of the participants reported a diagnosis of depression in conjunction with pain. According to Banks and Kerns (1996), 9 out of 14 prevalence studies that used stringent diagnostic criteria, reported prevalence rates of depression between 30% and 54% in adults with longstanding pain. Also, markedly higher rates of for example panic disorder, social phobia and posttraumatic stress disorder have been reported in the pain population (Tunks, Crook, and Weir, 2008).

Repeatedly, FM has been related to depressive symptoms and for example Cöster et al. (2008) stated that 54% of participants in their study reported mild to severe depression in conjunction with FM, and Kato et al. (2006) reported a co-occurrence of depressive symptoms in CWP of 40%.

2.3.3 Impact of pain on daily living and societal costs

For a substantial number of persons, longstanding pain has a negative impact in several life domains. These domains include, ability to: Sleep (65%); exercise (73%); walk (47%); do household chores (44%), and drive a car (47%) (Breivik et al., 2006). Pain also negatively affects relations and social life and hampers the ability to: Partake in social activities (48%); have sexual relations (43%); maintain family relationships (27%) and to lead an independent lifestyle (30%) (Breivik et al., 2006). Furthermore, pain is frequently associated with reduced concentration and memory functioning (Sjogren et al., 2005). In

two Swedish studies (Arvidsson et al., 2008; Cöster et al., 2008), results showed that persons with musculoskeletal pain, FM and CWP reported lower scores on factors related to HRQL compared with Swedish population data. Notably, Pleis and Coles (2003) found that over 32%, despite receiving treatments, reported limitations from pain that affected their ability to stand, walk, lift and carry.

Harker et al. (2012, p. 26) conclude that longstanding pain, apart from having a negative impact on functioning and general wellbeing, is also clearly related to increased sick leave and uptake of benefits and pension. Consistently, studies imply substantial societal costs in relation to longstanding pain. For example, one study reported that costs related to longstanding pain in the USA amounted to $560 and $635 billion annually (Gaskin and Richard, 2012). In Sweden, yearly costs related to chronic pain were estimated to SEK 7.5 billion for health-care utilization and medicines and SEK 80 billion for sick leave and production losses (SBU, 2006).

2.4 IMPROVING TREATMENTS OF LONGSTANDING PAIN

Turk (2003, p. 573) writes that pain remains a substantial problem despite increased knowledge of its neurobiological aspects and the development of novel pharmaceutical agents, neuroaugmentative procedures (e.g. spinal cord stimulation) and implantable drug administration systems. That is, even though the aforementioned treatments have showed efficacy, effects are limited. For example, Turk (2002) writes that potent medications reduce chronic pain by 30-40% and that spinal cord stimulation reduces pain by an average of 65% in selected patients. These figures are largely in line with those presented in similar reviews (e.g. SBU, 2006). Also, even when these studies report statistically significant reductions in pain, the improvements are often not accompanied by comparable improvements in physical or emotional functioning.

The limited effects of standalone medical treatments on longstanding pain further suggests the role of psychological factors (cognitions, emotions and behaviors), and the importance of providing patients with strategies that enable them to live with pain that remains after otherwise helpful medical interventions (Turk, 2003). However, also psychologically oriented treatments that have been found to be efficacious, e.g. behavioral medicine and multimodal treatments (SBU, 2010), have a number of issues in regard to their efficacy that requires further research.

In a substantial review of the empirical status of treatments for longstanding pain by the Swedish Council on Health Technology Assessment (SBU, 2006, 2010), the authors

in regard to these latter treatment approaches specifically mentioned that there is a lack of studies evaluating the effects of treatments on *costs* and *HRQL*, as well as the *cost-effectiveness* of these treatments. In order to evaluate the efficacy of treatments, adequate outcome measures are needed. In this regard, the importance of measuring the impact of pain on behavior in central life domains, i.e. *pain interference* has been stressed (Dworkin et al., 2005). Furthermore, several authors in the field (Kazdin, 2008; SBU, 2010) have highlighted the need for more theoretically based evaluations of how specific treatment components, but also situational and patient characteristics, influence the outcome. Below I will describe aspects related to: (1) The assessment of pain-interference; (2) the analyses of health-related costs and cost-effectiveness; and (3) the analytical models used to investigate how specific treatment variables and patient and situational factors influence the outcome. These three aspects are directly related to the aims of this thesis.

2.5 ASSESSMENT OF PAIN INTERFERENCE

The high prevalence of pain and related disability call for more knowledge regarding the impact of pain on behavior, i.e. pain interference, which in turn implies the need for reliable and valid questionnaires to assess this construct. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has emphasized the importance of assessing pain interference in relation to clinical trials. They have also stressed a number of issues that should be considered in the development of such questionnaires (Dworkin et al., 2005). To start with, the measures feasibility (e.g. the understandability of instructions and items) needs to be ensured, which is related to response rates and the administrative burden. Second, there is a need for questionnaires that can be used in a variety of research settings, for example when brief response times are prioritized (e.g. when frequent assessments are required). Third, measures enabling investigators to evaluate different groups with unique demographic profiles (e.g. children and adults) or disease characteristics are deemed important.

2.6 COST-EFFECTIVENESS

A cost-effectiveness analysis (CEA) is used to evaluate the costs and effectiveness of interventions aiming to improve health-related outcomes, e.g. HRQL and pain disability (Drummond, 2005). These analyses incorporate the assumption that resources, including health, are limited and that CEA can aid decision- and policy-making concerning e.g. resource allocation. Central to CEA is the incremental cost-effectiveness ratio (ICER),

which is calculated by subtracting the changes in average costs in one intervention (A) from the changes in average costs in another intervention (B). This figure is then divided with the difference resulting from the subtraction of the average effects in intervention (A) from the average effects in intervention (B) (Drummond, 2005).

Costs include all medical and non-medical costs of the participants, for example costs related to health care visits and medicines (direct medical costs), costs of other health-related services not directly associated with healthcare (direct non-medical costs), and costs related to employment status, sick leave, and reduced capacity at work and domestically (indirect non-medical costs). In this thesis the effects constitute changes on the primary outcome measure, i.e. on continuous data of pain-related disability. However, other gauges of the effects of treatment are often also used, e.g. the number of clinically significantly changed participants (Ferraz-Nunes, 2007).

2.7   PROCESSES OF CHANGE IN TREATMENT

Based on the results from a randomized controlled trial (RCT) utilizing an adequate design and statistical analyses we may conclude that a specific treatment caused change in the outcome, in a specific sense of the word 'caused' (Kazdin, 2007). However, as Kazdin (2007, p. 3) points out, "Demonstrating a cause does not say *why* the intervention led to change or how the change came about." As was done in the present thesis, *mediators* are often assessed and analyzed in order to investigate how treatment-related change occurs.

A mediator (m) is a variable that has a statistically important role to play between the intervention (x) and the outcome variable (y), and provides information of the *process of change* (Kazdin, 2007). When the analyses aim to in greater detail explicate the processes of change the term *mechanism of change* is used. Reasonably, the goal ought to be to understand these finer details of change, but the study of mediators constitutes an important early step (Kazdin, 2007). Also, highly relevant to the understanding of processes of change is the concept of a *moderator*, a variable (z) that has an influence on either the direction or the magnitude of the intervention's (x) effect on the outcome (y). For example, the outcome following treatment may show variation as a function of specific patient-characteristics, e.g. high levels of depressive symptoms.

Kazdin (2007) suggest that a better understanding of mechanisms of change may: (1) Lead to better order and parsimony among a number of current interventions, i.e. even though treatments differ in certain regards they may target similar processes of change; (2) clarify the relation between a specific treatment and its differential

outcomes, e.g. how a treatment has an effect on both disability and depressive symptoms; (3) facilitate optimization, i.e. the refinement of a treatment so that it more efficaciously addresses critical processes; (4) act as a further bridge between research and clinical practice, i.e. inform practice on requirements for effective treatment, for example what treatment components that should not be diluted; and (5) clarify moderators of treatment, which in turn may constitute a basis for selecting suitable patients for specific interventions. I will return to these aspects in the discussion section, but now I will provide a behavioral perspective on the role of *behaviors, cognitions* and *emotions* in longstanding pain.

2.8 A BEHAVIORAL APPROACH TO LONGSTANDING PAIN

The introduction of the gate control theory (Melzack and Wall, 1965) paved the way for the possibility to influence pain via cognitive, emotional, behavioral and motivational factors. Melzack and Casey (as cited in Turk, 2003) explicitly stated that:

> The surgical and pharmacological attacks on pain might well profit by redirecting thinking toward the neglected and almost forgotten contribution of motivational and cognitive processes. Pain can be treated not only by trying to cut down sensory input by anesthetic blocks, surgical interventions and the like but also by influencing the motivational-affective and cognitive factors as well (p. 574).

Likewise, Craig's (2003) view of pain as a homeostatic emotion and as a motivational behavioral drive, directly positions pain within a cognitive, emotive and behavioral framework. Motivation and behavior were also mentioned in relation to pain as part of a sickness response above (Van Houdenhove and Luyten, 2009). These aspects were further implied in the presentation of the epidemiological studies, illustrating that pain co-occurs with distress (e.g. depressive symptom and anxiety) and interferes with daily behavior and leads to negative consequences in different life domains (Harker et al., 2012).

In the next section I will give a brief introduction to a limited set of principles that have been of immense importance in the development of behavioral and cognitive behavioral treatments for longstanding pain, but also for the development of novel principles of complex human behavior. This in turn, has served the development of new treatment approaches as exemplified by ACT for longstanding pain.

2.8.1 Respondent and operant learning

In its fundamental form, respondent conditioning occurs when a neutral stimulus (NS) in close temporal proximity precedes an unconditioned stimulus (UCS) that elicits a reflex, an unconditioned response (UCR). Via this temporal pairing, stimulus functions of the UCS come to be associated with the NS. The NS is now referred to as a conditioned stimulus (CS) and can in turn induce a conditioned response (CR), analogue to the UCR.[1] Ramnerö and Törneke (2008), write that respondent conditioning is a process that gives something in the organism's context "[…] a biological function it did not have up to that point. Something that, up to that point, had one function (or none at all) now acquires a new one" (p. 64).

At the core of operant learning are: Situational factors that precede behavior, the *antecedent* (A); the *behavior* (B) of interest; and the *consequence* (C) that follows directly on the behavior. In this three-term-contingency (the ABC-unit) a specific antecedent factor, a *discriminative stimulus*, has its functions established by a previously experienced connection between a behavior and a consequence. In other words, based on the historical contiguity between a behavior and the resulting consequence, a discriminative stimulus signals the present availability of this consequence (Törneke, 2010). For example, based on previous similar experiences, the calling out of my surname "Kemani" at the dentist's office (A), signals the presence of a certain consequence (e.g. the dentist). Furthermore, this signal evokes movement towards the person calling my name (B), which brings me closer to the dentist (C). When analyzing behavior from this perspective, focus is on the *functional* relationships in the three-term-contingency, e.g. the consequential effects of behavior and not its descriptive properties. For example, a person raising a hand to alleviate shoulder pain behaves in an essentially different manner than a person that raises a hand to great a friend, even if the movements descriptively may be identical.

Consequences comprise two broad functions, behavior increasing (reinforcing) or behavior reducing (punishing) functions that in turn add something to the antecedent event (positive reinforcement/punishment) or removes something from the antecedent event (negative reinforcement/punishment) (Figure 1).

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[1] For an expanded and more critical examination of these relations see e.g. (Rescorla, 1988, p. 151) that describes respondent conditioning as the "learning of relations among events so as to allow the organism to represent its environment."

	Reinforcer	**Punisher**
Positive	Positive reinforcement	Positive punishment
Negative	Negative punishment	Negative reinforcement

Figure 1. Four types of relations involved in operant learning.

Often, learning takes place via the interaction between both respondent and operant principles. For example, respondent conditioning may occur when aspects of a certain food (NS) are associated with an inflammatory response (UCS) and abdominal pain (UCR), and acquires fear-functions (CR). A later refusal to eat said food (B) when it is offered (A), may lead to reduction of fear (C), and thus we are in the operant domain.

2.8.1.1 An operant view of motivation

In addition to discriminative functions, Michael (1993) points to antecedents with motivational functions that influence both the performance of behaviors and their consequences. These antecedent events, *motivational operations*, have a number of defining effects (Laraway et al., 2003). First, they have *value-altering effect*, in that they alter the effectiveness of reinforcers or punishers.[2] Second, they have a *behavior altering effect* in that they alter the frequency of behaviors related to these consequences. These effects include both an increase in responding (evocative effect) and a decrease in responding (abative effect).

Michael (2000) also makes a distinction between unconditioned motivating operations, for example pain, as well as conditioned motivating operations that have their functions via learning. As implied from this perspective, pain is conceptualized as a motivating operation. That is, when an individual is in pain there is an increase of the

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[2] The value-altering effect comprises four different types of effects. These are: (1) A reinforcer-establishing effect; (2) a reinforcer-abolishing effect; (3) a punisher-establishing effect; and (4) a punisher-abolishing effect (Laraway et al., 2003).

reinforcing effectiveness of pain reduction, and the current frequency of behavior (e.g. taking pain medication) that has been previously reinforced by pain reduction.[3]

Notably, Leigland (2005, p. 137) writes: "Moving into the interpretation and analysis of human values naturally involves a considerable increase in complexity, because verbal contingencies are involved in any distinctively human behavioral phenomenon." How to understand more complex aspects of Human motivation and values, as well as their clinical implications will be presented in more detail in the sections dealing with verbal behavior, i.e. Relational frame theory (RFT) and rule-governed behavior (RGB). First though, some key features of a related well-established psychological treatment model for longstanding pain, CBT.

2.9 COGNITIVE BEHAVIOR THERAPY

In the 1970's Fordyce (1976) showed how social and environmental contingencies were highly relevant in the shaping of pain behaviors. Contemporary with Fordyce, Aaron Beck developed cognitive therapy for depression (Beck, 1979). Over time concepts and techniques from cognitive therapy were merged with those of behavioral therapies for chronic pain (Turk, Meichenbaum, and Genest, 1983). Among others, procedures from cognitive therapy include, *cognitive restructuring*, *behavioral experiments*, *problem solving* etc. Contributions from behavior therapy include for example *exposure* and *applied relaxation* (AR). Also, CBT for longstanding pain includes a number of procedures from other traditions, e.g. mindfulness. Typically treatment includes homework in form of between-session activities to apply new skills and practice, for example relaxation practice. Before describing exposure and AR in more detail, I will outline a highly influential CBT-model of how longstanding pain and related disability develops and is preserved, the *fear-avoidance model*.

2.9.1 Fear, avoidance and catastrophizing

Lethem et al. (1983) initially introduced the fear-avoidance model, which posits that fear of pain leads to avoidance behavior, which is reinforced and in turn leads to maintenance and possibly an increase of fear and pain, and in the long run disability

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[3] In order for a stimulus to be conceptualized as a discriminative stimulus (S^D), Michael (2000) means that the history of learning needs to include a negative discriminative stimulus situation (S^Δ). In such a situation reinforcement (available in the S^D situation) is unavailable *and* effective, if obtained. In regards to pain, pain reduction is a consequence that ought to be unavailable and effective – also in the *absence* of pain. However, when pain is absent it is not clear how pain reduction, if obtained, also would be reinforcing. Thus, Michael (2000, p. 406) means that pain should be operationalized as a motivating operation and not as an S^D.

(Lethem et al., 1983). Over the years the model has been extended and refined. For example, *catastrophizing* has been included as a precursor to fear (Vlaeyen et al., 1995) and subsequent avoidance, disability, disuse and depression. Further adjustments to the model have illustrated that fear may also activate vigilance and tension (i.e. not solely avoidance), which potentially further exacerbates pain (Vlaeyen and Linton, 2000).

In a recent conceptualization by Flink, Boersma, and Linton (2013), catastrophizing is operationalized as the ongoing interrelations between thoughts, emotions and overt behavior, i.e. as a process. In this view catastrophizing is conceptualized as *repetitive negative thinking*, similar to worry and rumination, and has the function of reducing negative emotions. From this perspective, one possible downside of catastrophizing as a dominating strategy is that it obstructs constructive problem solving (Flink, Boersma, and Linton, 2013).

Fear-avoidance and catastrophizing have consistently been found to be associated with greater pain as well as pain-related disability (Sullivan et al., 2001; Vlaeyen and Linton, 2000). Studies on catastrophizing have focused on the relation between catastrophizing, pain and negative outcomes. A finding that has been repeated across studies is the relation between catastrophizing and ratings of pain intensity in both acute and longstanding pain. Catastrophizing has also been associated with increased disability and predicted disability better than pain or disease-related variables (Sullivan et al., 2001). Several interventions may be of relevance in interrupting the potential downward spiral fueled by catastrophizing, fear and avoidance. Exposure and AR constitute two viable candidates.

2.9.2 Exposure

Exposure procedures aim to facilitate the gradual increase of activities previously avoided due to pain and related distress and are explicitly included in some pain treatments (Boersma et al., 2004). The use of exposure as a procedure (for problematic anxiety and fear) within CBT is based on a model comprising dysfunctional beliefs and respondent and operant conditioning (Abramowitz et al., 2013). Traditionally, the aim of exposure has been to achieve extinction of a conditioned response, i.e. a reduction of fear or anxiety associated with a specific stimulus. However, research indicates that it might be more important in the long term to teach patients how they can act *with* their anxiety and that they can tolerate fear, during and after exposure (Craske et al., 2008). Exposure in vivo is a treatment approach within CBT for pain that has been specifically

developed for patients with increased pain-related fear. Several studies indicate the efficacy of exposure in improving catastrophizing fear, disability and pain (de Jong et al., 2008; Leeuw et al., 2008).

2.9.3 Applied relaxation

As regards AR, it has been extensively used within CBT (Thyer, 2000; Öst, 1987). The intervention is explicitly based on both respondent and operant principles. It was initially developed to help persons with anxiety to apply a specific type of relaxation at the first signal of discomfort, in order to stop the escalation of anxiety and to better manage symptoms. Similarly, AR has been used to help patients cope with longstanding pain and pain-related distress more effectively. Its efficacy in the area of pain has been illustrated in studies on migraine, tension type headaches, mixed headache, and musculoskeletal pain in neck, back, joints, and upper extremities (Gustavsson and von Koch, 2006; Jensen, Nygren, and Lundin, 1994; Linton and Götestam, 1984; Linton and Melin, 1983; Linton, Melin, and Stjernlöf, 1985; Ström, Pettersson, and Andersson, 2000).

2.9.4 Empirical support of CBT

The efficacy of CBT in improving pain, pain-related disability and mood has been indicated in systematic reviews and meta-analyses. For example, a Cochrane Review (Williams, Eccleston, and Morley, 2012) concluded that (based on 42 included RCTs) CBT at post-treatment had significant but small effects on pain and disability, and moderate effects on mood and catastrophizing, compared to treatment-as-usual or wait-list control conditions. However, at 6- to 12-month follow-up, significant effects were only found for mood. Also, when compared to active treatments conditions, CBT showed significant but small benefits for disability and catastrophizing at post-treatment but was not superior for pain or mood outcomes. With the exception of disability, there were no benefits at 6- to 12-month follow-up.

As regards CBT for FM, a review and meta-analysis (including 14 studies) indicated the efficacy of CBT in reducing depressed mood and self-efficacy. The effects (*d*) on depression were small at post-treatment, but large on self-efficacy at both post-treatment and at follow-up (Bernardy et al., 2013). However, CBT did not reduce pain, fatigue, sleep disturbances and HRQL at post-treatment and at follow-up. In addition, results indicated that operant behavioral therapy may reduce healthcare-seeking behavior of patients with FM.

Williams, Eccleston, and Morley (2012) state that there is no need for more RCTs of CBT for longstanding pain reporting group means. Instead, they recommend the generation of better theory to test hypothesis about processes and mechanisms related to specific treatment components and outcomes. In regard to this they write that: "[…] different types of studies and analyses are needed to identify which components of CBT work for which type of patient on which outcome/s, and to try to understand why" (the summary of Williams, Eccleston, and Morley, 2012, p. 3). Contextual behavioral science (CBS) may be able to contribute in regard to theory-based evaluations as it offers explicit scientific assumptions as well as a scientific agenda, and potentially a testable coherent theoretical framework of how to achieve behavior change.

2.10 CONTEXTUAL BEHAVIORAL SCIENCE

The scientific and theoretical assumptions underlying this thesis are highly overlapping with those expressed within CBS (Hayes, Barnes-Holmes, and Wilson, 2012). Assumptions in CBS have strong connections to American pragmatism (Bernstein, 2010), and its continued development within behavior analysis (Skinner, 1945). Specifically, it has been argued that functional contextualism (Pepper, 1942) should constitute the philosophy of science underlying CBS (Biglan and Hayes, 1996; Hayes and Long, 2013; Hayes, Hayes, and Reese, 1988). In the view of Hayes, Barnes-Holmes and Wilson (2012), functional contextualism provides the coherent scientific view and explicit assumptions of epistemology and truth needed to ensure that theory, methods and data cohere across time and situation.

From a functional contextual perspective, the basic unit of analysis is the behavior of whole organisms interacting in and with a current and historical context in such a way that act and context cannot completely be separated (Hayes and Long, 2013). Although the basic unit of analysis comprises the act of the whole organism, parts of the whole can be examined in a more highly defined manner (Hayes and Long, 2013). In regard to a given psychological phenomenon, e.g. the rubbing of a sore knee to alleviate pain, the specific contribution of non-pain-transmitting neurons in the spinal cord dorsal horns can be examined. However, from a CBS-perspective, analyses at other levels (e.g. biological) do not *explain* the psychological level, the situated actions of whole organisms, but are viewed as thoroughly connected to them (Hayes, Barnes-Holmes, and Wilson, 2012, p. 3). Importantly, RFT (discussed in the next section) is closely linked to CBS and morphs the functional unit of the act-in-context as functions no longer can be analyzed by

reference to past experiences, which is generally the case in traditional functional operant analyses.

As regards epistemology and truth Skinner (1976, p. 259) wrote that scientific knowledge "[…] is a corpus of rules for effective action, and there is a special sense in which it could be 'true' if it yields the most effective action possible." CBS is founded on similar tenets. Specifically, knowledge and truth are directly linked to the goals of prediction-and-influence, with precision, scope and depth, of entire organisms that interact with a situational and historical context (Hayes, Barnes-Holmes, and Wilson, 2012, p. 3). Analyses aim to simultaneously predict and alter acts in context, with a limited set of principles that apply to specific events (precision), apply to a wide range of events (scope), and cohere across scientific levels of analysis (depth).

In a number of previous articles several focus areas of CBS have been suggested, a few of which are of special relevance for the current thesis (Blackledge, Ciarrochi, and Deane, 2009; Hayes, 2008; Hayes et al., 2013; Vilardaga et al., 2009). These include: The development of a unified model of psychopathology, intervention and health using assessable terms tied to basic principles; the measurement of processes of change; and an emphasis on mediation and moderation analyses in applied studies on ACT. I will return to these areas in the discussion section.

2.10.1 Relational frame theory

In Skinners view, verbal behavior constituted behavior by a speaker that acquired its effect through the reinforcing behavior of a listener (Skinner, 1957). Furthermore, this type of behavior constitutes an antecedent for the behavior of the listener. For example, the statement: "Take these pills two times a day and the pain will be alleviated", is an antecedent (A) for the behavior of taking the pills two times a day (B) in order to achieve pain relief (C). According to Skinner, the antecedent functions as a *rule* in that it specifies both a behavior and a consequence (Skinner, 1976). Skinner underscored the contrast between behavior that is under the control of these rules and contingency-shaped behavior, i.e. behavior that is learned by means of direct experience of consequences. However, as described previously, in order for antecedents and consequences to acquire their functions and be able to influence behavior they need to be historically and situationally contingent on the behavior in question. These cornerstones of respondent and operant learning appear to be violated repeatedly when it comes to more complex human behavior. For example, this seems to be the case when an individual breaks free from

problematic dependency of painkillers based on the admonition: "Stop using these pills, or you will severely damage your liver!" In this scenario the avoided consequence, "severe liver damage" is a temporally remote and a fairly abstract consequence, something never previously encountered. In addition the direct contingencies comprise highly aversive consequences (e.g. withdrawal symptoms and increased pain), which ought to be highly motivating for continued use of painkillers.

Relational Frame Theory (RFT) is a set of behavioral principles that aim to explain complex human behavior of the sort discussed above, i.e. behavior that is not under the control of a history of direct learning and the direct contingencies in the present (Hayes, Barnes-Holmes, and Roche, 2001). The behavior of relational responding, or relational framing, is an ability that humans appear to learn early in life, through social reinforcement. This ability is characterized by three phenomena: (1) *Mutual entailment*; (2) *combinatorial mutual entailment*; and (3) *transformation of stimulus functions*.

Mutual entailment comprises the relations between two stimuli. For example, if you were told that paracetamol (X) is equivalent to acetaminophen (Y), then you will easily derive the mutually entailed relation of acetaminophen (Y) also being equivalent to "paracetamol" (X). Combinatorial mutual entailment illustrates the relations among three or more stimuli. For example, if someone told you that methadone (X) is more potent than codeine (Y) and codeine (Y) is more potent than acetaminophen (Z), then you, in addition to the mutually entailed relations, can derive that methadone (X) is more potent than acetaminophen (Z) and that acetaminophen (Z) is less potent than methadone (X). Notably, when the above behavior (relational responding) is established, humans do not need to be directly trained that e.g. methadone is more potent than acetaminophen, instead in the instance we are given information of how certain stimuli are related, we can *derive* this information based on the relations between stimuli (Figure 2).
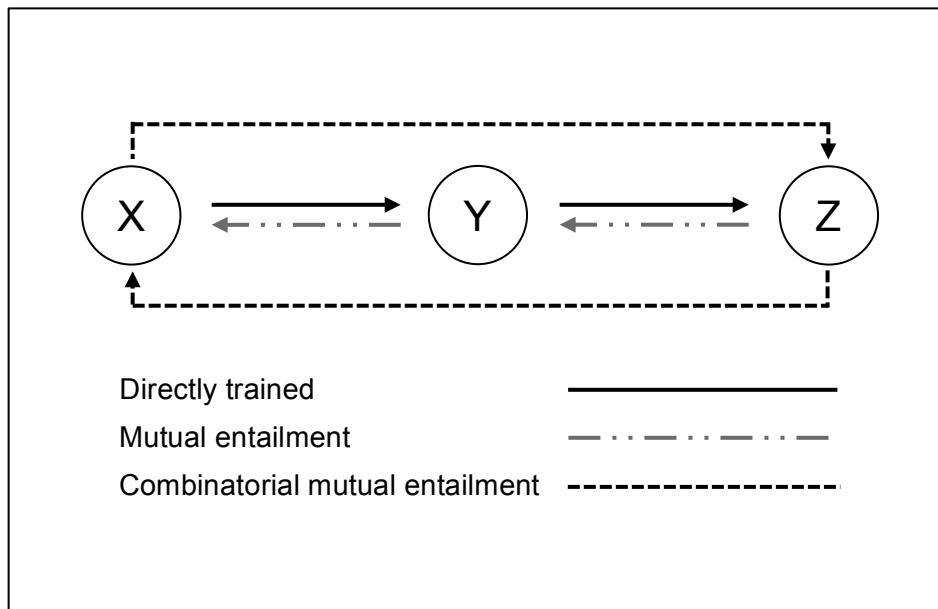
Figure 2. Mutual entailment and combinatorial mutual entailment are illustrated by the figure. Stimuli (represented by X, Y, Z in the figure) can be related in a vast number of ways. For example, they can be related by means of: Coordination (e.g. X is the same as Y and Z); comparison (e.g. X is more than Y, and Y is more than Z); and temporality (X comes before Y and Y comes before Z). In all these cases, only two relations need to be directly learned, the other four are derived

The third defining feature of relational framing is transformation of functions, which aims to capture how a stimulus function, e.g. fear, is "moved" from one stimulus to another and is transformed in accord with the specified relations. For example, imagine that a friend you view as trustworthy said that your toothache (X) could be a symptom of cardiac arrest (Y). This puts toothache (X) in a relation of mutual entailment with cardiac arrest (Y). Given other historical and situational contextual factors establishing cardiac arrest as related to possible death (Z), which you desperately want to avoid, your toothache has instantaneously become related to cardiac arrest and possible death. Thereby, the functions of toothache have been transformed in accord with these relationships, resulting in that you now feel much more distressed (Dougher et al., 2007).

As indicated by the examples so far, the social context determines: (1) Which relations that are established; and (2) which functions that are to be transformed via these relations. Furthermore, stimuli can be related in a number of different ways, in opposition with, in distinction to, hierarchically etc. (Hayes, Barnes-Holmes, and Roche, 2001). Given that there are many different ways of relating stimuli, it also follows that transformation of functions varies in accordance with these specific relations.

Notably, someone is doing the responding. From the above example involving cardiac arrest, it is clear that the increased distress is directly related to that something terrible could happen, to me. According to RFT, the experience of self is established from three different and interdependent relations: *I-you*; *here-there*; and *now-then* (McHugh, Stewart, and Hooper, 2012). The first two relations are spatial and the third is temporal. As with the other relations discussed above, RFT proposes that these three relations are also learned as part of regular language training that takes place via numerous everyday questions (e.g. "Can you see what I see?") and answers (e.g. "I can see!"). Importantly, the answers are always given from the perspective of I-here-now and for a verbally competent person this establishes an ongoing experience of in a specific sense being me (McHugh, Stewart, and Hooper, 2012). When we have become fluent in fitting experiences into the relations: I-you, here-there, and now-then, these perspectives can be included in relational responding as described previously, including transformation of functions (Törneke, 2010).

When learning to respond relationally, the reinforcement is social and generalized, and over time relational responding establishes coherence as a generalized reinforcer (the notion that things are logical) (Healy, Barnes−holmes, and Smeets, 2000). RFT posits that in principle, anything can be related to anything else. For example something never encountered can acquire discriminative functions for a certain behavior, and that which was reinforcing can be instantaneously turned into something emotionally punishing, in a respondent-like manner. Verbal behavior, according to RFT, is relational responding (mutual entailment, combinatorial entailment and transformation of functions), and according to this view, thinking is "[…] verbal behavior performed in such a way that the only possible observer is the person who is performing it — the person doing the thinking" (Törneke, 2010, p. 89).

2.10.2 Rule-governed behavior

Antecedents that have acquired their functions via relational responding as described above, can now specify behaviors and consequences in a highly flexible manner and function as rules or instructions. Rules change behavior via the specific transformations of functions resulting from contact with various elements that are included in the rule. Rules offer an explanation of our ability as humans to act in accord with consequences beyond direct contingencies. This ability enables us to achieve great things in the face of adversity, but can also establish rigid patterns of behavior with problematic long term

consequences (Törneke, Luciano, and Valdivia Salas, 2008). Three types of RGB have been delineated in the literature (Zettle and Hayes, 1982). Two are based on historical contingent reinforcement (*pliance* and *tracking*), and the third type (*augmenting*) interacts with these other two.

2.10.2.1 Pliance and tracking

Pliance is a basic form of RGB that is under the primary control, and corresponds with, the speaker mediated consequences specified in a rule (Zettle and Hayes, 1982). For example, when someone does what another person asks in order to receive the consequences described in the instruction it constitutes pliance. Tracking is RGB controlled by the assumed correspondence between the rule and the way the world works (Zettle and Hayes, 1982). An instance of tracking would be the behavior in line with the instruction: "If you start using your hand normally now, even though it hurts, you will regain functioning", assuming that this is done based on correspondence between the rule and the actual consequence of healing and regained functioning.

2.10.2.2 Augmentals

The third type of rules, augmentals, occur in combination with pliance or tracking and alter (augments) the value of the rules reinforcing or punishing consequences. According to RFT, the reinforcing or punishing values of consequences are established by means of specific verbal value-altering relational networks that become attached to these consequences by means of the social context. If an aspiring classical guitarist hears a physical therapist say: "If you start using your hand now, even though it hurts, you will be able to play the guitar soon again", and then starts using the hand again, this person may be augmenting. This may be the case as the consequence "to play the guitar soon again" has a specific importance and sense of meaning for this person. This also illustrates that augmental rule following is directly linked to human motivation (e.g. values) and can function as verbally established motivating operations (Plumb et al., 2009). Importantly, the types of rules described above are functional units. The topography of the rule is not conclusive for our understanding of it. Rather, it is the reinforcing contingencies that govern behavior that determine what kind of rule-following is at play.

2.11 ACCEPTANCE AND COMMITMENT THERAPY

ACT places a strong emphasis on interventions motivated by RFT, and aims to undermine the dominance that problematic verbal behavior has on other human behavior (Hayes,

Barnes-Holmes, and Wilson, 2012). ACT can also integrate established behavioral interventions like, e.g. exposure (Abramowitz et al., 2013) and behavioral activation (Martell, Addis, and Jacobson, 2001).

As proposed earlier, relational responding underlies (verbal) perspective taking, through which we discriminate I-here-now from other perspectives (e.g. "His", "Her", "The person I used to be"). This ability can be illustrated by the thought: "No one but me struggles with pain at work." Because my private events (events only observable by me), for example fear of being perceived as "lesser" by others, are directly related to my sense of self, they will likely acquire functions that have high impact on behavior. This can take place via rules that are self-generated as: "My colleagues must not find out about my struggle with pain." For a non-verbal organism in distress, avoidance of e.g. a predator is often a viable alternative. In contrast, the escape routes from the monsters produced by our own verbal activity are highly limited.

2.11.1 Experiential avoidance

Verbal monsters, e.g. distressing thoughts, are often not in themselves the real issue (Luciano Soriano, Rodriguez Valverde, and Gutierrez Martinez, 2004). Rather, problems arise when our efforts to get rid of these aversive experiences do not reap the wanted outcomes. This type of behavior constitutes a form of RGB, referred to as *experiential avoidance*, which is operationalized as actions that aim to control or eliminate thoughts, emotions and bodily sensations (Hayes et al., 1996, p. 1154). In addition, if rules that entail a relation of opposition between the private aversive phenomenon and a meaningful life are established, they are likely to function as augmentals (Törneke, 2010, p. 149). In this way, experiential avoidance is established. The relational networks that serve as augmentals, latch onto and intensify the aversive functions of consequences via abstract normative language arranged by the social context. As mentioned previously, a fundamental aspect of augmenting is its interaction with pliance and tracking that in turn may lead to insensitivity to direct contingencies.

For example, assume that a person tracks the rule "If I put the trip off, I will be able to rest a couple of days instead." When asked why it is important to rest a couple of days, the person might respond that traveling and being social is easier to handle without pain. Tracking of this sort may yield benefits in the short term, but it fails to track consequences in the longer term. Augmenting could potentially further complicate issues through a self-generated rule like: "I have to make sure pain doesn't bother me, since I cannot do the

things I want when I'm in pain." As a result, experiencing pain becomes even more aversive, since it is in opposition to "doing the things I like". This further motivates behaviors like "postponing", "resting" etc., which according to the rule should lead to better control over pain.

A problem with experiential avoidance as an overarching strategy is our limited ability to control private phenomena, thoughts, feelings and bodily sensations. Furthermore, it appears that a person may end up more closely in touch with the things aimed at avoiding when rules like those discussed here are followed (Abramowitz, Tolin, and Street, 2001; Wegner and Gold, 1995). Also, there is a substantial risk that these avoidance behaviors become a dominant aspect of life, which may result in the abandonment of other possibly valued behaviors.

Importantly, acting in fusion with these rules appear to play an important part in these problematic strategies. In ACT, the term *fusion* is used to illustrate that certain behaviors are completely dominated by, or fused with, functions established via relational responding (Blackledge, 2015). Putatively, behavior fused with a certain rule further increases the risk of doing things that in the long run have negative and restricting effects in a person's life.

Repeatedly, empirical data has indicated that experiential avoidance may be central to psychopathology (Campbell-Sills et al., 2006; Chapman, Gratz, and Brown, 2006; Chawla and Ostafin, 2007). From this perspective, Törneke (2010, p. 177) underlines two types of behavior that appear highly relevant to focus on clinically: (1) excessive behavior part of a broad functional class constituting experiential avoidance; and (2) alternative behavior that does not constitute experiential avoidance and preferably aims at globally desirable consequences for the person in question.

2.11.2 Behavioral flexibility

In line with the above, the ACT-therapist investigates the relation between the context surrounding a narrow and a rigid behavioral repertoire, and during the course of treatment aims to facilitate an alternative broader more flexible repertoire. In ACT, this part of a functional analysis also serves the purpose of helping the person experience the connection between what is done excessively and rigidly to handle the problem, and what the long term problematic consequences are. Potentially, the person gets in touch with the non-workability of what is done (e.g. "Getting rid of pain") in relation to what it aims at achieving (e.g. "Being able to do the things that matter for me"). Importantly, even

though the behavior in question might not be workable in the long run it is coherent. In other words, it makes sense from the perspective of the one using these strategies and the therapist needs to take this into account when assessing the workability of these behaviors.

As therapy progresses it becomes important to focus on alternative behavior, behavior that potentially could increase the meaning and vitality of living. This can be accomplished when the therapist gives explicit instructions, but it also occurs indirectly when the client generates new rules of living based own conclusions during the course of therapy (Törneke, 2010). In this regard, *values* are of specific importance in ACT. Values can be operationalized as a type of motivating augmental rules that include personally chosen adaptable patterns of action, which provides a strong sense of importance and meaning and reinforces sustainable coordination of behavior over time (Dahl, Lundgren, and Plumb, 2009, p. 9). From this perspective, values cannot be completed but instead serve to give behavior purpose or direction, as in the case of the value of being present in the relations to one's children and partner – with or without pain.

As mentioned, fusion entails the dominance of private events that have their functions established via relational responding. Importantly, these private events also constitute self-evident starting points, which further establish their dominance (Törneke, 2010). *Defusion* involves manipulation of the context by the therapist in order to undermine the process of problematic transformation of functions and weaken their ability to dominate behavior (Dahl, Lundgren, and Plumb, 2009, p. 29).

Acceptance is related to defusion and comprises behavior lacking verbally based avoidance occurring in relation to valued action (Blackledge and Barnes-Holmes, 2009, p. 54) and constitutes a willingness to experience private events in the moment without unnecessary attempts to alter their frequency or form (Levin and Hayes, 2009, p. 15). For example, the therapist via different interventions, attempts to establish I-here-now as the perspective from which the patient can learn to experience what is happening privately on an ongoing basis (the content that is here-now), but also to practice observance of thoughts as events occurring there and then (*self-as-context*) (Foody, Barnes-Holmes, and Barnes-Holmes, 2012). According to Törneke (2010, p. 191), all behavior is influenced by its context, i.e. the antecedents that precede behavior and the consequences that follow on it. The therapist can influence behavior dominated by problematic derived stimulus functions and avoidance by targeting these aspects of the context. In so doing a shift may occur, from behavior controlled by these problematic experiences, especially behavior

based on that these experiences are in opposition to valued action, to more flexible behavior that brings along these experiences in the valued direction of the individual (Törneke, 2010, p. 236).

2.11.3 Empirical support for ACT

In order to broadly present the number and types of studies that have been done on ACT in the area of pain we performed systematic database searches with the aim to include all empirical studies on ACT and pain (Kanstrup, Kemani et al., in manuscript). Preliminary results comprise 153 articles categorized as non-manipulation studies, treatment evaluations, laboratory studies and qualitative studies (not presented here).

2.11.3.1 Non-manipulation studies

In our search (Kanstrup, Kemani et al., in manuscript) 89 of the studies (58.2%) were categorized as non-manipulation studies, of which 83 were cross-sectional and 6 included repeated measures. The median number of participants was 160 (Range = 23-686). The majority of studies ($n = 60$) comprised participants reporting non-specific longstanding pain. Pain duration ranged from 18-219 months, with a majority of studies (67.1%) reporting a mean duration of > 5 years. Out of 100 reported samples 85 comprised participants with a mean or median age of 40-60 years. The distribution of females and males were reported for 104 samples in the studies, 102 of these (98.0%) had 50-100% female participants.

A general overview of the results illustrated the significant relation between acceptance/willingness and related constructs (e.g. avoidance and fusion) on pain-related disability. For example Payne-Murphy and Beacham (2014) conducted a cluster analysis based on self-reported levels of acceptance in persons suffering from longstanding pain, which resulted in three clusters (low, high and medium). Follow-up analyses implied that scores on pain-related disability differed across clusters and in accord with the hypothesized patterns, i.e. the low-acceptance cluster was associated with poorer outcomes and the high-acceptance cluster was related to better functioning. Similarly, in a fairly large sample ($n = 611$) of persons suffering from whiplash associated pain, experiential avoidance and fusion, explained a significant amount of variance in pain-related disability, life satisfaction and depression, also in comparison to pain-related fear of movement (Wicksell et al., 2010).

2.11.3.2 Laboratory studies

Eighteen (Kanstrup, Kemani et al., in manuscript) of the studies (11.8%) were classified as laboratory studies (see Table 3) and the median number of participants in these studies was 67 (Range = 20-219). The majority of studies were conducted with healthy participants e.g. students (16 studies), and 2 included participants with chronic pain diagnoses. In 15 studies the participants' mean or median age ranged from 19-29 years. Number of males and females were reported for 20 samples, where 16 consisted of 50-80% females. The cold pressor test was the most commonly used pain inducing strategy (10 studies), followed by mild electric shock (5 studies) and other methods (3 studies). An acceptance-based experimental manipulation was used in 15 studies, and thirteen of the studies used pain tolerance as the primary outcome measure. Three of these 15 studies investigated how instructions for higher or lower degree of acceptance were related to outcome. In addition, another two evaluated the incremental effect of an added values component to the acceptance manipulation; and in 2 an ACT-protocol was used. Control conditions consisted of, control-based strategies (10 studies), distraction (6 studies); and suppression (2 studies).

A meta-analytic review of experimental studies on acceptance strategies identified 30 studies (Kohl, Rief, and Glombiewski, 2012). Results illustrated small to medium between-group effects in favor of acceptance strategies in regard to pain tolerance, but acceptance was not superior to other emotion regulation strategies in relation to pain intensity and negative affect. In conclusion, the authors (Kohl, Rief, and Glombiewski, 2012, p. 998) write that acceptance strategies do not appear to be more effective than other emotion regulation strategies in reducing pain or negative affect, but appear significantly better on performance based tasks and pain tolerance.

Levin et al. (2012) conducted a meta-analysis of 66 laboratory-based component studies evaluating treatment elements and processes related to psychological flexibility and ACT (e.g. acceptance, defusion and values) These studies did not specifically pertain to pain, but included several of the laboratory studies found in our systematic search (Kanstrup, Kemani et al. in manuscript). Broadly, results provide support for the utility and theoretical coherence of constructs related to psychological flexibility. Significant positive effect sizes were observed for e.g. acceptance, defusion and values compared to inactive conditions. Greater effect sizes were found on theoretically specified targeted outcomes (e.g. pain tolerance). As in the meta-analysis by Kohl, Rief, and Glombiewski

(2012), effects were smaller on variables pertaining to the intensity and frequency of negative thoughts and feelings.

2.11.3.3 Treatment studies

Of the 41 treatment studies (Table 1) found in our systematic search (Kanstrup, Kemani et al., in manuscript), the majority of studies ($n = 25$) consisted of participants with non-specific chronic pain. Thirty-one of the studies included > 60% females and the majority of studies ($n = 29$) included participants with an age between 40 to 60 years. Pain duration (Range = 17.5-420 months) was reported in 30 studies. Eleven of these studies reported a mean or median pain duration between 5 to 10 years and 7 studies reported a mean or median pain duration of $\geq$ 10 years. The median sample size was 44 (Range = 1-252). Most studies ($n = 28$) were conducted in an outpatient setting, followed by residential or hospital settings (9 studies) and self-help and Internet interventions (3 studies). Twenty-three studies used the following control conditions: wait-list (7 studies); treatment as usual (7 studies); and active interventions (9 studies), including 5 studies comparing ACT to an established treatment, e.g. CBT. Three of the studies were case reports; 1 was an effectiveness trial; 21 were non-randomized trials with no control condition; 15 were RCTs; and 1 study was a randomized trial. Follow-up assessments were administered in most studies ($n = 33$). Of these, 14 reported a single 3-month follow-up, 7 reported a single 6-month follow-up, and 10 studies reported 2-3 follow-up assessments between 0.5-12 months. Two studies performed single long term follow-ups after 1 and 3 years. Seven of the studies included a mediation analyses to evaluate processes of change (see Table 1). Notably, only one of the studies included an analysis of the treatment's cost-effectiveness (Ljotsson et al., 2014).

Table 1. Treatment studies (*n* = 41)

Nr.	Study	n[a]	Pain type[b]	Design[c]	Control cond.[d]
1	(Dahl et al., 2004)	19	CS; NSCP	RCT	MTAU
2	(McCracken et al., 2005)	108	NSCP	NRTNC	−
3	(Wicksell et al., 2005)	1	NSCP	CR	−
4	(McCracken et al., 2007)	53; 234	NSCP	E-T	−
5	(Vowles et al., 2007)	252	NSCP	NRTNC	−
6	(Wicksell et al., 2007)	14	NSCP	NRTNC	−
7	(Vowles et al., 2008)	171	NSCP	NRTNC	−
8	(Wicksell et al., 2008)	21	WAD	RCT	TAU
9	(Lunde et al., 2009)	1	HA	CR	−
10	(Vowles et al., 2009)	11; 11	NSCP	NRTNC; NRTWC	CBT
11	(Wicksell et al., 2009)	32	NSCP	RCT	MDT
12	(Johnston et al., 2010)	24	NSCP	RCT	WL
13	(Vowles et al., 2010)	114	NSCP	NRTNC	−
14	(Wicksell et al., 2010)	21	WAD	RCT*	WL; TAU
15	(Carbonell-Baeza et al., 2011)	75	FM	NRTWC	TAU
16	(Ilgen et al., 2011)	13	NSCP; SUD	NRTNC	−
17	(Masuda et al., 2011)	1	SCD	CR	−
18	(McCracken et al., 2011)	168	NSCP	NRTNC	−
19	(Thorsell et al., 2011)	90	NSCP	RCT	AR
20	(Vowles et al., 2011)	108	NSCP	NRTWC	−

Table 1. Treatment studies (*n* = 41). Continued from the previous page.

Nr.	Study	n[a]	Pain type[b]	Design[c]	Control cond.[d]
21	(Wetherell et al., 2011)	114	NSCP	RCT*	CBT
22	(Wicksell et al., 2011)	32	NSCP	RCT*	MDT
23	(Dindo et al., 2012)	45	Migr.; Depr.	NRTWC	WL/TAU
24	(Huggins et al., 2012)	45	HIV	NRTWC*	−
25	(Jensen et al., 2012)	43	FM	RCT	WL
26	(McCracken et al., 2012)	40	NSCP	NRTNC	−
27	(Mo'tamedi et al., 2012)	30	HA	RCT	MTAU
28	(Wicksell et al., 2012)	40	FM	RCT*	WL
29	(Alonso et al., 2013)	10	NSCP	NRTWC	WL
30	(Baranoff et al., 2013)	186	NSCP	NRTNC	_
31	(Buhrman et al., 2013)	76	NSCP	RCT	DF
32	(Elander et al., 2013)	101	HrJP	NRTNC	_
33	(Gauntlett-Gilbert et al., 2013)	98	NSCP	NRTNC	_
34	(McCracken et al., 2013)	73	NSCP; FM; Depr	RCT	TAU
35	(Steiner et al., 2013)	28	FM	RT	Ed
36	(Vriezekolk et al., 2013)	25	RD	NRTNC	−
37	(Baranoff et al., 2014)	120	NSCP	NRTNC	−
38	(Ljotsson et al., 2014)	41	FM	NRTNC	−
39	(Luciano et al., 2014)	156	FM	RCT*	RPT; WL
40	(Vowles et al., 2014)	117	NSCP	NRTNC*	−
41	(Trompetter et al., 2014)	238	NSCP	RCT	EW; WL

[Note] The full references to the studies listed in the table are found in the Appendix. * indicates that the study includes a mediation analysis.

[a] Semicolon separated numbers indicate two (separate) samples.

[b] CS = Chronic stress; Depr. = Depression; FBS = Failed back surgery; FM = Fibromyalgia; HA = Headache; HIV = Human immunodeficiency virus; HrJP = Hemophilia related Joint Pain; Migr. = Migraine; NSCP = Non-specific pain; RD= Rheumatic Disease; SUD= Substance Use Disorder; WAD = Whiplash Associated Disorder.

[c] CR = Case Report; E-T = effectiveness-trial; NRTNC = Non-randomized Trial with No Control; NRTWC = Non-randomized Trial With Control, R = Randomized Trial; RCT = Randomized Controlled Trial.

[d] AR = Applied Relaxation; CBT = Cognitive Behavior Therapy; EW = Expressive Writing; Ed = Education; MDT= Multidisciplinary Treatment; MODF= Moderated Online Discussion Forum; MTAU = Maintenance Treatment as Usual; RPT= Recommended Pharmacological Treatment; TAU = Treatment as usual; Trad. = Traditional Therapy; WL = Waitlist.

Veehof et al. (2011) conducted a systematic review and meta-analysis of 22 acceptance-based interventions (i.e. not specifically ACT) for chronic pain with controlled (waitlist or TAU) and non-controlled designs. Primary outcome measures were pain intensity and depression. Secondary outcomes were anxiety, physical wellbeing and quality of life. The authors (Veehof et al., 2011) reported that that acceptance-based therapies had significant small effects on pain intensity and depression and small to medium effects on physical and mental health.

A recent systematic review of RCTs on ACT for longstanding pain reported results from ten studies (Hann and McCracken, 2014). Seven of the ten trials had inactive control conditions, and one included both inactive and active control conditions (Luciano et al., 2014). Between-group effects on outcomes related to physical functioning showed significant small to large effects in favor of ACT in five of the studies (Buhrman et al., 2013b; Luciano et al., 2014; McCracken, Sato, and Taylor, 2013; Wicksell et al., 2013; Wicksell et al., 2008). Likewise, results from two studies indicated significant medium to large effects on pain global disease impact in FM (Luciano et al., 2014; Wicksell et al., 2013). In three studies, significant medium to large effects were also found on general emotional distress, anxiety and depression (Buhrman et al., 2013a; McCracken, Sato, and Taylor, 2013; Wicksell et al., 2013; Wicksell et al., 2008). Only one study demonstrated a significant large effect on life satisfaction favoring ACT (Wicksell et al., 2008). Also, four studies produced significant small to large effects on measures related to psychological flexibility in favor of ACT (Buhrman et al., 2013a; McCracken, Sato, and Taylor, 2013; Wicksell et al., 2008).

Active control treatments were used in four studies including CBT, AR, education, and recommended medication. Results on most outcome measures indicated that ACT was not superior compared to active treatment conditions, but results showed significant small to large effects on aspects of psychological flexibility (e.g. pain acceptance) in favor of ACT (Steiner, Bogusch, and Bigatti, 2013; Thorsell et al., 2011).

2.12 SUMMARY

Several descriptive pain classifications may share underlying biological mechanisms (Plesh, Wolfe, and Lane, 1996; Yunus, 2007). Pain also appears to be biologically meshed with a number of other debilitating symptoms, e.g. fatigability (Van Houdenhove and Luyten, 2009). In addition, pain and related distress have strong ties to motivation (Craig, 2003; Michael, 2000; Van Houdenhove and Luyten, 2009).

Longstanding pain has a negative impact on functioning in a number of life domains for large numbers of persons (Breivik et al., 2006). Importantly, there remains a need to develop, refine and evaluate treatments aiming to help persons suffering from pain to live meaningful vital lives, also in the presence of persisting pain (Turk, 2003).

From the perspective of RFT and RGB, language and cognition (verbal behavior) amplifies the aversive stimulus functions of pain and related distress, and thereby further drives motivation characterized by experiential avoidance, fusion and inflexible behavioral repertoires (Törneke, Luciano, and Valdivia Salas, 2008).

CBS and ACT primarily conceptualize pain based on its contextual and functional relation to behavior, as illustrated by experiential avoidance. Key features of ACT include strategies that aim to undermine experiential avoidance, for example by means of strategies facilitating disengagement from and openness towards pain and related distress. These strategies aim at creating flexible behavioral repertoires guided by personal values and related goals (Törneke, 2010).

Previous research illustrates that CBT is an efficacious treatment, but that effect-sizes are moderate. Similarly, accumulating research indicates the efficacy of ACT, but also for ACT effect-sizes are small to moderate. In both ACT and CBT there is a continued need for: Adequate measures to assess the interference of pain in central life domains; evaluations of cost-effectiveness; and of theoretically based investigations of processes of change (Kazdin, 2007; SBU, 2006, 2010; Williams, Eccleston, and Morley, 2012). This brings us to the general and specific aims of this thesis.

3 GENERAL AND SPECIFIC AIMS

The general aims of the thesis were to evaluate the efficacy and processes of change in ACT for longstanding pain. Specifically, we wanted to: (1) Evaluate the efficacy of ACT delivered in a group setting for FM and non-specific longstanding pain; (2) perform a validation of a pain interference questionnaire; (3) evaluate the mediating functions of psychological inflexibility in ACT in relation to pain disability and pain interference; (4) analyze the cost-effectiveness of ACT. These aims are presented in relation to the individual studies below.

- In Study I we aimed to evaluate the efficacy of ACT for FM, and to investigate the role of psychological inflexibility as a mediator of improvement in pain disability and other outcomes.

- In Study II we aimed evaluate the efficacy and cost-effectiveness of ACT in comparison with applied relaxation (AR) for adults with longstanding non-specific pain.

- In Study III we aimed to evaluate the psychometric properties of a brief questionnaire, the pain interference index (PII), developed to assess the interference of pain on behavior in central life domains.

- In Study IV we aimed to investigate the putatively mediating roles of psychological inflexibility, catastrophizing and pain intensity in relation to pain interference in ACT and AR, as well as the temporal precedence of the mediator in relation to the outcome.

4   METHOD

All studies were conducted at the Karolinska University Hospital in Solna. Study I was done in collaboration with another research group at Karolinska Institutet.

4.1   STUDY I

4.1.1   Design, participants and procedure

Study I was an open RCT in which participants were randomized to ACT or to a waitlist control condition. The study was based on a superiority hypothesis, i.e. that ACT would perform better than the waitlist control condition. Randomization was done based on random number sequences generated by computer software. Administrators not involved in delivering treatment provided sealed envelopes containing study condition to the participants.

Treatments followed a written protocol and consisted of 12 weekly group sessions (5-6 participants in each group). Two psychologists conducted treatment in Study I. In ACT, the psychologists conducted ten sessions, and a pain physician with formal therapist training in CBT and ACT conducted two sessions (sessions two and eight) as an integrated part of treatment. The psychologists were licensed clinical psychologists with formal training in CBT, ACT and AR. Furthermore, they had clinical experience of behavioral treatments for patients suffering from longstanding pain. Treatment sessions were recorded on video and analyzed to formally assess treatment integrity, protocol adherence and therapist competence.

4.1.1.1   Participants and Procedure

Referrals came from primary care physicians. Eligibility was first assessed in brief telephone interviews. A pain physician and clinical psychologists then further assessed eligible participants based on inclusion/exclusion criteria. As functional magnetic resonance imaging (fMRI) was performed as part of the research project, women between 18 and 55 years of age, fulfilling the American College of Rheumatology classification criteria for FM (Wolfe et al., 1990) were considered eligible for study inclusion. Also, inclusion required a weekly average pain intensity of > 40 (visual analogue scale 0–100). Left-handed, pregnant and breastfeeding persons, and persons with metal implants or claustrophobia, were excluded. Discontinuation of ongoing treatments that risked influencing the patients' pain perceptions (e.g. mood stabilizers and strong opioids) was

required, as they were considered incompatible with treatment. However, if discontinued 48 hours prior to study assessments, small doses of non-steroidal anti-inflammatory drugs were allowed as rescue medication. Based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000), a semi-structured interview was constructed for the present study. Severe psychiatric co-morbidity resulted in exclusion from the study. Also, ongoing or planned (within 6 months) treatments based on CBT, or treatments for suicide ideation and intent, psychotic and severe depressive symptoms, were incompatible with participation in the current study.

4.1.2 Self-report measures and assessments

Primary and secondary outcomes, and the process measure, were assessed pre- and post-treatment as well as at 3-month follow-up.

4.1.2.1 *Primary outcome measure*

The disabling effects of chronic pain on daily activities were assessed using the Pain Disability Index (PDI) (Tait et al., 1987). The PDI consists of seven items regarding various activities that are rated on a 0-10 scale ranging from "no trouble" to "total disability". Several studies support the reliability and validity of the PDI (Tait, Chibnall, and Krause, 1990; Tait et al., 1987).

4.1.2.2 *Secondary outcomes measures*

Average pain intensity the past week was assessed using a single item ("What has your average pain level been the past week?"). The item was rated on a numeric rating scale from 0 ("No pain at all") to 6 ("Extremely painful") (Dworkin et al., 2005).

We assessed *HRQL* using the Short Form-36 Health Survey (SF-36) (Ware and Sherbourne, 1992). The SF-36 (36-items) provides summary scores for two overarching subscales: the physical component scale (SF-36-P) and the mental component scale (SF-36-M). Higher scores indicate better functioning. Previous research indicated that the questionnaire had adequate reliability and validity (McHorney, Ware, and Raczek, 1993; Sullivan, Karlsson, and Ware, 1995).

Depression was measured using the Beck Depression Inventory (BDI), which consists of 21 items that are rated on a 4-point scale (Beck et al., 1961). The BDI has been used frequently in studies with FM and is recommended as an instrument for detecting distress in patients with chronic musculoskeletal pain (Glombiewski et al., 2010).

Anxiety was assessed with the Spielberger Trait-State Anxiety Inventory (STAI) (Spielberger et al., 1983). The questionnaire consists of two scales comprising 20 items each that concern anxiety. Items are rated on a 4-point scale from 'not at all' to 'very much so'. Instructions vary regarding the temporal aspect of the two scales in order to measure state and trait aspects of anxiety. The questionnaire has been recommended to use in the assessment of anxiety in FM (Gowans et al., 2002).

Self-efficacy, the perceived ability to perform various activities with pain, such as visiting friends, was assessed with the Self-Efficacy Scale (SES) (Denison, Asenlof, and Lindberg, 2004). The instrument comprises 20 items that are rated on an 11-point scale, from 'not at all confident' (0) to 'very confident' (10). The reliability of a Swedish version was illustrated in a study with persons suffering from subacute, chronic or recurrent musculoskeletal pain (Denison, Asenlof, and Lindberg, 2004).

We assessed *FM impact* on different aspects of health and functioning using the Fibromyalgia Impact Questionnaire (FIQ). This questionnaire was developed to assess current health status and includes 10 items measuring aspects of physical function, psychological distress, pain, sleep, stiffness and well being (Burckhardt, Clark, and Bennett, 1991). The instrument has been extensively used in studies on FM and previous research has indicated the measure's reliability, validity and sensitivity to change in (medical) treatments targeting symptom reduction (Bennett, 2005).

4.1.2.3   Process measure

The Psychological Inflexibility in Pain Scale (PIPS) consists of 12 items rated on a 7-point scale ranging from "never true" (1) to "always true" (7). Higher scores indicate greater psychological inflexibility (range 12–84). The scale consists of two subscales measuring *experiential avoidance* (8 items) and *cognitive fusion* (4 items). In this study the total scale was used. The statistical properties of the questionnaire have been found adequate in two previous studies Results from previous studies indicate the adequacy of the questionnaires psychometric properties, test–retest stability, sensitivity to change and demonstrates its ability to detect indirect effects in ACT (Wicksell et al., 2009; Wicksell et al., 2008; Wicksell, Olsson, and Hayes, 2010, 2011).

4.1.3 Analytical approach

4.1.3.1 Treatment outcome

In Study I outcome data were evaluated using linear mixed models. Time-specific residuals were estimated in the model and random coefficients (i.e., random intercept and linear slope) and their covariance were retained when they significantly contributed to the model. Models were fitted with full information maximum likelihood estimation.

4.1.3.2 Mediation analysis

In Study I mediation analyses were conducted with study condition as different levels of the independent variable, pre–post change scores in the process variable as mediator, and pre- to follow-up changes in the outcome variables as dependent variables. A product of coefficients approach with bootstrap resampling ($n = 5000$) was used to evaluate the product of two relations: the treatment's impact on the process variable (the *a*-path), and the process variable's effect on the outcome variables, with control for the effects of treatment modality (the *b*-path) (MacKinnon, Fairchild, and Fritz, 2007). The mean value for the *ab*-product across the bootstrapped samples provides a point estimate of the mediating effect, and bias-corrected confidence intervals are derived from the obtained distribution of *ab*-scores (Preacher and Hayes, 2004, 2008). If lower and upper bounds do not contain zero, the mediating effect is significant at the level specified in the analysis.

4.2 STUDY II

4.2.1 Design, participants and procedure

Study II was an open RCT in which participants were randomized to ACT or to AR. The study was based on a superiority hypothesis, i.e. that ACT would perform better than AR. On the basis of a simulation study of the statistical power of latent growth modeling, Study II had sufficient power (0.80) to detect a large effect with a conventional alpha level (0.05) given sample size and the 5 assessment occasions (Fan, 2003). Administrators not involved in treatment randomized participants in blocks of 12 to ACT or AR using an online random numbers service (www.random.org), and provided participants with sealed envelopes containing study condition.

Treatments followed written protocols and consisted of 12 weekly group sessions (5-6 participants in each group). Three psychologists delivered ACT (one of the

therapists delivered treatment in both ACT and AR). In ACT, the psychologists conducted ten sessions and a pain physician with formal therapist training in CBT and ACT conducted two sessions (sessions two and eight) as an integrated part of treatment. In AR three psychologists conducted all 12 sessions. All psychologists were licensed clinical psychologists and had formal training in CBT, ACT and AR, and clinical experience of behavioral treatments for patients suffering from longstanding pain. Treatment sessions were recorded on video and analyzed to formally assess treatment integrity, protocol adherence and therapist competence.

4.2.1.1   Participants and procedure

Participants were referred from primary and tertiary care units in Stockholm County, Sweden, to the Behavioral Medicine Pain Treatment Services (BMPTS) at the Karolinska University Hospital. Psychologists and pain physicians assessed participants for inclusion during a 20-month period. Patients were eligible for inclusion if: they were between 18-65 years of age; they had longstanding pain ($\geq$ 6 months); no further medical assessments were required; pain medication had been stable the past 2 months and no changes in pain medication were planned.

Patients were excluded if they participated in a concurrent CBT-based treatment. However, if no treatment changes were planned, participation in an ongoing (for $\geq$ 2 months) non-medical, non-CBT-based treatment was allowed. Psychiatric co-morbidity that may have significantly interfered with treatment and needed to be addressed primarily and separately (e.g. high risk of suicide, psychotic symptoms and severe depressive episode) resulted in exclusion. The Mini International Neuropsychiatric Interview (MINI) was used to screen for psychiatric comorbidity (Sheehan et al., 1997). Also, participants were excluded if they were unable to respond to the questionnaires in Swedish.

4.2.2 Self-report measures and assessments

Primary and secondary outcomes, and the process measure, were assessed pre- and post-treatment as well as at 3- and 6-month follow-up.

4.2.2.1   Primary outcome measure

As in Study I the PDI was used to assess pain disability (see Study I above for more information).

4.2.2.2   Secondary outcome measures

Average pain intensity the past week was assessed using the same one-item question as in Study I (see Study I above for more information). We used the Short Form-12 (12-items) to assess HRQL. SF-12 provides summary scores for two overarching subscales: the physical component scale (SF-12-P) and the mental component scale (SF-12-M). Higher scores indicate better functioning. The reliability and validity of the questionnaire have been found adequate (Luo et al., 2003).

In this study a*nxiety* and *depression* were assessed using the Hospital Anxiety and Depression Scale (HADS) that consists of 14 items in total. HADS has two subscales, Anxiety (HADS-a) and Depression (HADS-d) and items are rated on a 4-point scale. Studies indicate that HADS has adequate reliability and validity in assessing anxiety and depression in medical settings (Lisspers, Nygren, and Soderman, 1997; Zigmond and Snaith, 1983).

4.2.2.3   Process measure

The Chronic Pain Acceptance Questionnaire (CPAQ) was used to measure *acceptance of pain*. The Swedish version used here consisted of 19 items rated on a numeric rating scale from 0-6, with higher scores indicating higher degree of acceptance. A number of studies have supported the reliability and validity of the questionnaire (McCracken and Eccleston, 2003, 2006; Vowles et al., 2008; Wicksell, Olsson, and Melin, 2009).

4.2.3 Analytical approach

4.2.3.1   Treatment outcome

In Study II continuous outcomes were analyzed using latent growth curve modeling (Bollen and Curran, 2006; Muthén, 1997) A piecewise function was specified to model non-linear change across all assessments and to evaluate time and treatment effects during distinct time periods of the trial within the same analysis (Raudenbush and Bryk, 2002). A two-piece growth model was estimated for each measure. Specific time coefficients were provided for the active treatment phase (Piece 1; pre-, mid-, and post-treatment), and for the follow-up phase (Piece 2; 3-, and 6-month follow-up). Loadings for linear change over time were specified for each piece with an intercept centered at the first assessment (pre-treatment). To evaluate the potentially different impact of treatments over the distinct time periods of the trial, the linear slope of Piece 1 and Piece 2, were regressed on a fixed predictor representing treatment (ACT = 0.5, AR = -0.5). Time-specific residuals were

estimated in the model and random coefficients (i.e., random intercept and linear slope) and their covariance were retained whenever they significantly contributed to the model. Following the principle of intention-to-treat, analyses used all available data from randomized participants. The models were fitted with full information maximum likelihood estimation. Between-group effect sizes (*d*) for growth models were calculated based on recommendations by Feingold Feingold (2009b) and within-group effect sizes were calculated based on recommendations by Morris and DeShon (2002).

4.2.3.2 Clinical significant change

Clinically significant change was estimated based on the Jacobson-Truax criteria (Jacobson and Truax, 1991). Estimation was done by establishing a cut-off for clinical significance and a reliable change index. Based on previous research we adopted a cut-off for clinically significant change of an SD = 1 below the participants' mean pretreatment PDI score and utilized a 90% confidence interval (Jacobson et al., 1999; Vowles et al., 2014).

4.2.3.3 Cost-effectiveness

Assessments and analyses of health economic factors included all costs (i.e. had a societal perspective). All costs were extrapolated to a 3- month period, primarily because this time period better accounted for the costs of ACT and AR during the active treatment phase.

Intervention costs were calculated by multiplying the time spent by the therapists in treatment with the Swedish national tariff for visits to a licensed clinical psychologists/ pain physician (ACT: psychologist and physician; AR: psychologist). Costs related to healthcare visits (direct medical costs) were calculated by multiplying the reported number of visits with the cost for that particular visit (e.g., visit to a general practitioner) as specified in Swedish national tariffs. Costs for medicines were obtained by multiplying the amount of medicine used with the market price in Sweden.

Direct non-medical costs were calculated using a mean value of the service (e.g., the mean cost of a homeopathic consultation). Productivity losses were based on the human capital approach, which means that monetary losses associated with work loss and work cutback were based on the average gross earnings in Sweden for the duration of the reported sick leave. All costs were converted to US$ for the reference year 2013.

The incremental cost-effectiveness ratio (ICER) was estimated by subtracting the changes in total costs (ie, the change of the sum of all the costs in the aforementioned

cost-domains) in AR from the changes in total costs in ACT and dividing this difference with the difference resulting from the subtraction of the total effects on pain disability in AR from the total effects on pain disability in ACT. This procedure was bootstrapped 5000 times, which generated probabilistic values of the treatment groups' incremental costs in relation to their incremental treatment benefit. These values (ICERs) were plotted in cost-effectiveness planes to evaluate and illustrate the potential cost-effectiveness of ACT compared with AR.

In the cost-effectiveness analyses missing data were imputed using the multiple imputation procedure. The Mann-Whitney U test for independent samples was used to analyze potential cost-differences between conditions at the different assessment points. Also, costs-differences within conditions over time were evaluated using the sign test for related samples. Lastly, we evaluated the association between cost reductions, pain disability, and pain intensity by using non-imputed bootstrapped regression (5000 replications) models. More specifically, we included treatment condition as a control variable and regressed the changes in costs (pre-assessment to post-assessment) on the change scores (pre-assessment to post-assessment) in pain disability and pain intensity.

4.3 STUDY III

4.3.1 Design, participants and procedure

Study III utilized a cross-sectional design comprising a sample of adults with non-specific pain, including participants from Study II. The sample size ($n = 205$) was determined to be large enough for the analyses based on recommendations by e.g. Guadagnoli and Velicer (1988).

4.3.1.1 Participants and procedure

Participants were referred from primary or tertiary care units in Stockholm County, Sweden, to the BMPTS at the Karolinska University Hospital. Adult patients between 18 and 85 years with longstanding (> 3 months) pain were considered eligible for inclusion in the study. Patients were excluded if they were unable to respond to the questionnaires in Swedish. Patients were included in the study during a period of 4 years. Pain diagnoses were coded based on ICD-10 classifications (World Health Organization., 2004).

4.3.2 Self-report measures and assessment

Assessments were performed at the first visit at the clinic.

4.3.2.1 Independent variable

The Pain Interference Index (PII) was developed as a brief instrument to assess to what degree pain interferes with day-to-day behavior in several central life domains. The items in PII were based on the interference scale in the BPI (Cleeland and Ryan, 1994) and the MPI (Kerns, Turk, and Rudy, 1985). The PII consists of six items regarding various activities that are rated on a 0-6 scale from "no trouble" to "total disability", with a maximum total score of 36 points. The patient is asked to what degree pain has: 1) made it difficult to study/work; 2) made it difficult to do leisure activities; 3) made it difficult to spend time with friends; 4) affected mood; 5) affected the ability to do physical activities; and 6) affected sleep. Two previous studies indicate the measures reliability and validity in youths and young adults with longstanding pain (Holmström et al., Accepted manuscript; Martin et al., 2015).

4.3.2.2 Dependent variables

As dependent variables in this study we used ratings of average pain intensity the past week, the PDI, SF-12-M and SF-12-P and HADS-d. See Study II above for more information on the respective measures.

4.3.3 Analytical approach

4.3.3.1 Psychometric analyses

First, the frequency distributions were examined to identify items with extremely skewed response distribution or low variability. Then we controlled that item inter-correlations between variables did neither correlate with too few other variables, nor correlate too highly. To ascertain that no items showed low correlations with the overall score of the questionnaire (i.e. lower than .25) item-total statistics were analyzed. Also, the adequacy of the sample size and the factorability of the correlation matrix were assessed. Next, a principal component analysis (PCA) was performed to examine the factor structure among the items, i.e. if the items included in the instrument represent one or more factors. Also, Cronbach's alpha was used to evaluate internal consistency, with $\alpha \geq .80$ considered adequate (Cortina, 1993).

To characterize relations between sex and age (background variables), average pain intensity past week (control variable), pain interference and criteria variables (PDI and SF-12-P and SF-12-M), bivariate correlations (Pearson's r) were calculated. The questionnaire's concurrent criteria validity was further examined using ordinary least

squares regression models. Specifically, we examined if the PII explained a significant amount of variance in the criteria variables PDI, SF-12-P, SF-12-M and HADS-d. Sex and age (background variables) were included as the first and second steps in the models. Pain interference was entered as the last step, with and without the prior inclusion of pain intensity (control variable). All included predictors were retained in the final model.

4.4 STUDY IV

4.4.1 Design, participants and procedure

See Study II above.

4.4.2 Self-report measures and assessments

Data comprised weekly assessments from Study II of the primary outcome and the process variables.

4.4.2.1 Primary outcome measure

The PII was used as the primary outcome measure in this study (see Study III above for more information).

4.4.2.2 Process measures

Average pain intensity the past week was assessed using the same one-item question as in Study II (see Study II above). The catastrophizing subscale from the Coping Strategies Questionnaire (CSQ) (Rosenstiel and Keefe, 1983) was used to assess pain-related catastrophizing. The subscale consists of six items reflecting thoughts and feelings that might arise when people experience pain. The extents to which these thoughts have been present are rated on a seven-point scale from 0 ("never") to 6 ("always"). The Swedish version of the scale has been found to have satisfactory internal consistency and test-retest reliability (Jensen and Linton, 1993). The Psychological inflexibility in Pain Scale (PIPS) was used to assess psychological inflexibility (see Study II above).

4.4.3 Analytical approach

4.4.3.1 Mediation analyses

In Study IV Longitudinal mediation based on session-to-session changes was modeled using a linear mixed-effects regression model for repeated measures. Full information maximum likelihood was used to estimate model parameters (and standard errors), and to

facilitate model parameter estimation based on all participants who provided at least one valid observed data point on the dependent variable. The proposed mediators (psychological inflexibility, catastrophizing, and average pain intensity the past week) served as lagged time-varying predictors of subsequent changes in the outcome. In other words, the hypothesized mediators constituted predictors (week 1 through week 11) of subsequent changes in the outcome (week 2 through week 12). Thereby, changes in the putative mediators temporally preceded the outcome in these analyses. In this mediation model (lower level mediation) the variables time, mediator and outcome were measured at Level 1 and variation across individuals was allowed as a function of a Level 2 predictor (constituting a moderator variable), in this case treatment condition (Kenny, Korchmaros, and Bolger, 2003). Thus, we tested moderated mediation, i.e. the moderating effect of treatment condition (ACT or AR) on the mediators' effect on pain interference. Independent groups effect sizes (d) for growth models were calculated when applicable, using formulas provided by Feingold (2009) and Morris and DeShon (2002).

4.5   INTEGRITY, ADHERENCE AND COMPETENCE

4.5.1   Study I and Study II

In ACT, treatment integrity, protocol adherence, and therapist competency were evaluated using a scoring protocol specifically developed for clinical studies on ACT (Plumb and Vilardaga, 2010), with minor adjustments for use with pain patients. For AR, an adapted version of the protocol was constructed. Fourteen (Study I) and sixteen percent (Study II) of the sessions with ACT-specific and AR-specific content were randomly selected. Two CBT-trained psychologists with formal training in ACT and AR, not otherwise involved in the study performed the ratings following training in how to use the manual. Ratings of ACT included both ACT-consistent items (e.g. "Defusion") and ACT-inconsistent items (e.g. "Experiential avoidant change strategies"). Similarly, ratings of AR included AR-consistent items (e.g. "Applied in-session practice") and AR-inconsistent items (e.g. "Willingess"). To establish the degree of similarity between coders' ratings of treatment consistent items, treatment inconsistent items, overall adherence to treatment manual, and overall competency inter-rater reliability was calculated.

4.6 TREATMENT DESCRIPTION

4.6.1 Study I

4.6.1.1 ACT-protocol

The ACT-intervention was organized into four phases. During phase 1 (sessions 1 and 2) the dysfunctional character of longstanding pain and pain-related behaviors were discussed. This was done with the aim to alter the context in which pain symptoms and avoidance behaviors occurred and to initiate a shift in perspective from symptom reduction to valued living. In phase 2 (sessions 3 and 4) the workability of previous strategies to reduce pain and improve functioning were specifically addressed and the utility of a more flexible behavioral repertoire in relation to pain and distress was emphasized. Also, personal values were formulated and clarified. Phase 3 (sessions 5 and 6) focused on disengagement from verbal processes, to decrease the negative impact of certain thoughts and experiences on behavior (defusion), and to notice and willingly experience unpleasant private experiences that could not be directly changed, when doing so served valued ends. In phase 4 (sessions 7 to 12) participants defined short and long term behavioral goals based on personal values. Also, they practiced the application of ACT consistent strategies to manage pain and distress in daily life as part of a gradual increase of previously avoided valued activities. In the final session, central aspects of treatment as well as relapse prevention strategies were discussed.

Throughout treatment, defusion and acceptance strategies were practiced by the participants in the form of in-session exercises as well as in homework assignments carried out between sessions. Illustrations and metaphors were commonly used to clarify central concepts, such as defusion and acceptance. Exposure to personally important situations and activities previously avoided due to pain were central to treatment and aimed at increasing the ability to act in accordance with personally held values, also in the presence of interfering pain and distress (i.e. psychological flexibility).

4.6.2 Study II

The Act protocol was identical to the one presented for Study I.

4.6.2.1 AR-protocol

The AR treatment was based on the original protocol by Öst (1987), adapted for use with longstanding pain. Also, the length, number and format of sessions were matched with the

ACT protocol. As with the ACT-intervention, the protocol was divided into different phases. In the first phase (sessions 1 to 4) the rational of using AR in the context of longstanding pain was presented, based on previous research and established relationships between fear, anxiety, stress, muscle tension, negative thoughts and pain. Furthermore, AR was presented as an alternative behavioral strategy to manage and reduce the negative impact of pain on daily life, which would be gradually introduced during the course of treatment. Furthermore, it was stressed that successful application of AR required thorough in-session as well as between-session practice. Two sessions focused on therapist guided in-session practice of the long version of progressive relaxation (i.e. with prior tensing of the muscles before relaxing them). One session comprised the brief version of progressive relaxation (i.e. without tensing of the muscles).

Phase two (session 5 to 7) consisted of conditioned and differential relaxation. Conditioned relaxation was taught by prompting participants to think "inhale" just prior to inhaling and to think "relax" just before exhaling, while being in a relaxed state achieved by previous performance of the brief version of progressive relaxation. Differential relaxation comprised the prior application of brief progressive relaxation combined with conditioned relaxation, after which participants performed certain tasks (e.g. writing, standing and walking).

During the final phase (session 8 to 12), practice of rapid relaxation was done in one session and two sessions focused on continued practice and application of rapid relaxation in daily life. Participants were encouraged to use rapid relaxation in situations where pain and pain-related distress increased. Furthermore, alternative ways of applying rapid relaxation were presented, for example by: Performing rapid relaxation prior to initiating a pain provoking activity; by repeatedly performing rapid relaxation during the pain provoking activity; or by performing scheduled rapid relaxation during the course of the day. The final two sessions focused on repetition of central concepts and skills, troubleshooting, and relapse prevention strategies.

4.7   ETHICAL CONSIDERATIONS

The Ethical Review Board in Stockholm approved all studies and all participants gave their written informed consent to participate in the studies.

5 RESULTS

5.1 STUDY I

In total, 82 women diagnosed with FM were referred to the study and of these 47 individuals were considered eligible and were further assessed by psychologists and pain clinicians. Forty-three of these fulfilled the inclusion criteria, out of which two declined participation. Three participants in ACT discontinued treatment and one participant in the control condition dropped out of the study between pre- and post-assessments. Furthermore, data from one participant were considered unreliable due to lack of assessment date and this individual was therefore removed from the analyses.

5.1.1 Treatment outcome

The mixed-effects model analyses illustrated significant improvements in pain disability in ACT compared to the control condition, as shown by a significant linear time by treatment interaction. Effect size calculations (d) showed medium between-group effects at post-assessment (0.75) and at follow-up (0.73). A significant linear time by condition interaction was also found in in favor of ACT on the mental aspect of HRQL; FM impact; self-efficacy; depression; and state and trait anxiety. For the secondary outcome measures significant between-group effect sizes varied between 0.42 and 0.73 at post-assessment. At follow-up assessment the between-group effects ranged from 0.39 to 1.05. Also, ACT improved significantly in psychological inflexibility compared to the control condition at post-treatment assessment ($d = 1.05$) and follow-up assessment ($d = 0.71$).

5.1.2 Mediation analysis

Mediation analyses were restricted to outcome variables where a significant time by condition interaction was found. Also, mediation analyses were only conducted if there was a significant relation between pre– and post-assessment changes in psychological inflexibility and if there were pre-assessment to follow-up changes in outcome. Results illustrated that decreases in psychological inflexibility (pre- to post-treatment assessment) significantly mediated the improvements in pain disability (pre-treatment to follow-up assessment). Also, psychological inflexibility significantly mediated change in: FM impact; self-efficacy; depression; and state and trait anxiety (secondary outcome measures).

5.2 STUDY II

Of 109 assessed patients, 60 met inclusion criteria. Those excluded reported higher levels of sick leave and catastrophizing compared to those included in the study.

5.2.1 Treatment outcome

Average scores and standard deviations from assessments of pain disability, pain intensity, mental and physical aspects of HRQL, symptoms of anxiety and depression and pain acceptance for the five assessment points are presented in table 2.

Table 2. Means and standard deviations for all outcome measures.

Variable	Cond.	Mean (*SD*) Pre	Mid	Post	3mfu	6mfu
PDI	ACT	39.1 (14.0)	31.6 (15.6)	28.8 (16.1)	28.5 (16.6)	31.2 (19.0)
	AR	40.7 (14.1)	42.5 (14.6)	40.3 (13.6)	35.0 (18.8)	34.0 (16.2)
Pain	ACT	4.3 (.79)	3.9 (1.2)	3.7 (1.4)	4.3 (1.0)	4.4 (1.3)
	AR	4.4 (1.0)	4.2 (1.3)	4.0 (1.5)	4.1 (1.3)	4.1 (1.5)
SF-12-M	ACT	38.8 (8.9)	41.8 (10.0)	40.9 (10.4)	39.9 (12.6)	39.3 (10.8)
	AR	37.7 (10.0)	36.3 (10.8)	34.9 (10.7)	37.6 (13.7)	38.8 (13.8)
SF-12-P	ACT	29.4 (8.5)	33.3 (10.0)	34.9 (9.1)	36.6 (10.9)	39.3 (10.2)
	AR	29.4 (7.6)	32.1 (7.6)	32.1 (8.2)	34.3 (10.1)	32.3 (9.8)
HADS-a	ACT	9.0 (3.9)	8.1 (3.5)	7.3 (3.8)	8.1 (5.6)	9.1 (5.1)
	AR	10.3 (4.9)	9.9 (4.8)	9.0 (4.6)	8.9 (5.1)	9.2 (5.1)
HADS-d	ACT	10.0 (4.1)	9.1 (4.7)	7.1 (4.8)	7.5 (5.0)	8.4 (5.6)
	AR	9.6 (4.3)	8.9 (3.8)	9.1 (5.3)	8.2 (5.8)	8.4 (5.5)
CPAQ	ACT	43.1 (16.3)	55.7 (15.4)	61.4 (14.5)	64.2 (19.1)	63.4 (21.2)
	AR	40.6 (15.5)	43.3 (19.3)	43.0 (17.5)	50.0 (19.5)	50.2 (21.9)

[Note] Means and standard deviations are based on observed data. CPAQ = Chronic Pain Acceptance Questionnaire; HADS-a = Hospital Anxiety and Depression Scale-anxiety; HADS-d = Hospital Anxiety and Depression Scale-depression; PDI = Pain Disability Index; SF-12-M = Short Form-12 mental subscale; SF-12-P = Short Form-12 physical sub-scale.

There were significant reductions across conditions over time (linear) during the treatment period (piece 1) on pain disability ($d = 0.54$), the physical aspect of HRQL ($d = 0.79$) and pain intensity ($d = 0.34$). Also, there was a significant time by treatment interaction (differential treatment effect) in pain disability ($d = 0.61$) during piece 1, in favor of ACT (Figure 3). Reductions in pain disability over time did not reach, statistical significance from post-treatment to 6-month follow-up (piece 2). However, there was a significant time by treatment interaction on pain disability ($d = 0.63$), in favor of AR (piece 2). There were no significant time or differential treatment effects seen in the physical aspect of HRQL during piece 2, indicating that improvements during piece 1 were maintained

across conditions. During piece 2 pain intensity approached, but did not reach statistical significance ($p < 0.1$) over time and in regard to differential treatment effects, implying a slight increase in pain intensity in ACT during piece II.

There was a significant decrease over time in piece 1 in anxiety ($d = 0.33$) and depression ($d = 0.41$) across conditions. There were no significant changes over time or in regard to differential treatment effects for Piece 2 on anxiety and depression. This suggested that the positive treatment-effects found in piece 1 were maintained in piece 2. During treatment there was a significant improvement in pain acceptance both over time and in regard to the differential treatment effects ($d = 0.90$). There was a significant improvement over time and across groups in acceptance in piece 2, but no significant time by treatment interaction, suggesting that the differential effects of treatments in favor of ACT during the treatment phase were maintained at 6-month follow-up.
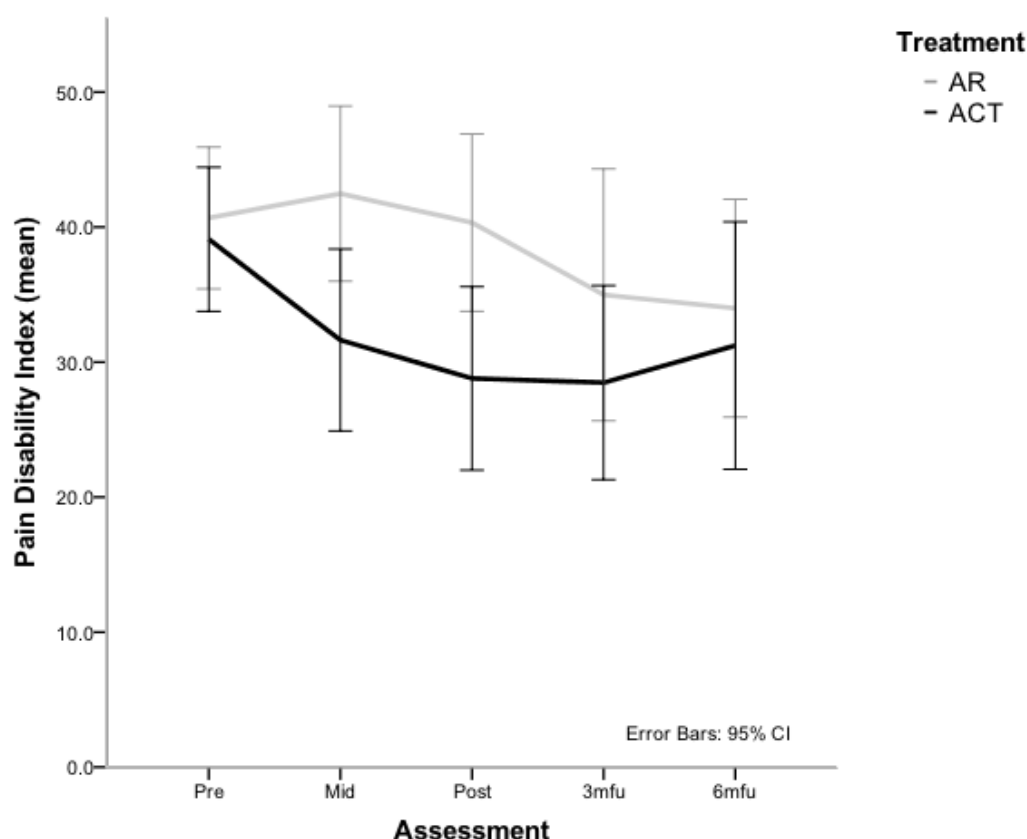
Figure 3. The graph is based on average scores in pain disability (Table 2) and represents change in ACT and AR, from pre-treatment to post-treatment assessment (piece 1), and from post-treatment assessment to 6-month follow-up (piece 2).

5.2.2 Clinically significant change

On the basis of a cut-off for clinical significance (a score < 25.8 on the PDI) in combination with a 90% confidence interval, 5 individuals in the ACT condition and none in AR met criteria for reliable and clinically significant change at post-assessment. At 3-month follow-up, 4 individuals in the ACT condition met these criteria, compared with 5 in AR. Four participants in ACT and 2 in AR met criteria for reliable and clinically significant change at 6-month follow-up. There was a marginally significant difference in clinically significant change between groups in favor of ACT at post-assessment (p = 0.056).

5.2.3 Costs and cost-effectiveness

There was a statistically significant decrease in work cutback at 3-month follow-up for AR and significant reductions in gross total costs at post-assessment and at 3-month follow-up for ACT. Furthermore, results illustrated that that pre-treatment to post-treatment change scores across conditions in pain intensity during the active treatment phase were correlated with changes in indirect non-medical costs. Lastly, pre- to post-treatment changes in pain intensity correlated with changes in total costs (including intervention costs) between pre- to post-treatment.

   The cost-effectiveness evaluation was based on plots of simulated ICERs (incremental cost-effectiveness ratios) in the quadrants of the ICER plane (Figure 4). At post-assessment, 99% of the simulated ICERs were located in the southeast quadrant, illustrating that ACT was more cost-effective than AR. At 3-month follow-up, 78% of the ICERs were found in the southeast quadrant and 15% in the southwest quadrant, illustrating that ACT remained more cost-effective compared with AR, although slightly less than at post-assessment. At 6-month follow-up the scatter is more centered, which indicates that there are no differences in cost reduction or effectiveness between the two conditions.
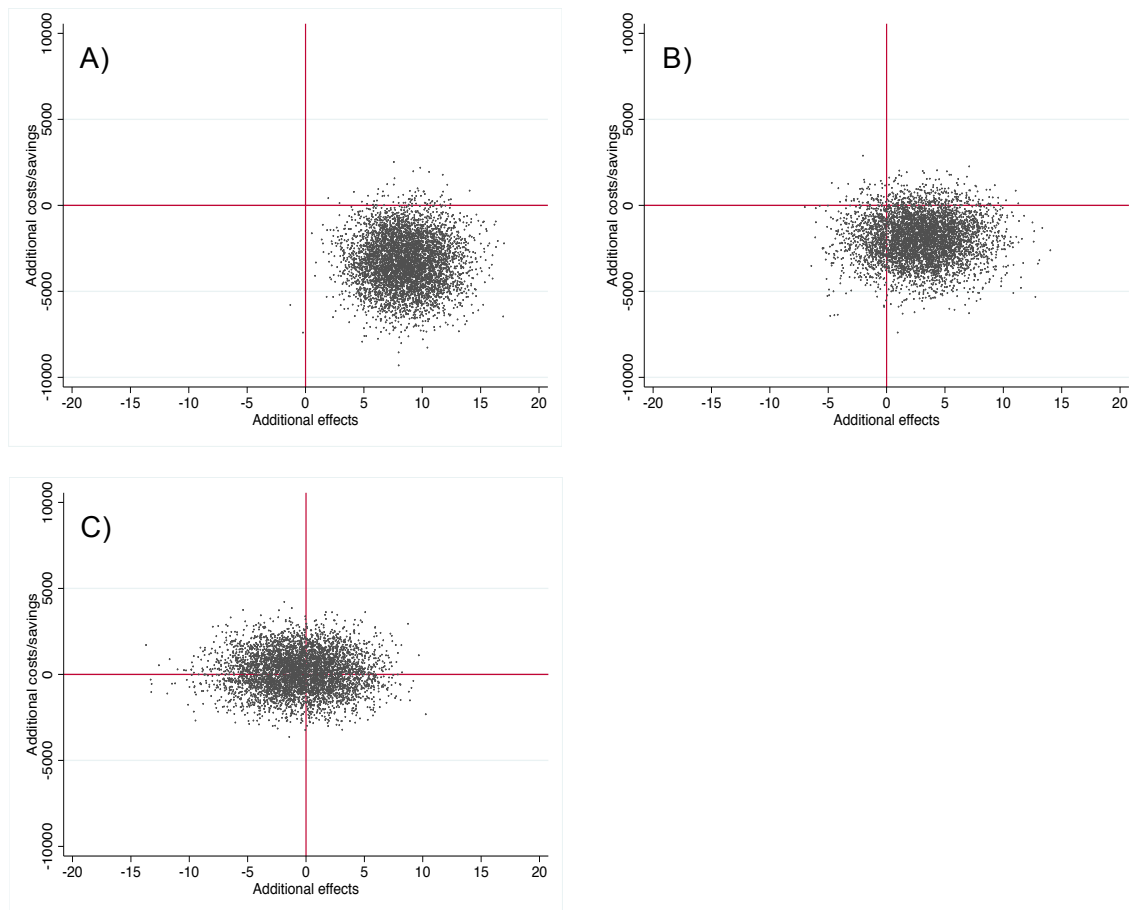
Figure 4. Cost-effectiveness planes comprising 5000 bootstrapped ICERs. The planes illustrate comparisons of ACT and AR based on change scores in total costs (including the cost of the interventions) and pain disability (assessed with the PDI): At post-treatment assessment (A); 3-month follow-up (B); and at 6-month follow-up (C).

5.3 STUDY III

In total 239 patients were eligible for study inclusion and of these 12 failed to fill out the requested questionnaires, resulting in an inclusion of 227 participants in the study. Of the 227 included participants, 22 were excluded from the reliability analyses due to missing one or more PII-items, thus the PCA was based on data from 205 individuals.

5.3.1 Psychometric analysis and concurrent criteria validity

Initial analyses indicated the factorability of the dataset and that all items could be included in the PCA. Following PCA, a one-factor solution was deemed the most adequate, based on one component attaining an eigenvalue > 1.0 and the corresponding scree plot. Items included in the PII had an adequate internal consistency, as illustrated by a Cronbach's alpha of .85 (Cortina, 1993). Significant bivariate correlations (Pearson's *r*) were found between the PII and: Average pain intensity the past week (0.52), the PDI

(0.67), physical and mental aspects of HRQL (0.48 and 0.42 respectively) and depression (0.45). Results from the hierarchical regression analyses (controlling for, sex, age and average pain intensity the past week) illustrated that PII explained an incremental significant amount of variance in: pain disability (29%); the physical aspect of HRQL (12%); the mental aspect of HRQL (10%); and depressive symptoms (14%). Thus, results from the correlation and regression analyses indicated the concurrent criteria validity of the measure.

5.4 STUDY IV

5.4.1 Mediation analysis

Means and standard deviations for the weekly assessments of pain interference and psychological inflexibility are presented in table 3.

Table 3. Means and *SD*s for the weekly assessments of the primary outcome (PII) and the hypothesized mediator (PIPS) in ACT.

	PII		PIPS	
	ACT	AR	ACT	AR
	Mean (*SD*)		Mean (*SD*)	
Week 1	26.4 (7.0)	26.7 (7.4)	58.5 (12.5)	58.7 (13.4)
Week 2	23.3 (8.8)	26.2 (7.3)	53.8 (12.3)	59.0 (13.2)
Week 3	23.8 (8.1)	27.0 (7.0)	51.8 (12.6)	57.7 (13.2)
Week 4	23.0 (8.6)	26.9 (7.5)	51.5 (15.0)	61.0 (13.3)
Week 5	21.9 (9.7)	24.4 (6.6)	52.0 (15.3)	56.3 (12.8)
Week 6	19.5 (8.9)	25.2 (9.0)	50.2 (16.2)	57.7 (15.2)
Week 7	22.0 (9.1)	27.7 (4.8)	48.5 (14.3)	63.0 (12.4)
Week 8	20.9 (9.5)	26.5 (6.6)	48.2 (16.7)	61.3 (12.5)
Week 9	20.9 (9.4)	24.3 (8.8)	49.1 (16.5)	58.6 (16.1)
Week 10	22.9 (8.6)	24.2 (6.9)	48.7 (16.8)	57.2 (15.1)
Week 11	18.8 (8.9)	23.2 (8.1)	44.5 (14.9)	55.7 (16.6)
Week 12	17.4 (8.9)	26.6 (9.1)	39.6 (15.8)	59.3 (16.8)

[Note] Means and standard deviations are based on observed data. PII = Pain Interference Index; and PIPS = Psychological Inflexibility in Pain Scale.

Results from the outcome analyses using linear mixed models showed a significant medium ($d = -0.57$) main linear effect of time in the ACT-condition on PII (Figure 5), which indicated a decrease in pain interference. There was no significant effect of time in the AR-condition and no significant differential linear change between treatments from first to last session on PII.
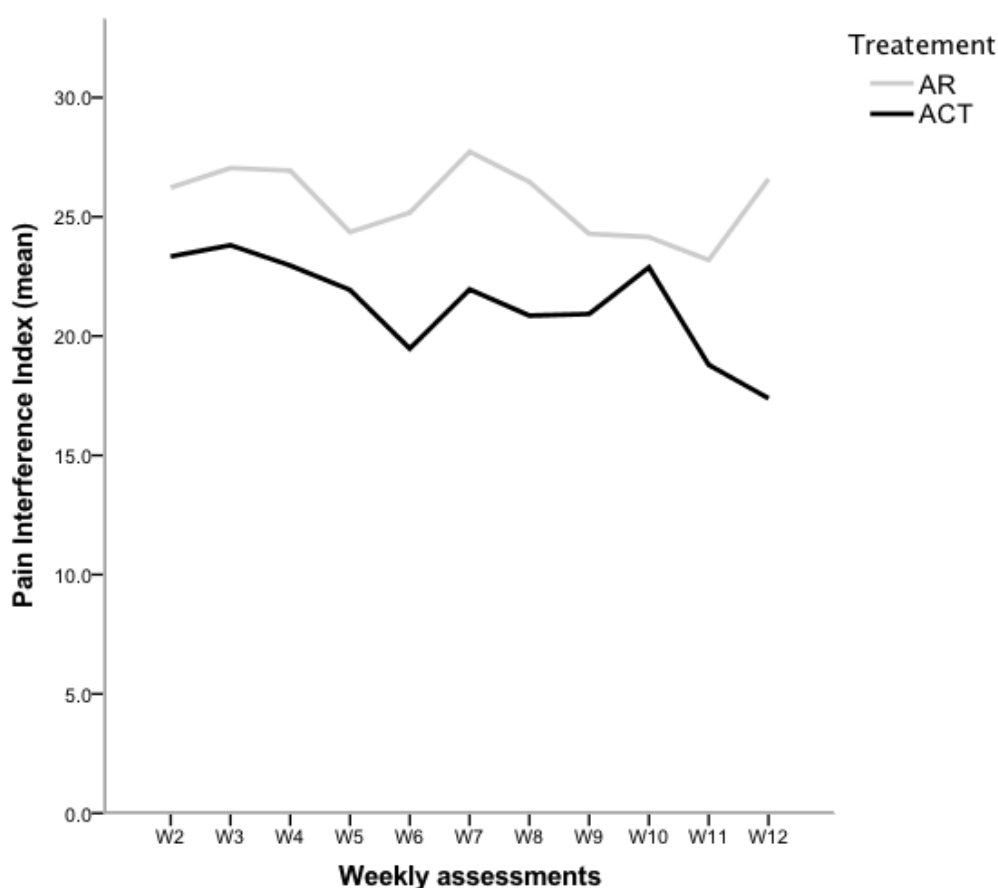
Figure 5. The graph is based on average scores in pain interference (Table 3) and represents session-to-session change in ACT and AR during treatment, from week 2 to week 12.

In the model with psychological inflexibility as the mediator, the effect of time (over treatment sessions) on the mediator (*a*-path) as a function of treatment (ACT or AR) was significant. This indicated that ACT had a significantly stronger effect ($d = 0.92$) on psychological inflexibility. There was no statistically significant difference on the mediator to outcome relation (*b*-path) as a function of treatment. The asymmetric confidence interval test of indirect effects revealed that psychological inflexibility was a significant mediator in ACT, but not in AR (Figure 6). In the model with pain intensity as the meditator, there were no significant changes over time in *a*- and *b*-paths as a function

of treatment, resulting in a non-significant indirect effect in both conditions. There was a significant difference in *a*-paths as a function of condition in the model with catastrophizing as the mediator, implying that ACT had a significantly stronger effect ($d =$ 0.38) on catastrophizing compared to AR. However, the test for difference in *b*-paths by treatment was non-significant, and the indirect effect of catastrophizing was non-significant in both groups. Thus, results imply that changes in psychological inflexibility mediated improvements in pain interference for ACT but not AR, and that catastrophizing and pain intensity did not mediate improvements in pain interference in either treatment.
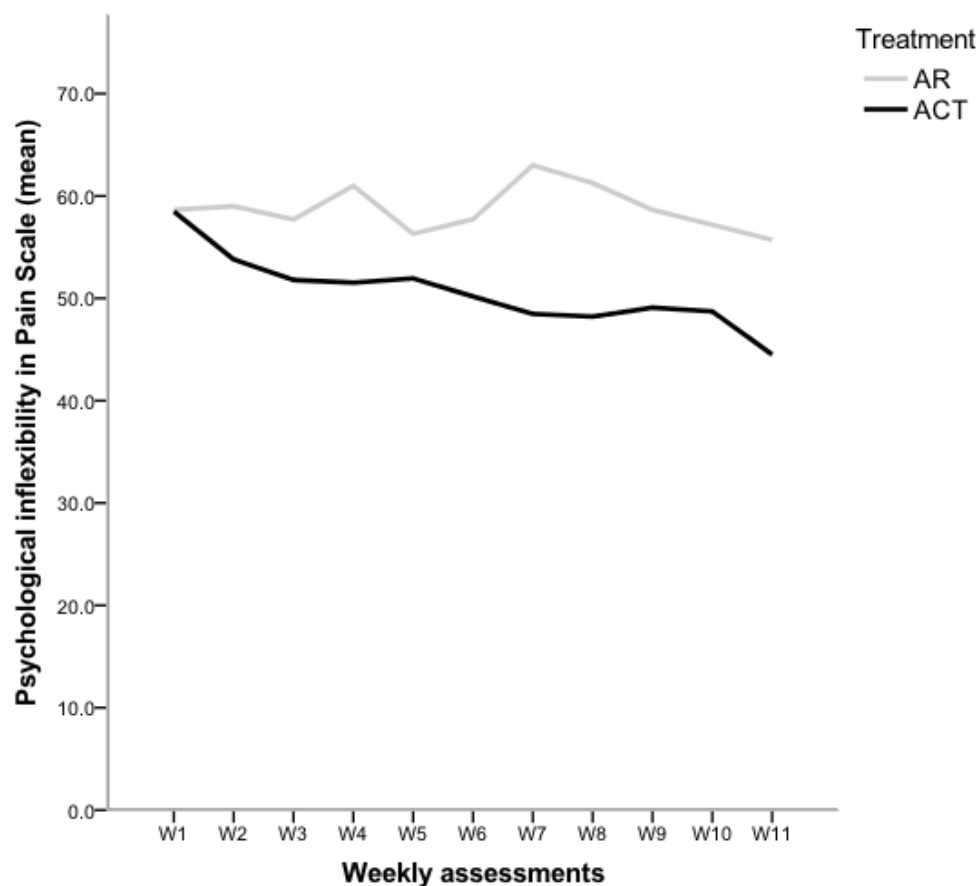
Figure 6. The graph is based on average scores in psychological inflexibility (Table 3) and represents session-to-session change in ACT and AR during treatment, from week 1 to week 11.

5.5 INTEGRITY, ADHERENCE, AND COMPETENCE

In both Study I and Study II, ratings showed adequate levels of treatment integrity, protocol adherence, and therapist competence. In Study II inter-rater agreement was calculated based on the scores of two raters. Except for ratings of AR competency, that lacked systematic agreement, there was an acceptable degree of agreement, suggesting that items were rated similarly across coders.

6 DISCUSSION

In this doctoral project we evaluated the efficacy of ACT for longstanding pain, a contextual behavioral treatment approach aiming to undermine the impact of pain and related distress on behavior. More specifically the efficacy of this approach in improving pain-related disability, pain interference and HRQL was evaluated. Importantly, we also investigated if improvements in psychological inflexibility were functionally related to improvements in pain disability and pain interference. In addition, an evaluation of the effect of treatment on health-related costs and a cost-effectiveness analysis were performed. Lastly, the psychometric properties of a brief pain interference questionnaire were analyzed. The questionnaire's utility as an outcome measure was also explored in the aforementioned process analyses. Below I discuss the different studies in relation to previous research, aspects of reliability and validity, relevant theory and future directions. Before concluding I also touch upon some clinical aspects related to the theoretical and clinical approach taken in the thesis.

6.1 STUDY I AND STUDY II

During the treatment phase, results from both Study I and Study II indicated significant moderate improvements in pain disability in favor of ACT compared to the control conditions. In Study I the between-group effect was maintained at three-month follow up. During the follow up period in Study II, results indicated significant moderate effects in pain disability in favor of AR compared to ACT. However, average scores in pain disability (Table 2 and Figure 3) indicated that the improvements during treatment in the ACT-group were largely retained during the follow-up phase. The small to moderate improvements in pain disability following ACT are in line with previous evaluations of ACT for both FM and non-specific pain (e.g. Luciano et al., 2014; Wetherell et al., 2011). In addition, the moderate effects of ACT on pain disability directly following treatment are similar to those of CBT for longstanding pain (Williams, Eccleston, and Morley, 2012).

Notably, the delayed effects on pain disability in AR complicate the interpretation of the results, and to my knowledge previous research does not indicate if these patterns of results should be expected. There were no significant differences between conditions in further treatment seeking (psychological, physiotherapeutic, or complimentary) during the

follow-up period. However, other confounding factors that were not assessed could explain these postponed effects.

In Study I there was a significant large between-group effect on the mental aspect of HRQL in the ACT-condition that was retained at three-month follow-up. In Study II there was a significant moderate effect on HRQL across conditions (ACT and AR) that was maintained during the follow-up phase. As regards mood, there were significant small to moderate effects on depression and anxiety in favor of ACT in Study I, from pre-treatment assessment to three-month follow-up. Results from Study II illustrate small significant improvements in depression and anxiety across conditions, from pre-treatment assessment to six-month follow up. In regard to HRQL, broad comparisons with previous studies are difficult to make, as it appears that this outcome has not been widely evaluated in ACT and CBT for longstanding non-specific pain (Hann and McCracken, 2014; Williams, Eccleston, and Morley, 2012). In regard to FM, results indicate that CBT does not improve HRQL at post-treatment assessment or at follow-up (Bernardy et al., 2013). The results on depression and anxiety in Study I and Study II largely correspond with previous research. Hann and McCracken (2014, p. 223) write that ACT had small to large effects on anxiety, depression and general emotional distress in four out of seven studies using an inactive control. Results from the meta-analysis by Williams, Eccleston, and Morley (2012, p. 12) indicate that CBT, when compared with inactive control conditions, had moderate effects on mood at post-treatment assessment and a small effect at follow-up. However, no effects on mood were found when compared to active treatments. According to Bernardy et al. (2013), there were small effects on mood at post-treatment assessment in CBT for FM.

Results on pain intensity diverged somewhat between studies. In Study I there were no significant reductions in pain intensity following ACT, but results from Study II showed significant moderate reductions of pain intensity across conditions during the treatment phase. Findings from other evaluations of ACT have not shown a consistent pattern of pain reduction following treatment (Hann and McCracken, 2014). Results from a meta-analysis of laboratory-based studies evaluating components in the ACT-model, e.g. acceptance (Levin et al., 2012), illustrated that there were no significant differences between more control-oriented strategies (e.g. distraction) and acceptance-based strategies in reducing the subjective intensity of e.g. pain during a laboratory-induced stressor. In regard to pain, results indicate that CBT may have a small effect on pain intensity at post-treatment assessment when compared to inactive control conditions, but not in

comparison with active control conditions (Williams, Eccleston, and Morley, 2012). Similarly, in the meta-analysis by Bernardy et al. (2013) the authors write that CBT does not appear do reduce pain in FM.

6.1.1 Clinically significant change

In Study II approximately 20% of the participants in ACT, but none in AR, achieved clinically significant improvements in pain disability at post-treatment assessment. However, at follow-up assessments proportions were similar across treatments. Clinical significant change has been evaluated only in a limited number of studies of ACT for longstanding pain, and similarly there is lack of studies investigating clinically relevant change in CBT for longstanding pain (Williams, Eccleston, and Morley, 2012). In ACT, these evaluations have been done in different pain populations and various methods for classifying responders have been used (McCracken, MacKichan, and Eccleston, 2007; Trompetter et al., 2015; Vowles et al., 2014). Although small, the proportions of participants achieving clinical significant change in regard to disability in Study II are comparable with those presented by e.g. McCracken, MacKichan, and Eccleston (2007), and Vowles et al. (2014).

6.1.2 Cost-effectiveness

Results from Study II also showed that ACT was more cost-effective than AR at post-assessment and at 3-month follow-up, but that the conditions did not differ at 6-month follow-up. Furthermore, results indicated a significant gross total cost reduction at post-treatment and at 3-month follow-up for ACT, and a significant decrease in work cutback at 3-month follow-up for AR. Additionally, results indicated that reductions in pain intensity during treatment, across treatment conditions, were related to cost reductions in indirect non-medical costs and total costs during this time period.

The total cost reductions following ACT and the correlation between reductions in symptoms and total costs during treatment, correspond with one previous study in which we collaborated with another research group in evaluating an internet-delivered ACT-based treatment for FM (Ljotsson et al., 2014). A few studies have indicated the cost-effectiveness of CBT for longstanding pain and its effect on health-related costs (Linton and Nordin, 2006; Turk, 2002).

6.1.3 Future directions

As regards cost-effectiveness, more studies are needed that evaluate the effects of both ACT and CBT (Ehde, Dillworth, and Turner, 2014) on health economic outcomes. In addition, health economic analyses in Study II were performed within a ordinary least squares regression framework and future studies should evaluate the relationship between treatment-related changes in cost-variables and other outcomes, as well as potential process-variables, using more appropriate longitudinal designs, assessment methods and statistical analyses.

In regard to clinically significant change, Williams, Morley and Eccleston (2012, p. 14) mean that researchers should develop measures with high ecological validity that can index clinical improvement and enhance, or possibly replace, statistical change. Central treatment interventions in ACT aim at establishing behavior guided by values, i.e. approach behavior governed by appetitive motivating functions. A few clinical studies have investigated the role of valuing as a process of change in ACT for longstanding pain (e.g. Vowles et al., 2014) and results indicate its potential as a process of change in ACT. This variable also appears relevant to evaluate as an outcome (Wilson et al., 2010), which could also be used in analyses of clinical significant change. Notably, potential side effects of treatments, resulting in clinically significant deterioration were not evaluated within this doctoral project, but should be investigated in future studies.

In regard to processes of change, researchers have increasingly pointed to the limitations in knowledge gained from head to head trials testing two therapies against each other based solely on outcome differences (Williams, Eccleston, and Morley, 2012). Many of these trials have not been able to show clear outcome differences in competing psychological treatments. Repeatedly, these studies also fail to provide information of which treatment aspects that account for change, also when differences are found. Thus, the need to investigate the specific aspects of treatment that influence change in the outcome, and situational and participant characteristics that influence treatment effects, have been stressed by several researchers (Kazdin, 2007; Williams, Eccleston, and Morley, 2012). Potentially, a better understanding of these aspects may guide further refinement and development of treatments, and potentially also improve the effects of treatment. I will specifically discuss avenues for further process research when discussing the results of the mediation analyses. Importantly, we also need to assess adequate outcomes, i.e. outcomes that are closely related to what we want to achieve in treatment, which brings us to Study III.

6.2 STUDY III

As mentioned in the background, the importance of measuring the impact of pain in central life domains has been recommended by IMMPACT (Dworkin et al., 2005). Potentially, measures assessing pain interference, i.e. the impact of pain on behavior, may be particularly well suited for evaluations of treatments like for example ACT, that specifically target variables related to interference, e.g. experiential avoidance. Notably the PII was especially developed to be brief and easily understood, which we deemed key for use in process evaluations with frequent assessments.

Results from Study III supported a single factor structure and showed satisfactory internal consistency among the items. Furthermore, the PII explained a significant amount of incremental variance in pain disability, physical and mental HRQL and depression, which indicated adequate concurrent criteria validity. One previous study from our group has investigated the reliability and concurrent criteria validity of the questionnaire in a sample of adolescents suffering from non-specific pain (Holmström et al., Accepted manuscript) and another study (Martin et al., 2015) has performed a validation of an English version of the questionnaire in persons, from 6 to 24 years, with neurofibromatosis and cancer, but also of a parent version of the questionnaire. Both these studies reported internal consistencies and concurrent criteria validity similar to the results in Study III. Notably, the questionnaire's sensitivity to change was implied in Study IV, and these results line up with one previous study evaluating ACT for children and adolescents in which the questionnaire was also used as an outcome measure (Wicksell, Olsson, and Hayes, 2011).

Apart from early strides (Hayes, Nelson, and Jarrett, 1987), psychometrics have not been thoroughly discussed from a contextual viewpoint. However, as presented earlier, the CBS-approach to truth is pragmatic and in accord with this assumption it has been suggested that self-report questionnaires should display treatment or research utility, above and beyond other properties (Hayes, Barnes-Holmes, and Wilson, 2012). Treatment utility refers to the measures ability to guide clinical work. For example, it should assess outcomes (e.g. pain interference) relevant to central treatment targets (e.g. experiential avoidance), and thus also show a relation to these processes, in such way that for instance "dosages" can be adjusted and potentially improve outcomes. Similarly, the questionnaire's ability to model change in regard to specific research aims is referred to as its research utility (Hayes, Barnes-Holmes, and Wilson, 2012).

6.2.1 Future directions

Hayes, Barnes-Holmes, and Wilson (2012) mean that questionnaire development ought to be done in parallel with a more articulated contextual assessment theory and related methods. Experience sampling (Bolger, Davis, and Rafaeli, 2003) may be of relevance in this regard. This method entails assessment of individuals on several occasions over the course of a day, via e.g. a smart phone, in regard to cognitions, emotions, behaviors and the context in which they occur. As regards ACT, assessments related to experiential avoidance, valued living, pain interference etc. (i.e. outcome and process variables) appear specifically relevant. In addition, actigraphy data or frequent sampling of biological data appears highly relevant to gather in conjunction with self-reported data.

6.3 STUDY I AND STUDY IV

Kazdin (2007) means that inferences and conclusions about mediators demand consolidation of several criteria and below I will discuss the results from the mediation analyses in relation to: (1) the *strength* of the relation between treatment and the mediator and the mediator and the outcome; (2) the *specificity* of the proposed mediator in relation to other potential mediators; (3) the *experimental manipulation* of the mediator and the *timeline* between mediator and outcome; and (4) the consistency of the mediator across studies and its *coherence* in relation to the broader scientific field.

6.3.1 Strong associations between treatment, mediator and outcome

A strong relation between the intervention (x) and the hypothesized mediator of change (m), and an association between the putative mediator (m) and the therapeutic outcome (y) is important in building a case for the mediating functions of a variable (Kazdin, 2007). These requirements also assume an effect of the intervention on the outcome. Study I and Study II illustrated that ACT had significant moderate effects on the primary outcome, pain disability during treatment in comparison to the control conditions. Likewise, results from Study IV showed that ACT had a significant moderate effect on pain interference.

In regard to the effect of treatment on the mediator, the between-group effect-size in Study I was large at post-treatment assessment and moderate at three-month follow-up on psychological inflexibility. In Study II there was a large between-group effect on pain acceptance in favor of ACT at post-treatment assessment, an effect that was maintained at 6-month follow-up. In Study IV both the within group and the between-

group effect sizes were large on psychological inflexibility in favor of ACT at post-treatment assessment.

As regards the mediator to outcome relationship, results from Study I illustrated a significant moderate relation between the mediator and pain disability and Study II indicated a significant relationship between psychological inflexibility and pain interference in ACT. In Study I results illustrated the mediating role of psychological inflexibility for pain disability, but also for a number of secondary outcomes (FM impact, self-efficacy, depression and anxiety). The results from the mediation analyses in Study IV suggest that reductions in pain interference were mediated by improvements in psychological inflexibility, but not by changes in catastrophizing or pain intensity. In addition, the results indicated that changes in psychological inflexibility preceded changes in pain interference.

In Study IV change processes in AR were also explored. The anticipation was that relaxation would constitute a trained skill, an alternative behavior to previously used avoidance strategies that participants could apply in relation to distressing antecedents. For example, thinking dominated by thoughts related to catastrophizing (e.g. "I can't handle this pain!"). Results from a study by Smeets et al. (2006) in which catastrophizing mediated changes in disability during physical therapy (i.e. an intervention that did not include explicit procedures to alter cognitions), indicated the possibility of similar effects following AR. However, no such mediating effect was seen in Study IV. AR did not have a significant effect on the process or the outcome variable, and most likely this was a direct consequence of low power. Thus, the processes of change in AR for chronic pain remain unclear and future studies should further explore these aspects, as results from both Study II and other previous studies (e.g. Gustavsson and von Koch, 2006) indicates the utility of this treatment approach for longstanding pain.

6.3.2 Specificity of the mediator

If the specificity of the proposed mediator can be shown in relation to several other plausible mediators, the argument for its mediating functions have been substantially strengthened (Kazdin, 2007). Study IV included two additional putative mediators, catastrophizing and pain intensity. However, these variables were not found to mediate change in pain interference and, given that psychological inflexibility exclusively mediated change in ACT, these results imply the specificity of this variable in Study IV. These results also correspond with results from previous mediation analyses in two RCTs

in which we tested the specificity of psychological inflexibility and related constructs as mediators in ACT for whiplash-associated disorder (Wicksell, Olsson, and Hayes, 2010), and ACT for pediatric non-specific pain (Wicksell, Olsson, and Hayes, 2011). In these studies, results showed that changes, specifically in psychological inflexibility and its related constructs, compared to several other putative mediators, e.g. pain intensity and catastrophizing, mediated changes in pain interference, pain disability and quality of life in the ACT-conditions.

However, findings from other studies illustrate that variables that are typically targeted in ACT also appear to mediate changes in outcome in other types of treatments. This implies that these treatments may be functionally similar, or that certain processes of change are not specific to any one treatment (Arch et al., 2012). Furthermore, processes that are not explicitly proposed as processes of change in ACT have been shown to mediate outcomes in ACT (Wetherell et al., 2011). Experimental studies that aim to provide support for one specific mediator while ruling out several other mediators ought to have utility in investigations of specificity. Also, experiments that assign participants to different levels of a specific mediator with the aim to show a dose-response relation, i.e. that greater provocation of the mediator is linked to larger change in the outcome, would be highly useful (Kazdin, 2007; MacKinnon and Luecken, 2008). On a related note, it appears highly relevant to investigate how combinations of components affect their function (Levin, et al., 2012), for example by systematically comparing combinations of components (e.g. defusion and values) with isolated components (e.g. defusion).

6.3.3 Manipulation of the mediator and establishment of its timeline

Adequate experimental control and direct manipulation demonstrates cause and reinforces the possibility of the suggested mediator being responsible for change in the outcome variable (Kazdin, 2007). Pearl (2009, p. 100) states that: "Every claim invoking causal concepts must rely on some premises that invoke such concepts […]." Randomization of participants to different interventions is such a premise on which we can build causal claims of those interventions. The mediation analyses performed in the present thesis (Study I and Study IV) were done based on data from RCTs, which provides support to causal claims (of the kind presented by Pearl above) of how the intervention influences the mediator and the outcome. However, it should be noted that the relation between the mediator (m) and the outcome (y), controlling for the treatment condition (x), reflects a correlation and not a causal relation (MacKinnon, Fairchild, and Fritz, 2007). This

association is a not a result of randomization, i.e., individuals have not been randomized to different levels of the mediator. One way to address causality is to provide support of the temporal precedence of the mediator in relation to the outcome, i.e. assessment of the proposed mediator needs to be done before the outcome. Furthermore, it needs to be shown that the mediator actually changes before the outcome (Kazdin, 2007). This was the approach taken in Study IV. However, the design and analyses used in Study IV is still an oversimplification of how treatment influences trajectories of change across variables and individuals. For example, most likely, individuals change at different rates in both psychological inflexibility and pain interference during treatment and more sophisticated growth models may better address temporality between variables over time (e.g. Ljotsson et al., 2013).

Importantly, from the perspective of the philosophical assumptions of CBS the analysis of mechanisms is not done in order to find out how the world "really" works. Rather the explicit goal of evaluating mechanisms and processes of change is done in line with the other stated aims of prediction and influence. In other words, it is the utility of a mechanism, or process, in relation to a specific outcome of interest within a specific context that is a gauge of its "truth". This shifts the focus to investigations of the specific circumstances under which a particular strategy works. For example, possibly ACT for longstanding pain has stronger effects on persons scoring high on experiential avoidance and fusion prior to initiating treatment, in such a way that the mediated effect is dependent on baseline levels of the mediator (MacKinnon, Fairchild, and Fritz, 2007).

While being aware of the potential drawback in regard to external validity, Kazdin (2007, p. 20) wrote: "Controlled studies of therapy in research rather than clinical settings are more important now than ever before. The careful control afforded by such research is precisely what is needed to identify mediators and mechanisms." Thus, experimental studies may facilitate precise manipulation of the mechanisms under investigation and careful study of the precedence of the mechanism in relation to the outcome. Also, these studies can be done within the population of interest, e.g. specific subgroups of person suffering from chronic pain (which in part would address the issue of validity). Likely, well-controlled experiments may also serve as an arena to investigate mechanisms of change in regard to multiple levels of analysis e.g. both on an observable overt behavioral level and in relation to biological levels of analysis. Potentially, single-case studies using experimental designs, e.g. multiple baseline studies (Heyvaert and Onghena, 2014), could also be of benefit in relation to the exploration of processes of change in clinical settings,

and serve as a source of further hypotheses generation. These studies could explore a number of questions related to processes of change, e.g. specificity, manipulation and timeline, and could also employ varying methods of assessment (e.g. experience sampling).

6.3.4 Coherence of the mediator within a broader scientific context

Importantly, identification of a process of change in a psychological treatment model is not achieved based on the results from a few clinical trials. Rather, it is achieved as results from multiple lines of work within the broader scientific community in question converges in a coherent manner (Kazdin, 2007). Behavioral inflexibility, characterized by experiential avoidance and narrow and rigid behavioral repertoires may, with some qualification, live up to these criteria of convergence and coherence.

Previous research, also without explicit CBS-affiliations, in the area of pain using various methodological approaches supports this notion (Hann and McCracken, 2014; Kohl, Rief, and Glombiewski, 2012; Levin et al., 2012). Furthermore, results in the current thesis converge with results of ACT for related health-issues, for example tinnitus (e.g. Hesser, Westin, and Andersson, 2014), as well as with more general trends within CBT, as exemplified by the refined views of exposure and the growing utilization of acceptance-based interventions (Arch and Craske, 2008; Craske et al., 2008; Veehof et al., 2011).

Furthermore, other developments within CBT, including the focus on trans-diagnostic approaches, unified protocols (Barlow, Allen, and Choate, 2004; Linton, 2013) and the suggested relevance of context sensitivity (Linton, 2013) appear to mesh nicely with the theoretically and functionally based transdiagnostic approach outlined in the current thesis project. Ideally, further discussions should be initiated across specific treatment traditions on how to move the field forward in regard to the processes that appear central for achieving change in behavioral treatments for longstanding pain. Before I move on to a brief discussion of the role of theory in regard to clinical practice I will address some methodological considerations.

6.4 METHODOLOGICAL CONSIDERATIONS

6.4.1 Limitations

Reliable treatment credibility data would have provided an opportunity to analyze the participants' perception of treatments, and the potential relation between these perceptions

and session attendance, attrition rates and treatment outcome. The sample sizes in the outcome studies were small, which may have influenced the stability of parameter estimates and associated standard errors, which suggests that comparisons between treatments, including the results pertaining to indirect effects should be interpreted cautiously.

However, the statistical models used to evaluate outcome (Study I and Study II) and mediation (Study IV) has several advantages over more commonly used methods. For example, it has been shown that latent growth modeling has outperformed traditional repeated measures ANOVA in small to moderate sample sizes in terms of statistical power in all examined situations (Fan, 2003). Also, these models often provide more reliable estimates of treatment effects in the presence of missing data (Lane, 2008).

Furthermore, we did not calculate an effect-size of the indirect effect, proportion mediated or other potential gauges of the mediated effect, which would have enhanced the interpretation and discussion of the findings. Notably, in regard to the analyses in Study IV the calculations are complicated by the fact that the indirect effect is a product of two regression coefficients, and it has been shown that a sample size of $n > 500$ is required to get reliable specific effect size measures for the *ab*-product (e.g., proportion mediated) (MacKinnon and Luecken, 2008). However, as mentioned earlier we did perform effect-size calculations of significant changes in the mediators over time in ACT.

All analyses in the current thesis were based on self-reported data. In regard to the treatment evaluations, changes of self-report can be a result of the participant's expectations of the particular treatment, and furthermore the covariance between measures (e.g. process and outcome measures) may be explained by shared method variance. Although these limitations apply to most clinical and psychometric evaluations within CBT and ACT, alternative ways of obtaining data in clinical settings (as discussed previously) should be explored (Hesser et al., 2009).

6.4.2 Strengths

Both Study I and Study II comprised RCTs, which supports the causal relation between intervention and the mediators and outcomes. In relation to this, Study II is one of few that has compared ACT for longstanding pain with an established behavioral intervention, and that has evaluated the cost-effectiveness of these interventions. Furthermore, both treatment studies were assessed in regard to treatment fidelity, protocol adherence and therapist competence, which to our knowledge has not been done as of yet in studies on

ACT for longstanding pain. Furthermore, assessment of treatment in this way is critical to ascertain that the proposed processes were in actuality adequately targeted. Finally, in Study IV session-to-session data and an appropriate data analytic model was used. This enabled an evaluation of the temporal precedence of the mediator in relation to the outcome and allowed examination of individual differences in change over time in both process and outcome variables. In contrast to studies with pre- and post assessments, this approach allowed for a more adequate analyses of mediation (Kazdin and Nock, 2003).

6.5 CLINICAL ASPECTS

As discussed above, the results from the outcome and mediation analyses converge with results from previous research of ACT (Hann and McCracken, 2014; Levin et al., 2012), as well as with more general trends within CBT (Barlow, Allen, and Choate, 2004; Craske et al., 2008; Linton, 2013; Veehof et al., 2011). Thus, it appears highly relevant to clinically target experiential avoidance and aim at increasing behavioral flexibility.

The treatments evaluated in the current thesis were delivered by means of protocols specifying in fair detail what was to be done during and across sessions. Following detailed procedural protocols of this sort is useful under a number of circumstances (Waller, 2009). However, as indicated by the moderate effect sizes and limited number of participants achieving clinical significant change in the studies in this thesis, as well as across studies in CBT and ACT, a number of patients do not improve following treatment as delivered using these types of protocols. As has been stressed repeatedly, in the background and in the discussion, studies that more thoroughly investigate mediation and moderation are highly relevant in this regard.

In relation to this, potentially, patients may under some circumstances benefit from more tailored interventions based on individual conceptualizations and adapted appli-cations of empirically supported treatment components. In this regard, it has been recommended that clinicians should cultivate better working knowledge of the theoretical base of CBT, in order to better conceptualize and intervene in relation to patients with for example multiple debilitating symptoms and problems (Herbert, Gaudiano, and Forman, 2013; McKay, Taylor, and Abramowitz, 2010). This requires a choice of an adequate theory, but also a determination of what level of theory that is adequate, and with which fluency clinicians should be able to apply this theory.

Reasonably, the theory should rest on a fairly solid empirical base. A review by Dymond et al. (2010) reported a total of 62 empirical and 112 non-empirical publications

on RFT from 1991 to 2008. The empirical articles showed overall support of the basic tenets of the theory. In the service of precision (and scope and depth) RFT may be found lacking in direct accessibility. The ACT-model comprises an effort to link RFT terminology with more accessible and applicable mid-level terms, like "fusion", "values" etc. (Hayes, Barnes-Holmes, and Wilson, 2012). Notably, recent efforts have been made to yet more directly connect RFT to clinical practice, from a broader cognitive behavioral perspective (e.g. Törneke, 2010; Villatte, Villatte, and Hayes, In press).

Potentially, a more detailed grasp and fluency of a theoretical model, *for example* RFT, may be important in tailoring interventions (Foody et al., 2014), specifically for certain sub-groups of patients. Possibly, tailoring treatments in this way could also increase the effects of behavioral interventions for chronic pain. Herbert, Gaudiano, and Forman (2013) argue this case and conclude that the best way to resolve questions of the above sort is through research. For example, they suggest RCTs in which practicing clinicians could be randomized to limited theoretically based training and supervision or to a condition focused on building theoretical based skills. In addition, evaluations of processes of change and cost-benefit analyses could readily be included also in these types of studies (Herbert, Gaudiano, and Forman, 2013, p. 587).

6.6 MAIN CONCLUSIONS

Results indicate the utility of using a relatively brief ACT intervention in a group format for persons suffering from FM and non-specific longstanding pain. Primarily, significant effects were seen in disability during treatment. Furthermore, ACT may have utility in reducing costs and being a cost-effective treatment. In Study III results indicated that the PII is a reliable and valid measure to assess pain interference in adults, and its sensitivity to change and utility in evaluations of processes of change was indicated in Study IV.

Results also suggest the mediating function of psychological inflexibility in regard to pain disability and pain interference. Results from Study IV further illustrate the mediating function of psychological inflexibility in relation to pain interference in ACT, compared to catastrophizing and pain intensity, based on a model in which change over time was modeled using session-to-session data to examine temporal relations between mediator and outcome. In sum, results add to the growing body of work indicating the clinical utility of ACT, and further suggest the role of psychological inflexibility as an important treatment target in longstanding pain.

7 APPENDIX (TABLE 1)

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8   ACKNOWLEDGEMENTS IN SWEDISH

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