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WHAT MAKES COGNITIVE BEHAVIOR THERAPY WORK? AN INVESTIGATION OF PSYCHOLOGICAL AND INFLAMMATORY PROCESSES

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WHAT MAKES COGNITIVE BEHAVIOR THERAPY WORK? AN INVESTIGATION OF PSYCHOLOGICAL AND INFLAMMATORY PROCESSES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Background: Common mental disorders (CMDs; anxiety disorders, depression, insomnia and stress-related disorders) cause significant suffering, reduced functioning and impaired quality of life. Cognitive behavior therapy (CBT) is an effective treatment, but there is considerable room for improvements in outcomes. Increased knowledge regarding potential mechanisms of change in CBT could inform treatment development. Investigation of both psychological and inflammatory processes could be one way of moving the field forward.

Aims: The aim of this thesis was to investigate processes and correlates of therapeutic change in CBT for CMDs. Based on two clinical trials set in primary care in which CBT for CMDs were tested (Study I and II), this thesis investigated mediators of change in CBT for exhaustion disorder (Study III), processes of change in CBT for social anxiety disorder (Study IV), and inflammatory correlates of change in CBT for CMDs (Study V).

Methods: In the clinical trials (Study I, $N = 211$; and Study II, $N = 396$), primary care patients with CMDs were treated with CBT, delivered in different formats. Based on the effects found in these trials, further analyzes were conducted in Study III, IV and V, with regard to processes related to outcome. In Study III, mediators of change were analyzed in patients with a primary exhaustion disorder ($N = 82$), randomized to CBT or another active psychological treatment. In Study IV, the effect of changes in proposed maintaining processes were analyzed in relation to symptom change in guided self-help CBT for social anxiety disorder ($N = 61$). In Study V, inflammatory cytokines were measured before and after treatment with CBT and analyzed in relation to psychiatric symptoms ($N = 367$).

Results: The results of the clinical trials (Study I and II) showed beneficial effects of disorder-specific CBT for CMDs. In Study III, CBT led to larger effects on symptoms of exhaustion than the comparator, and this difference in effects was mediated by improvements in sleep quality and perceived competence. In Study IV, several of the putative change processes (i.e., estimated probability and cost of negative social events, self-focused attention, avoidance, and safety behaviors) predicted subsequent changes in social anxiety. However, all of these processes except for avoidance were also predicted by prior symptom reduction. In Study V, we found no robust associations across the study sample between inflammatory cytokines and psychiatric symptom severity. Further, the marked symptom improvement was not tracked by reductions in cytokines.

Conclusions: CBT for patients with CMDs in primary care yielded favorable effects on psychiatric symptoms. In CBT for exhaustion disorder, sleep disturbance and perceived competence may be important treatment targets. In social anxiety disorder, several of the proposed maintaining processes seem to be part of positive reciprocal cycles, where improvements in processes and symptoms influence each other. Avoidance showed a unidirectional effect on subsequent symptoms and might thus be of specific clinical relevance. The results also suggest a limited role of inflammatory processes in symptomatic improvements following CBT for CMDs.

LIST OF SCIENTIFIC PAPERS

- I. Salomonsson S, Santoft F, Lindsäter E, Ejeby K, Ljótsson B, Öst L-G, Ingvar M, Lekander M, Hedman-Lagerlöf E. Cognitive-behavioural therapy and return-to-work intervention for patients on sick leave due to common mental disorders: a randomised controlled trial. *Occupational and Environmental Medicine* 2017; 74(12): 905-12.
- II. Salomonsson S, Santoft F, Lindsäter E, Ejeby K, Ljótsson B, Öst L-G, Ingvar M, Lekander M, Hedman-Lagerlöf E. Stepped care in primary care - guided self-help and face-to-face cognitive behavioural therapy for common mental disorders: a randomized controlled trial. *Psychological Medicine* 2018; 48(10): 1644-54.
- III. Santoft F, Salomonsson S, Hesser H, Lindsäter E, Ljótsson B, Lekander M, Kecklund G, Öst L-G, Hedman-Lagerlöf E. Mediators of change in cognitive behavior therapy for clinical burnout. *Behavior Therapy* 2018; In press.
- IV. Santoft F, Salomonsson S, Hesser H, Lindsäter E, Ljótsson B, Lekander M, Kecklund G, Öst L-G, Hedman-Lagerlöf E. Processes in cognitive behavior therapy for social anxiety disorder: predicting subsequent symptom change. Submitted manuscript.
- V. Santoft F, Hedman-Lagerlöf E, Salomonsson S, Lindsäter E, Ljótsson B, Kecklund G, Lekander M, Andreasson A. Inflammatory cytokines in patients with common mental disorders treated with cognitive behavioral therapy. Manuscript.

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LIST OF ABBREVIATIONS

CBT	Cognitive behavior therapy
CMDs	Common mental disorders
COMBO	Combined CBT and RTW-I
CRP	C-reactive protein
CSR	Clinician's Severity Rating
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Exhaustion disorder
HPA	Hypothalamic–pituitary–adrenal
ICD	International Statistical Classification of Disease and Related Health Problems
IL	Interleukin
NATs	Negative automatic thoughts
RTW-I	Return-to-work intervention
SAD	Social anxiety disorder
TNF- α	Tumor necrosis factor alpha

1 INTRODUCTION

Hungarian physician Ignaz Semmelweis proposed, in mid 19th century, that hand wash could be a vital step towards decreasing childbed mortality ¹. He suggested that cadaverous matter, carried by medical students from autopsy room to mother in labor within the hospital, was the pathological pathway that caused maternal death. Later, germ theory of disease with the discovery of microorganisms made progress with wide-reaching consequences.

Analogously, increased knowledge on how changes unfold in psychological treatment has the potential to greatly improve outcomes. There are today evidence-based treatments for several of the most common psychiatric disorders. Nonetheless, many patients are not helped sufficiently. To move the field forward, and ultimately be of better help, we need to know more about how change comes about in treatment. From the perspective of a therapist, this concerns what should be said and done to promote change in patients, or their context, that is instrumental for therapeutic effects. Maximizing therapeutic improvement is not only the main goal for patients, it is presumably the greatest reward working as a psychologist.

Stockholm, January 2019

2 BACKGROUND

2.1 COMMON MENTAL DISORDERS AND MAINTAINING PROCESSES

2.1.1 Definition of common mental disorders

Anxiety disorders, depression, sleep disturbance and stress-related disorders are highly prevalent²⁻⁶ and associated with significant suffering, reduced functioning, and impaired quality of life⁷⁻⁹. These disorders are sometimes referred to as common mental disorders (CMDs)¹. Specifically, in this thesis CMDs denote the disorders displayed in Table 1. These disorders, with the exception of exhaustion disorder, are defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), the most widely used taxonomy for psychiatric syndromes. The core symptoms for each CMD according to DSM-5, the fifth and current version of the system¹¹, are displayed in Table 1. Core features of exhaustion disorder, a disorder accepted in the Swedish version of the International Statistical Classification of Disease and Related Health Problems, tenth revision (ICD-10)¹², are also shown in Table 1.

Although CMDs are covered broadly in the present thesis, particular focus is placed on the investigation of processes in exhaustion disorder (ED) and social anxiety disorder (SAD). Therefore, these disorders will be described in more detail. ED is classified among reactions to severe stress, ICD-code F43.8 in the Swedish version of the ICD-10¹². The main characteristic is prolonged exposure to non-traumatic stressors, which has resulted in aversive cognitive, emotional and physical symptoms. Symptoms of psychological and physical exhaustion have to be present for at least 2 weeks, developed as a consequence of identifiable stressors present for at least 6 months. A significant lack of psychological energy dominates the picture, combined with disturbed concentration or memory, decreased ability to cope with demands, emotional instability, sleep disturbance, substantial physical weakness and physical symptoms such as ache, palpitation, dizziness, or sensitivity to sound. Symptoms should cause clinically significant suffering or impairment^{12,13}. ED frequently co-occurs with depression, anxiety and sleep disturbances, but can occur without these conditions^{13,14}. Notably, clarifying its relation to other disorders, especially depression, was an important aspect of development and classification of ED¹². The concept of burnout, and particularly clinical burnout, can be viewed as an international equivalent to ED¹⁴. A main difference, however, is the focus on work stressors in burnout, while ED criteria do not explicitly point to the source of stress. Rather, stressors in ED often reside both in work and non-work life¹⁵. In Sweden, ED is one of the leading causes of long-term sick leave¹⁶.

SAD is defined according to DSM-5¹¹ by: (a) Marked fear of one or more situations where the individual is exposed to scrutiny by others; (b) The individual fears acting in a way, or showing anxiety, that will lead to being negatively evaluated; (c) The social situations almost

¹ The term often refers to anxiety disorders and depression only¹⁰, but will include sleep disturbance and stress-related disorders in the present thesis because of their high prevalence.

always provoke anxiety; (d) The social situations are avoided or endured with intense fear or anxiety; (e) The fear/anxiety is out of proportion to actual threat; (f) The fear/anxiety/avoidance has lasted 6 months; and (g) The fear/anxiety/avoidance leads to significant distress or functional impairment. The studies in the present thesis were conducted before the change from DSM-IV to DSM-5. Although some changes in diagnostic criteria have been made that may have clinical implications (e.g., the shift from focusing on embarrassment and humiliation to the broader fear of negative evaluation may capture a larger group of patients) ^{17,18}, the criteria are largely similar in the two versions.

Table 1. *Core symptoms for each common mental disorder*

Disorder	Core symptoms (duration criteria)
Social anxiety disorder	A persistent fear of one or more social situations where the individual is exposed to scrutiny by others, associated with fear of being negatively evaluated (> 6 months)
Panic disorder	Recurring, unexpected panic attacks, associated with worries about additional attacks and/or their implications and/or behavioral changes (> 1 month)
Generalized anxiety disorder	Excessive worry concerning a number of events, and difficulties to control the worry (> 6 months)
Obsessive-compulsive disorder ^a	Presence of obsessions (recurrent and persistent thoughts, urges, or impulses; associated with anxiety or suffering) and/or compulsions (repetitive behaviors or mental acts, aimed at reducing anxiety or preventing feared outcomes)
Post-traumatic stress disorder ^a	Exposure to a traumatic event, leading to intrusive symptoms; avoidance of trauma-related stimuli; alterations in cognitions and mood; and alterations in arousal and reactivity (>1 month)
Specific phobia	Intense fear or anxiety when exposed to specific objects or situations (> 6 months)
Major depressive disorder	Consistent depressed mood and/or loss of interest/pleasure in daily activities (>2 weeks)
Insomnia	Difficulties initiating or maintaining sleep, or non-restorative sleep (>3 months, at least 3 nights per week)
Adjustment disorder	Emotional or behavioral symptoms in reaction to one or more identifiable stressors
Exhaustion disorder ^b	Physical and psychological exhaustion (> 2 weeks), developed as a consequence of prolonged exposure to identifiable stressor(s) (> 6 months)

Note. Core symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) ¹¹. Although there are some changes in diagnostic criteria from the former version (DSM-IV) ¹⁹, core symptoms are largely unchanged. ^aObsessive-compulsive disorder and post-traumatic stress disorder are found among *obsessive-compulsive and related disorders* and *trauma and stressor-related disorders*, respectively, in the DSM-5, but are for conceptual reasons listed among the anxiety disorders in this table. ^bCriteria according to the Swedish version of the International Statistical Classification of Disease and Related Health Problems, tenth revision (ICD-10) ¹².

2.1.2 Processes that maintain common mental disorders

Although mechanisms that maintain a disorder in some instances differ from treatment mechanisms, they are often interchangeable²⁰. Thus, for effective treatment of CMDs, understanding of their maintaining processes is of importance as it gives clues to treatment components that could effectively act on these processes. One pragmatic division of processes into categories, although not separate entities in reality, can be made using the distinction psychological process (e.g., behavioral and cognitive) vs. biological/physiological process (i.e., inflammation in the present thesis). These constitute two perspectives, or observational levels, in the pursuit of understanding the mechanisms that maintain these disorders. In the following, hypothesized maintaining processes of CMDs will be outlined. For psychological processes, generic maintaining factors for CMDs will be reviewed briefly, but the main focus will be on exhaustion disorder and social anxiety disorder. For inflammatory processes, the scope will include all CMDs.

2.1.3 Maintaining processes - psychological

2.1.3.1 Generic maintaining factors

A cognitive-behavioral account of psychiatric disorders is based on learning theory and/or cognitive/information processing theory. Following is a brief description of key assumptions.

From a learning theory perspective, CMDs can largely be understood from classical and operant principles. Stimuli functions (e.g., from an unconditioned stimulus) can transfer to other stimuli (a conditioned stimulus) due to pairing²¹. This way, a former neutral stimulus can elicit a similar response (conditioned response) as elicited by the unconditioned stimulus (unconditioned response). For example, a car accident may cause former neutral stimuli (e.g., driving a car, traffic in general, certain sounds, or a particular road) to elicit strong emotional reactions, for example intense fear. Further, the conditioned stimulus and response now act as antecedents for operant behavior, that is, behavior that is emitted due to its consequences. Behavior probability is increased by reinforcement (positive or negative) and decreased by punishment (positive or negative)²². To build on the former example, avoidance of high-traffic areas or planning the driving route ahead might be strengthened by the effect of reducing fear and anxiety (negative reinforcement). This way the behavior has beneficial effects in the short term (e.g., decrease in aversive feelings), while the long-term effects are that the conditioned stimuli (e.g., driving on busy roads) continues to elicit fear, as extinction (presenting the conditioned stimulus without the unconditioned stimulus) is hindered. Importantly, avoidance in its various forms impedes value-driven behavior that could provide access to positive reinforcement, which can result in long-term consequences for mood. Thus, emotional problems can be viewed as acquired through classical conditioning and maintained through operant conditioning. Of note, the behavioral principles just described interact with language and cognition so that the impact of direct contingencies can be altered (e.g., stimuli can be related without actual pairing, as described in relational frame theory, and verbal stimuli in the form of instructions/rules can come to compete with direct contingencies)²³.

This line of research is gaining support ²⁴, but the following section will rather describe the traditional information processing perspective of cognition, which is a central theoretical basis for many evidence-based treatments for CMDs.

According to cognitive theory, maladaptive cognitions are central to the maintenance of emotional distress ²⁵. In Beck's cognitive model of emotional disorders, enduring negative beliefs (e.g., about failure and self-worth in depression, and danger/threat in anxiety) lead to biased information processing (based on the negative beliefs) which in turn result in negative automatic thoughts (i.e., negative and threat-focused thoughts, interpretations and images) ²⁶. For example, an important cognitive bias, especially in anxiety disorders, is the overestimation of the probability of an aversive event, as well as the overestimation of the potential cost of such an event ²⁷. Also, selective attention biased toward negative information is found in emotional disorders ^{28,29}. As to behaviors, they have a central role also in cognitive theory, although their role is framed differently compared to learning theory. Avoidance, escape and safety behaviors (i.e., behaviors intended to prevent feared catastrophes) hinder corrective information that could have positive impact on cognitive content ³⁰⁻³².

Thus, dysfunctional behaviors and distorted thinking are core units of analyses regarding maintenance of mental disorders. These patterns come in several forms, for example avoidance of feared stimuli or deficits in relaxing behaviors/skills, or biased thinking that involves overestimation of threat or concerns limited confidence in one's own abilities to cope ³³. Hypothesized maintaining processes of specific disorders often lean on learning theory, cognitive theory, or a combination of the two. The general principles of these theories are often detailed to the specific disorder in development and research on maintaining processes. Below follows a description of central maintaining factors in exhaustion disorder and social anxiety disorder, respectively. The processes outlined for exhaustion disorder are mostly consistent with learning theory, while the ones for social anxiety disorder are based on a cognitive maintenance model.

2.1.3.2 *Exhaustion disorder*

The present thesis focuses specifically on deficits in recovery as a central factor in the genesis and maintenance of stress-related problems ³⁴⁻³⁶ (although numerous other theories of the potentially aversive consequences of prolonged exposure to non-traumatic stressors exist). Reactions to exposure to stress do not, in this perspective, constitute a long-term problem as long as adequate recovery is present. Recovery refers to psychophysiological unwinding, that is, both mental and physiological relaxation ³⁴. Figure 1 is based on the model by Geurts and Sonnentag ³⁴, and displays a theoretical model that links stress exposure and potential aversive long-term consequences. Exposure to stressful life circumstances or events (only referred to as work stress in the original model) activate physiological systems (e.g., the sympathetic nervous system and the hypothalamic-pituitary-adrenal [HPA] system) to enable effective handling of the stressor at hand ^{34,37}. In the short term, this effort is associated with harmless load reactions such as accelerated heart rate and temporary fatigue. However, with

incomplete recovery, physiological systems do not stabilize which can result in long-term health problems such as chronic fatigue and tension, as well as somatic disease ³⁴.

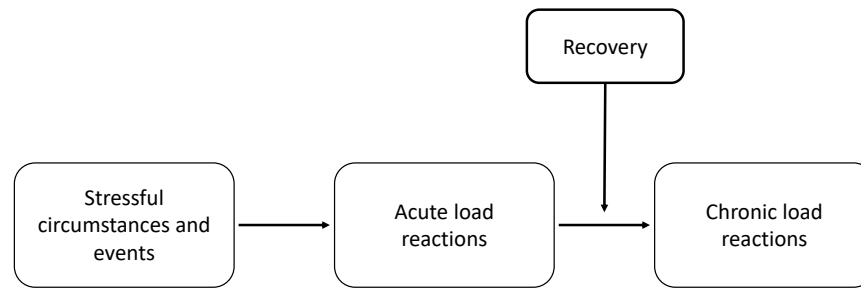


Figure 1. Model of relations between stressors, load reactions and recovery based on the model by Geurts and Sonnentag ³⁴.

Given the importance of recovery, what factors impede this beneficial process? From a learning theory perspective, deficits in recovery (i.e., recuperating behaviors) can be viewed as caused by external and internal events that reduce such behaviors, i.e., the absence of reinforcers or the presence of punishers ³⁸. For instance, taking breaks at work could be followed by both punishment (e.g., comments from colleagues and feelings of guilt) and lack of reinforcement (e.g., limited social interaction available), leading to reduced future probability of the behavior. This is in line with a behavioral account of depression, which emphasize that reinforcement is more readily provided for depressed behavior (in this context equivalent to stress-induced, or acute load induced, behavior) than for non-depressed behavior (recuperating behavior in the context of stress) ³⁹. Moreover, antecedents of recuperative behavior might be largely lacking, i.e., clear environmental triggers for such behaviors are absent.

Further, cognitive factors, such as worry and rumination, can play a central role in prolonging physiological activation ⁴⁰. Worry can be defined as a chain of negative thoughts and images, uncontrollable in nature, and concerns mental problem-solving of future events with possibly negative outcomes ⁴¹. Rumination, in the context of stress, can be defined as negative, repetitive and passive focus on stressors and problems ^{34,40,42}. These perseverative cognitions (i.e., worry and rumination) can impede psychophysiological unwinding and prolong the effect of stressors. In other words, lack of psychological detachment from stressors is an important contributor to incomplete recovery ⁴³ and perseverative cognitions have been found predictive of exhaustion and fatigue ^{44,45}. From a behavioral perspective, worry and rumination can be viewed as verbal behaviors, maintained by both negative and positive reinforcement (e.g., being associated with inactivity it reduces exposure to the actual problems at hand, and it might be intermittently followed by a feeling of things making sense) ^{38,46}.

Finally, sleep is central to recovery, a fundamental source of deactivation and psychophysiological unwinding. Low sleep quality (particularly nonrestorative sleep and

trouble falling asleep) have been found associated with poor recovery, which in turn relates to level of exhaustion⁴⁷. Also, insufficient sleep may predict future exhaustion³⁶, and sleep disturbance is a common feature in exhaustion disorder^{14,48}. Thus, sleep disturbance seems to be an important factor in both the development and maintenance of exhaustion. Importantly, a factor contributing to sleep disturbance in stress is perseverative cognitions⁴³.

2.1.3.3 *Social anxiety disorder*

Several models that detail key cognitive and behavioral factors central in the maintenance of social anxiety disorder (SAD) exist⁴⁹⁻⁵². These models are all relatively consistent and emphasize the same main processes including negative social-evaluative cognitions, attentional bias, avoidance and safety behaviors, and anticipatory and post-event processing⁵³. Findings of systematic reviews shows empirical evidence for the importance of these processes in the maintenance of SAD⁵³⁻⁵⁶.

Presumably the most influential and empirically supported model of maintaining processes in SAD is the cognitive model of Clark and Wells published in 1995⁵². The model is displayed in Figure 2 (for clarity, not all causal arrows are depicted) and stipulates the following^{52,57,58}: When an individual with SAD enters a social situation, negative beliefs are activated. These consist of negative assumptions about themselves and the social environment, and specifically revolve around acting in an unacceptable way that will lead to catastrophic consequences. This leads to a perception of social danger/threat (negative automatic thoughts) that triggers anxiety, including somatic and cognitive symptoms. Further, four processes are outlined that maintain negative beliefs and social anxiety. First, perception of social danger results in a shift to self-focused attention and the individual starts to monitor and observe herself, with a corresponding decrease in observation of the social environment. This initiates what is referred to as 'processing of self as social object'. Second, and as a consequence, interoceptive information is used to make inferences about the impression made on others, often resulting in excessively negative self-judgements. Thus, the individual uses anxious feelings and distorted images to create an impression of how she appears to others. Third, safety behaviors, both overt and covert, are used to prevent feared outcomes and reduce the risk of negative evaluation. However, they result in maintained negative beliefs, and increase feared symptoms as well as self-focused attention. Fourth, although not explicated in the graphic model, anticipatory and post-event processing (i.e., worry and post-mortem rumination) are emphasized as important maintaining factors for social anxiety. Worry about an upcoming social event puts the individual in an anxious and self-focused mode, which reduces the likelihood of noticing being accepted by others. It can also lead to avoidance of the situation altogether. Post-mortem rumination means to review a social situation in detail after the event, and includes using interoceptive information to infer performance, which (again) results in an overly negative evaluation.

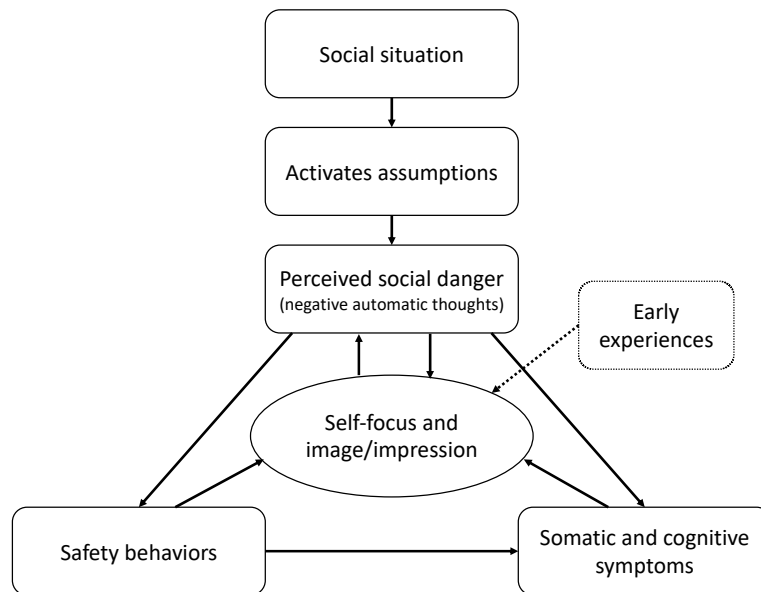


Figure 2. Cognitive model of social anxiety disorder according to Clark and Wells ⁵².

An interesting addition to the original model concerns that the content and meaning of negative and distorted self-images, a key factor in the maintenance of SAD, may be linked to memories of socially traumatic events ^{59,60}. Thus, adverse social experiences (e.g., being bullied by peers) may be involved in the development of negative images (distorted witnessing the self from an observer’s perspective), which are activated in later social situations. In some current versions of the model, *early experiences* have been added as a factor affecting *self-focus and image/impression* ⁶¹.

2.1.4 Maintaining processes - inflammatory

In addition to what can be termed psychological factors, investigation of biological processes that potentially contribute to, and maintain, CMDs can give additional information on how to relieve symptoms. During the past decades, immune dysregulation, and specifically inflammatory markers such as pro-inflammatory cytokines, has gained scientific interest as a factor involved in mental disorders.

2.1.4.1 Immune-to-brain communication

Pro-inflammatory cytokines are proteins that act as messengers in the immune system and coordinate local and systemic inflammation. They also communicate about bodily states to the brain through humoral and neural pathways ⁶². This way, immune activation can induce the so called “sickness response”, a motivational state that promotes recovery, including loss of appetite, depressed mood, anxiety, sleepiness, increased pain sensitivity, withdrawal from social activities, and fatigue ^{63,64}. Experimentally, when lipopolysaccharide (endotoxin) is administered to healthy individuals (to mimic a real bacterial challenge) a transient inflammatory response is induced and symptoms of the sickness response are displayed ^{64,65}. In the face of immunological challenges (e.g., bacteria, viruses and parasites), this response promotes adaptive behavioral changes (e.g., triggers resting and limits exposure to additional

pathogens). However, when inflammation is elevated over prolonged periods, the sickness response might be maladaptive. Pro-inflammatory cytokines can impact serotonin, norepinephrine and dopamine, important regulators of affect ⁶⁶, and when chronically elevated contribute to symptoms central to CMDs. Although not clearly established, possible sources of low-grade inflammation are psychosocial stress, physical inactivity, poor diet, smoking, obesity, altered gut permeability, disturbed sleep and vitamin D deficiency ⁶⁷.

2.1.4.2 *Brain-to-immune communication*

Importantly, the immune-brain relation is bidirectional, i.e., the brain also communicates to the immune system. For example, threat (or perceived threat) activates the fast sympathetic pathway and the relatively slower hypothalamic–pituitary–adrenal (HPA) pathway. This results in secretion of norepinephrine, epinephrine and cortisol, neurotransmitters and hormones that the immune system express receptors for ⁶⁸. Thus, psychological challenges can, as well as pathogens, impact the immune system. A recent meta-analysis investigated the effects of acute laboratory stress on inflammatory markers ⁶⁹. Results showed that psychological stress (e.g., induced by social evaluative threat or a difficult puzzle task) lead to significant increases in inflammatory markers (although large variability between individuals was found). Equally, prolonged exposure to stressors can affect and dysregulate the immune system ⁷⁰.

2.1.4.3 *Inflammation in common mental disorders*

Chronic low-grade elevations of inflammatory markers might be one physiological factor contributing to symptoms in CMDs. The association between CMDs and inflammation has especially been studied with regard to depression. Several meta-analyses of cross-sectional associations have found elevated inflammatory markers in depressed patients compared to healthy controls ⁷¹⁻⁷³. For anxiety, a recent meta-analysis found inflammatory markers to be elevated in people with anxiety disorders, including post-traumatic stress disorder and obsessive-compulsive disorder, compared to healthy controls ⁷⁴. However, this difference was accounted for by post-traumatic stress disorder (i.e., no associations were found in the remaining disorders, however examined with lower statistical power). Consistently, a previous meta-analysis of post-traumatic stress disorder found elevated inflammatory markers compared to healthy controls ⁷⁵, while results for other anxiety disorders are mixed ⁷⁶⁻⁷⁸. A meta-analysis on sleep disturbance found associations with elevated inflammatory markers ⁷⁹. For stress-related symptoms of burnout, elevated inflammatory markers have been found compared to controls ⁸⁰, but there are also negative findings ^{81,82}.

The causal relation between emotional symptoms and inflammation is yet to be elucidated. For example, a meta-analysis of longitudinal studies found small but significant associations between inflammatory markers and subsequent depressive symptoms ⁸³, but studies also support that depressive symptoms predict subsequent changes in inflammatory markers ⁸⁴. Given the bidirectional communication between the central nervous system and immune system, effects might be reciprocal. Nonetheless, inflammatory activity might be a

physiological process that contribute to CMDs, and symptomatic improvement following effective treatment might involve changes in inflammatory processes.

2.2 COGNITIVE BEHAVIOR THERAPY (CBT) AND CHANGE PROCESSES IN COMMON MENTAL DISORDERS

2.2.1 Effectiveness of CBT

Cognitive behavior therapy (CBT) is an umbrella term that includes a variety of treatments based on cognitive and/or learning theory, that share a common focus on the relations between thought, behavior and emotion. Due to the extensive empirical study of its effectiveness, CBT is argued to be the gold standard of psychotherapies⁸⁵. Meta-analyses of randomized controlled trials have shown face-to-face CBT to be effective/efficacious, yielding large effect sizes, for anxiety disorders⁸⁶⁻⁹², depression⁹³ and insomnia^{94,95}. Also, CBT delivered as guided self-help has shown to be efficacious for these disorders⁹⁶⁻⁹⁸. For stress-related disorders the evidence base for CBT is less convincing than for other CMDs. For work-related stress, a synthesis of systematic reviews found CBT to produce larger effects than other interventions⁹⁹. However, meta-analyses of diagnosed samples have failed to find superior improvements of CBT compared to control conditions for both adjustment disorder¹⁰⁰ and exhaustion disorder¹⁰¹. Although recent randomized trials have found promising results of CBT for these disorders^{102,103}, the effectiveness of CBT remains uncertain.

Important from a dissemination perspective, stepped care models have been suggested as a viable solution to increase access to evidence-based psychological treatments¹⁰. In such models, patients are first offered a low-intensity treatment (e.g., guided self-help, requiring less time from the professional) and those patients who do not respond are stepped up to treatment of higher intensity (e.g., face-to-face treatment)¹⁰⁴. However, results of previous research on stepped care models for CMDs have been mixed¹⁰⁴⁻¹⁰⁹, and it is still unclear whether patients who do not respond to guided self-help CBT would benefit from face-to-face CBT.

Moreover, effects of CBT for CMDs have most commonly been evaluated with regard to symptom improvements. Outcomes focusing on function, such as reductions in sick leave following CBT, have been investigated but to a lesser extent. A recent meta-analysis found that psychological interventions, including CBT, significantly reduced sick leave, but that effect sizes were small¹¹⁰. There was no significant difference in effect between the interventions that were compared to care as usual in this meta-analysis, e.g., return-to-work interventions (RTW-I) that had a clear work-focus and interventions that mainly focused on symptom reduction (e.g., CBT) produced similar effects on sick leave.

Further, even though CBT produces significant improvements in symptoms, a substantial proportion of patients are not sufficiently helped. For anxiety disorders, reviews have found that between a third and half of patients were classified as non-responders at post-treatment ^{111,112}. For depression, we showed in a recent meta-analysis of CBT in primary care that although CBT was more effective than control conditions, 51% of patients were classified as non-responders post-treatment ¹¹³.

In sum, even though CBT is very helpful for many patients, there are several areas that could be improved. Aside from issues concerning delivery models that can increase accessibility and questions concerning how return to work from sick leave can be ameliorated, there is also room for considerable improvements in symptom reduction. Investigation of mechanisms of change in CBT for CMDs is one important way to enhance treatments effects. As of today, we know little about how change comes about in CBT, hindering optimal treatment delivery.

2.2.2 Mechanisms of change

What changes unfold during CBT that lead to improvement? One crucial way of enhancing CBT's effectiveness is to increase knowledge of treatment mechanisms. Mechanisms in this context refer to the basis of the effect of CBT, that is, the chain of events or processes that explain how therapeutic change comes about ¹¹⁴. In essence, key treatment components (i.e., the active ingredients) lead to enduring changes in mechanisms (e.g., cognitions or behaviors), which in turn lead to some beneficial outcome (i.e., the goal of treatment, e.g. reduction in anxiety or increased function) ^{115,116}. Identifying change mechanisms is vital for treatment development and gives information on how to optimize key treatment components ²⁰. Also, research on mechanisms can provide suggestions on how to streamline treatments, by removing ineffective components from the treatment protocol. For the clinician, this revolves around the critical question of what should be said and done to maximize the probability of effectively helping the patient. A better understanding of mechanisms can also help to discover moderators of treatment outcome (i.e., characteristics that affect the relation between an intervention and outcome) which concerns matching patients with treatment to improve benefit ^{20,117}.

Although change mechanisms are far from fully elucidated for any psychiatric disorder ^{20,114}, knowledge from different scientific approaches (e.g., experimental and observational research on psychopathological processes) continuously contribute with small pieces of the puzzle. One essential area of research in this respect is the study of processes and mediators in the context of clinical trials. A mediator is a variable that statistically explains the relationship between an independent variable (e.g., treatment) and a dependent variable (e.g., anxiety) ¹¹⁴. Baron and Kenny ¹¹⁸ introduced a path diagram to depict the causal chain involved in mediation, as well as an analytic strategy to establish mediation. The diagram is displayed in Figure 3.

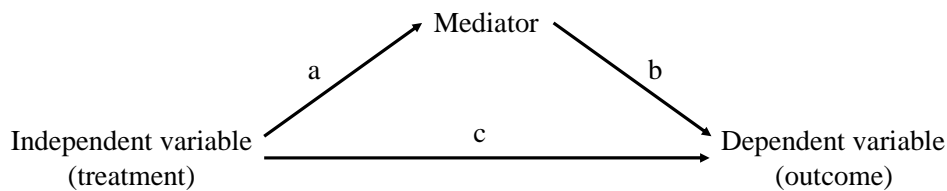


Figure 3. Mediation model by Baron and Kenny ¹¹⁸.

Baron and Kenny suggested that a variable function as a mediator when the following criteria are met: (1) the independent variable affects the mediator (i.e., the a-path), (2) the mediator affects the dependent variable (i.e., the b-path), and (3) the previously significant effect of the independent variable on the dependent variable (i.e., the c-path) is reduced or eliminated when controlling for the mediator (i.e., paths a and b). Although seminal, the analytic procedures proposed by Baron and Kenny have received criticism (e.g., concerning that significant mediation can exist even in the absence of a significant c-path) and alternative methods have been recommended ¹¹⁹. Nevertheless, the conceptual aspects of investigating the respective causal paths are still relevant.

In clinical trials, investigation of pre-to-post changes in proposed processes and outcome can be a first step to look for associations that might give suggestions for future research. However, a vital criterion for a mediator is that it precedes outcome. The influential article by Kazdin from 2007 ¹¹⁴ highlights evaluation of a timeline, i.e., the temporal precedence criterion. This concerns the above described b-path, i.e., the effect of the mediator on the outcome. Both potential processes/mediators and outcome need to be assessed at several times during treatment to answer the crucial question of the temporal relations between changes in mediator and outcome. Of note, a statistically established mediator gives clues to mechanisms of action, but does not necessarily mean that a mechanism has been revealed, i.e., the mediator could be a proxy for another variable ¹¹⁷. As argued by Kraemer and colleagues, “all mechanisms are mediators, but not all mediators are mechanisms” ¹²⁰ (p. 878). Further, a mediator might give some explanation of how change came about, but leave much more to be investigated. For example, finding that self-efficacy mediates improvements in anxiety does not explain how change in self-efficacy leads to that change (i.e., multiple other processes could be involved) ²⁰. Nevertheless, a mediator points the direction for future inquiries and the study of processes and mediators in clinical trials is a step towards understanding mechanisms of change.

2.2.3 CBT and psychological change processes

2.2.3.1 Key treatment components in CBT and proposed mechanisms

Simplified, CBT components can broadly be categorized as behavioral (e.g., behavioral activation and exposure) or cognitive (e.g., cognitive restructuring and behavioral experiments) based on their supposed target. Although sometimes used in isolation, several components are often incorporated in treatment packages, including psychoeducation on the

nature of core symptoms; behavioral activation; exposure; cognitive restructuring; behavioral experiments; safety behavior manipulation; relaxation; and response and relapse prevention¹²¹. In the following, a short description of four key components related to presumed change processes is outlined.

Behavioral activation, originally designed for treatment of depression, is based on the assumption that insufficient positive reinforcement is the cause of depressed mood¹²². Correspondingly, behavioral activation is a reinforcement-based treatment, aiming to reduce avoidance and increase activation to access positive reinforcement and consequently improve mood^{38,123}. Given the recurrent reduction in goal-directed and pleasant activities across mental disorders, it has been suggested that rather than constituting a treatment for depression, behavioral activation should be a broadly integrated part in psychotherapy¹²⁴.

Exposure refers to the systematic approach to feared stimuli. Depending on the feared stimuli, exposure can be categorized *in vivo* (i.e., approach to a real-life situation, such as public speaking for a person with social anxiety disorder), *imaginal* (e.g., memory work in post-traumatic stress disorder), or *interoceptive* (e.g., exposure to feared bodily sensations in panic disorder). The mechanism by which exposure exerts its effects on anxiety/fear is suggested to be fear extinction: the conditioned stimulus is faced repeatedly in the absence of the associated aversive event (i.e., the unconditioned stimulus)¹²⁵. Previously, habituation (i.e., fear reduction during exposure) was thought a necessity for fear extinction, but a more modern view rather stresses the importance of inhibitory learning (although habituation might still be involved)^{125,126}. Inhibitory learning means that the therapeutic goal is not to eliminate the association between the conditioned and unconditioned stimulus during exposure. Rather, new learning comes to compete with it (i.e., that the conditioned stimulus no longer predicts the unconditioned stimulus)¹²⁵. Thus, the conditioned stimulus now has two meanings (i.e., one that can elicit fear, and one signaling safety).

Cognitive restructuring is a treatment component that aims to (a) identify key maladaptive beliefs and thoughts central to emotional distress, and (b) evaluate and challenge them to generate more adaptive and functional thinking patterns²⁶. Its proposed mechanism of change is that changes in biased information processing and negative thinking is responsible for reductions in emotional symptoms. In other words, cognitive reappraisal is the core process believed to be affected by this strategy, and subsequently have impact on symptoms.

Behavioral experiments refer to confrontation with anxiety-provoking situations to test whether feared outcomes actually occur⁵⁸. Safety behaviors are dropped and focus of attention is directed to maximize disconfirmation of negative predictions⁵⁷. Behavioral experiments draw on information-processing theory and can be viewed as an extension of cognitive restructuring¹²⁷. Behavioral experiments overlap with exposure, especially within its inhibitory learning framework, but differences between the two have been outlined, for example the testing of explicit cognitions in the former¹²⁵.

Given that treatment protocols often include several components, elucidation of component-mechanism-outcome relations is generally difficult. Even in cases where treatments have distinct components that link to suggested mechanisms, the proposed causal pathways are not always supported by empirical data. There are some influential studies that have contributed with important knowledge in this regard. For example, a component-analysis of depression treatment randomized patients to (a) behavioral activation, (b) behavioral activation + work to modify automatic thoughts, or (c) behavioral activation + work to modify automatic thoughts + focus on core schemas¹²⁸. Results showed there was no difference between treatments in outcomes (i.e., depressive symptoms and diagnostic status), and importantly, they all produced similar changes in maladaptive cognitions. As suggested in a review evaluating mechanisms of change in treatment of depression, cognitive changes seem to mediate therapeutic improvement, but changes in cognition might not be specific to cognitive interventions¹²⁹. Thus, what might intuitively seem to be related (e.g., cognitive restructuring and cognitive change), could in fact also involve other causal routes (e.g., behavioral activation and cognitive change).

In the following three sections, I will describe processes potentially relevant for treatment outcome in more detail within three different areas: (a) psychological change processes in CBT for exhaustion disorder, (b) psychological change processes in CBT for social anxiety disorder, and (c) inflammatory correlates in CBT for CMDs broadly.

2.2.3.2 Change processes in CBT for exhaustion disorder

No evidence-based treatments exist for exhaustion disorder (ED). The treatment protocol used in the present thesis was developed by our research group, and is based on a model highlighting deficits in recovery, particularly recuperating activities but also associated with sleep, as central maintaining factors of exhaustion³⁴⁻³⁶.

Treatment content is displayed in Table 2. It includes several typical CBT components. Behavioral activation is a central focus in treatment, based on the protocol by Lejuez and colleagues¹²³. It includes all parts of the original protocol (monitoring of activities and mood states, identification of values and specific activities in accordance with values, prioritizing among activities, activity scheduling, and evaluation of consequences of behaviors/activities) but places a specific focus on increasing activities that serve a recuperating function. For example, concerning monitoring of activities and their consequences, patients not only rate pleasure and importance of activities, but also recuperating effects. Thus, in addition to its original focus on alleviating depression, the behavioral activation component in the present protocol aims at increasing recovery, presumably by frequently inducing relaxation both mentally (e.g., slow thoughts down) and physiologically (e.g., decreased arousal). The behavioral activation component is present in every session of treatment as well as in homework exercises. Additionally, a brief relaxation exercise is taught to patients early in treatment as a specific activity for recovery, and frequent use is encouraged.

Increased recovery from sleep may be vital for exhaustion improvement⁴⁷. Strategies to enhance sleep quality were included in treatment if deemed meaningful to the specific patient. These strategies includes both specific components (such as limiting time in bed and adhering to scheduled sleep times) and more indirect approaches that also could be part of the behavioral activation (such as increasing light exposure, physical activity and daytime relaxation). The treatment also includes functional analyses and exposure, as anxiety (and associated fear-avoidance patterns) is common in ED¹⁴.

Table 2. *Session content and homework exercises of cognitive behavior therapy for exhaustion disorder*

Session	Main focus of session	Main homework
1	Psychoeducation about stress, exhaustion disorder and CBT	Monitoring of activities; idiosyncratic model of development of exhaustion
2	Recuperating activities, brief relaxation technique	Monitoring of activities; planning of recuperating activities
3	Life areas, values and activities	Monitoring of activities; planning of recuperating activities; register values and activities
4	Life areas, values and activities	Monitoring of activities; planning of recuperating activities; register values and activities, and prioritize among activities
5	Scheduling of activities (recuperating and according to values)	Activity scheduling and monitoring
6	Emotion-driven behaviors, functional analysis and exposure	Activity scheduling and monitoring; functional analyses
7	Emotion-driven behaviors, functional analysis and exposure	Activity scheduling and monitoring; functional analyses
8-10	Optional: sleep, communication skills or dysfunctional assumptions	Activity scheduling and monitoring; functional analyses; according to chosen component
11	Relapse prevention	Action plan

Note. Treatment was scheduled for 9 to 13 weekly sessions. CBT = cognitive behavior therapy.

Although it is theoretically reasonable to target recovery, research on processes and mediators of change in CBT for stress and burnout generally, and ED specifically, is scarce. Consequently, there is limited knowledge regarding crucial processes of change in ED. However, a few trials give clues to potential process targets.

One trial, consistent with the theoretical model put forth earlier, investigated the effects of a recovery-focused program³⁵. Participants with stress-related complaints took part in a group-based intervention that focused on increasing behaviors with recuperating effects. Relaxation training was also included in the program. Main findings were that frequency of recovery behaviors increased, while perceived stress, anxiety, depression and exhaustion decreased. Further, changes in frequency of recovery behaviors, as well as worry, predicted symptom change. Although results were promising, some methodological limitations (e.g., that the trial

was not randomized and that assessments were only conducted pre- and post-treatment) hinder conclusions regarding both effects on outcome and presumed change processes.

Another study relevant to the presumed importance of recovery investigated teachers with sleeping problems and work-related strain⁴³. Participants were randomized to an internet-based recovery intervention or waitlist control condition. The intervention primarily focused on promoting restorative behavior, but also included specific sleep-enhancing strategies and meta-cognitive techniques to target perseverative cognitions. An important finding was that increased number of recuperating activities was associated with reductions in perseverative cognitions, which in turn was associated with improvements in sleep. Of importance for causal claims, assessments of mediators (recovery behaviors and perseverative cognitions) and outcome (insomnia severity) were not repeated throughout the treatment period.

In a study by Ebert and colleagues¹³⁰, employees with elevated symptoms of perceived stress were randomized to a CBT-based intervention delivered via the internet or a waitlist control group. The intervention consisted of problem-solving, relaxation and emotion regulation techniques. In a pre-to-post mediational analysis, a significant indirect effect of emotion regulation on perceived stress was found in the intervention group relative to the waitlist. In line with the authors' description of limitations, other potential mediators were not measured and the mediator as well as outcome were not measured during treatment.

Another study randomized participants (a non-clinical sample at risk of strain and burnout) to a group-based CBT intervention (acceptance and commitment therapy) or a waiting list control group¹³¹. Assessments were completed at baseline, mid- and post-treatment and at six months follow up. Results showed that decrease in emotional exhaustion between mid-treatment and follow up was mediated by increase in psychological flexibility (i.e., the ability to focus in the present and move towards goals/values even when aversive thoughts or feeling are present) mid-treatment to post-treatment in the treatment group relative to the control condition.

In sum, there is to date limited research on potential processes/mediators of change in stress and burnout. Current studies have focused on elevated symptoms, but none have investigated clinical samples. Further, studies have typically not used repeated measures of mediators and outcome during treatment, hampering conclusions regarding temporal precedence. In the context of limited knowledge of how change unfolds in ED, generic processes (i.e., relevant across treatments and disorders) have been suggested to be important for symptom improvement. Two such processes, perceived competence and therapeutic alliance, might also be pertinent in CBT for ED. Perceived competence refers to an individual's belief in the ability to cope¹³². Therapeutic alliance refers to the working collaboration between patient and therapist¹³³. Both these processes might be related to behavior change, but might also influence outcome on their own^{132,134}.

2.2.3.3 Change processes in CBT for social anxiety disorder

CBT targets the presumed maintaining factors of social anxiety disorder (SAD) in several ways, aiming to achieve decreases in a variety of judgmental biases, self-focused attention, and avoidance and safety behaviors. The self-help treatment used in the present thesis¹³⁵ consist of components typically included in CBT protocols for SAD. Treatment components map to the presumed maintaining processes and include, for example, challenging evidence of NATs and behavioral experiments to correct negative social-evaluative cognitions, dropping of safety behaviors, practice in shift of attention to promote reduction in attentional biases, and exposure exercises to break patterns of avoidance as well as maintenance of fear-associated stimuli. Treatment content is displayed in Table 3.

Table 3. *Session content and homework exercises of self-help cognitive behavior therapy for social anxiety disorder*

Chapter	Main focus of the chapter	Main homework
1	Psychoeducation about SAD, CBT and self-help treatment	Self-screening for SAD
2	Thoughts in social anxiety and the cognitive model of SAD by Clark and Wells ⁵²	Self-monitoring of NATs and idiosyncratic model of SAD
3	Thinking errors and challenging thoughts	Self-monitoring of NATs and anxiety-triggered behaviors; challenging evidence for negative thoughts; goal-setting
4	Challenging thoughts through behavioral experiments	Behavioral experiments
5	Rationale for exposure	Establishing an anxiety hierarchy; exposure exercises
6	Focus of attention and manipulation of safety behaviors	Practice in shift of attention; behavioral experiments with and without safety behaviors
7	Problem-solving revolving exposure exercises	Continued exposure exercises, with additional attention on safety behaviors
8	Social skills in relation to previous avoidance	Assertiveness-training
9	Relapse prevention	Action plan including key learning from each chapter; goal evaluation

Note. Although not the main theme of any specific chapter, anticipatory and post-event processing is also covered in the treatment. SAD = social anxiety disorder; CBT = cognitive behavior therapy; NATs = negative automatic thoughts.

Several clinical trials of CBT have investigated the proposed maintaining factors according to the cognitive model of SAD as change processes. However, a majority of studies have used pre-post (or pre-mid-post) designs that impose limitations regarding causal inferences of process-outcome relations. Nevertheless, these studies provide valuable information insofar that CBT seem to reduce negative social-evaluative cognitions, self-focused attention,

avoidance, and safety behaviors, and that changes in these processes are related to outcome¹³⁶⁻¹⁴⁴. Thus, prior research support that CBT for SAD affects the outcome (i.e., the c-path in a traditional mediational analysis) and processes (i.e., the a-path), and that processes statistically account for change in the outcome (i.e., the mediated/indirect effect).

In addition, a few studies have used designs that fulfill one of the key criteria for the mediational b-path, namely temporal precedence, i.e., whether change in the processes occur before change in outcome¹⁴⁵⁻¹⁵⁰. In these studies, repeated assessment of processes and outcome during treatment has enabled analytic methods to investigate the timeline of change in CBT for SAD. An effect on subsequent social anxiety has been found for negative cognitions¹⁵⁰, overestimated probability and cost of negative social events^{145,149}, self-focused attention¹⁴⁵⁻¹⁴⁷, avoidance^{146,148}, safety behaviors¹⁴⁵, and anticipatory and post-event processing¹⁴⁶. Of note, the studies that also analyzed the possibility of a reversed direction of effects (i.e., reductions in social anxiety predicting subsequent changes in the presumed processes) found support for this claim regarding several of the investigated processes^{145,147-149}. An illustrating example comes from the analysis by Hoffart and colleagues¹⁴⁵. In this study, cognitive therapy for SAD resulted in a unidirectional effect of reductions in safety behaviors on subsequent reductions in social anxiety. However, the remaining processes investigated (i.e., self-focused attention, estimated probability and cost) predicted subsequent social anxiety, but were also predicted by prior reductions in social anxiety. Thus, a reciprocal relationship between the presumed processes of change and social anxiety has been found in previous research, and the true role of these processes is yet to be established. Importantly, limited evidence is available for the notion that changes in the proposed processes are responsible for reductions in social anxiety, and not vice versa. To streamline CBT for SAD, enhance its effectiveness and develop new treatment approaches, such information is vital.

2.2.4 CBT and inflammatory processes

Inflammatory processes, and specifically elevated levels of pro-inflammatory cytokines, might contribute to CMDs. Reversing this dysregulation could be part of symptom improvements following CBT. For example, cognitive and behavioral strategies could affect inflammatory markers through changes in HPA-axis and sympathetic activity¹⁵¹. For instance, reducing anxiety through exposure might affect sympathetic pathways that have impact on immune activity. More indirectly, CBT could impact potential sources of low-grade inflammation, such as diet and physical activity⁶⁷. Increased knowledge on physiological aspects of therapeutic change could offer insights to the potential benefit of novel treatment approaches (e.g., anti-inflammatory medication for depression¹⁵², or CBT in conjunction with exercise¹⁵³).

To the best of my knowledge, seven studies have investigated the potentially anti-inflammatory effects of CBT in CMDs^{151,153-158} (not including studies where patients had comorbid somatic conditions). Although designs vary across studies, symptoms and inflammatory markers were measured pre- and post-treatment in all of them. The specific

inflammatory markers measured differ between studies: interleukin-6 (IL-6) and C-reactive protein (CRP) were the most commonly assessed, followed by tumor necrosis factor alpha (TNF- α) and IL-8.

Five studies focused on depressive disorder. They all included measurement of IL-6 pre- and post-treatment. In three of the studies, IL-6 was significantly decreased after CBT ^{154,156,159}, but did not change in two ^{151,153}. CRP was assessed in three studies and decreased significantly in one ¹⁵⁹, but not in the other two ^{151,153}. TNF- α was assessed in two studies, and decreased significantly after CBT in both ^{156,159}. Further, three of the five studies also investigated if a reduction in inflammatory markers was associated with a reduction in depressive symptoms. Such a correlation was found in two of the studies ^{151,154}, while no significant relationship was found in one ¹⁵⁶. For insomnia, one study showed that CBT reduced systemic inflammation (measured by CRP) compared to a control condition ¹⁵⁷. Further, decreased CRP was associated with remission of insomnia at the follow-up 12 months post-treatment ¹⁵⁷. One study investigated inflammatory markers (IL-6, IL-8 and CRP) in CMDs broadly (depression, anxiety and stress-related disorders) ¹⁵⁸ and none of the markers were reduced following treatment.

In sum, results as to the potentially anti-inflammatory effects of CBT for CMDs are inconclusive. The findings of a recent meta-analysis, including studies on both CMDs and somatic conditions, confirm that there are inconsistencies between studies: in 14 of 23 studies at least one inflammatory marker was reduced following CBT, while in the remaining nine studies levels were unchanged or increased ¹⁶⁰. Thus, the role of inflammation in CBT for CMDs needs further investigation. Particularly, studies on diverse samples of patients with CMDs are largely lacking.

2.3 SUMMARY

Because of its strong research support, CBT has a prominent position among psychotherapies in the treatment of CMDs. Nevertheless, there is considerable room for treatment improvement. More knowledge about processes at work might lead to more effective and streamlined treatment. Exhaustion disorder and social anxiety disorder are two highly prevalent CMDs, but how change comes about in CBT for these disorders is to a large extent unknown. Moreover, inflammatory processes might be involved in symptomatic improvement across CMDs, but prior research is limited. Building on two large scale clinical trials of CBT for primary care patients, this thesis attempts to add pieces to the filling of these gaps of knowledge.

3 AIMS OF THE THESIS

Study I and II are effectiveness trials of CBT in a primary care setting. For the purpose of the present thesis, the treatment effects on symptoms found in these two clinical trials constitute the base for investigating processes and correlates of therapeutic change, the focus of Study III, IV and V.

- STUDY I:** The aim of Study I was to evaluate the effectiveness of three interventions: CBT, a return-to-work intervention (RTW-I), or a combination of the two (COMBO), on psychiatric symptoms and sick leave for primary care patients on sick leave due to CMDs. We hypothesized that CBT (alone or in the COMBO-intervention) would result in significant between-group effects on psychiatric symptoms compared to RTW-I. We also hypothesized that RTW-I (alone or in the COMBO-intervention) would generate significant between-group effects on sick leave compared to CBT.
- STUDY II:** The aim of Study II was to investigate a stepped care model for primary care patients with CMDs. In step 1, all patients received guided self-help CBT. In step 2, the additive effect of face-to-face CBT, compared to continued guided self-help CBT, was evaluated for patients not in remission after step 1. We hypothesized that approximately 50% of the patients would be in remission after guided self-help CBT in step 1. Further, we hypothesized that stepping up treatment intensity to face-to-face CBT would result in superior improvements compared with patients receiving continued self-help CBT in step 2.
- STUDY III:** The aim of Study III was to investigate mediators of change in CBT, relative to RTW-I, for exhaustion disorder (patients with at primary exhaustion disorder in Study I were analyzed). We had no a priori hypotheses concerning significant mediators due to limited prior research.
- STUDY IV:** The aim of Study IV was to investigate processes of change in patients with social anxiety disorder receiving guided self-help CBT (patients with a primary social anxiety disorder in Study II were analyzed). We hypothesized that improvements in the maintaining processes according to the cognitive model of social anxiety would predict subsequent improvements in social anxiety.
- STUDY V:** The aim of Study V was to investigate inflammatory markers in patients with CMDs: at baseline and after CBT (patients from Study I and II were included). We hypothesized that higher level of inflammation would correlate to more severe psychiatric symptoms at baseline. We also hypothesized that inflammatory markers would decrease after CBT, and that this reduction would correlate to symptom improvement.

4 THE EMPIRICAL STUDIES

The distribution of patients' primary disorders in the clinical trials (Study I and II) guided the choice of disorders to focus on for further analyses of psychological change processes (Study III and IV), as putative process variables were specific for each disorder. The distribution of primary disorders among patients in the studies is displayed in Table 4. Exhaustion disorder (Study III) was the only suitable diagnosis to analyze from Study I. The choice to focus on social anxiety disorder (Study IV) was based on the sample size in Study I, and that process measures were judged to be of particular high quality for this disorder. Inflammatory markers (Study V) were analyzed across both clinical trials, irrespective of primary disorder.

Table 4. *Primary disorder/problem area for patients in Study I-V, expressed as number of patients*

Disorder	Study I	Study II	Study III	Study IV	Study V
Exhaustion disorder	125	27	82		108
Major depressive disorder	27	78			59
Adjustment disorder	27	85			66
Generalized anxiety disorder	10	69			49
Post-traumatic stress disorder	7	-			5
Social anxiety disorder	6	64		61	39
Panic disorder	4	36			18
Obsessive-compulsive disorder	3	8			5
Insomnia	2	29			18
Total	211	396	82	61	367

Note. Specific phobia was not the primary disorder in any case, and is therefore not included in the table.

For the purpose of the present thesis, Study I and II will be described with emphasis on aspects relevant to Study III-V (e.g., long-term treatment effects will not be described here). Also, as methods and results are thoroughly described in the respective papers (Study I-V), I will only describe them briefly here.

4.1 STUDY I: COGNITIVE-BEHAVIOURAL THERAPY AND RETURN-TO-WORK INTERVENTION FOR PATIENTS ON SICK LEAVE DUE TO COMMON MENTAL DISORDERS: A RANDOMISED CONTROLLED TRIAL

4.1.1 Methods

4.1.1.1 Procedure and inclusion

Consecutively recruited adult patients ($N = 211$) from four primary clinics were randomized to cognitive behavioral therapy (CBT), a return-to-work intervention (RTW-I), or a combination of the two (COMBO). Main inclusion criterion was that patients were on a current sick leave due to a CMD (i.e., social anxiety disorder, panic disorder, generalized

anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, major depressive disorder, insomnia, adjustment disorder, or exhaustion disorder).

4.1.1.2 Primary outcomes

Primary outcomes were (a) psychiatric symptom severity on principal disorder measured by the 0-8 scored clinician-administered Clinician's Severity Rating (CSR)¹⁶¹, and (b) sick-leave status, collected from the registry of the Swedish social insurance agency, 12 months after start of treatment.

4.1.1.3 Treatments

The CBT condition consisted of available evidence-based disorder-specific protocols, applied for the patients' principal disorder. The specific protocols were: cognitive therapy for social anxiety disorder⁵⁷, panic disorder¹⁶² and post-traumatic stress disorder¹⁶³; applied relaxation for generalized anxiety disorder¹⁶⁴, exposure with response prevention for obsessive-compulsive disorder¹⁶⁵; behavioral activation for depression¹²³; CBT for insomnia¹⁶⁶; and an unpublished protocol, developed by the research group, for adjustment disorder and exhaustion disorder (described in the background of this thesis).

The RTW-I condition aimed specifically at helping the patient back to a sustainable work situation. The treatment was developed by the research group, influenced by previous research suggesting that sick-leave issues should be addressed early in treatment, that the employer should be involved in the process, and that graded exposure to the work place is important^{167,168}. The RTW-I included CBT-based psychoeducation on behavioral activation, exposure, recovery to counteract stress, sleep strategies and problem solving. The COMBO condition was a combination of CBT and RTW-I.

4.1.1.4 Statistical analyses

Mixed-effects models were used to estimate differences between conditions in CSR and days on sick leave. Cohen's *d* was used to estimate effect sizes for psychiatric symptoms. Chi-squared tests were used to estimate differences between conditions in proportions of patients on sick leave.

4.1.2 Results

Main findings were that (a) CBT led to significantly larger improvements in psychiatric symptom severity measured by CSR than RTW-I (Cohen's $d = 0.4$) at post-treatment, but no other differences in CSR between conditions were found, and (b) there were no differences between conditions in either days on sick leave or proportion of patients on sick leave.

4.1.3 Conclusion

CBT outperformed RTW-I in reducing psychiatric symptoms. However, when adding RTW-I to CBT (i.e., the COMBO condition), it was not superior to RTW-I alone, implying that the effects of CBT were somehow attenuated when making the intervention more extensive and

complex. Further, contrary to our hypothesis, the RTW-I (alone or in the COMBO condition) did not reduce sick leave compared to CBT. The question of how to more effectively help patients on sick leave due to CMDs back to a healthy work situation remains to be answered.

4.2 STUDY II: STEPPED CARE IN PRIMARY CARE - GUIDED SELF-HELP AND FACE-TO-FACE COGNITIVE BEHAVIOURAL THERAPY FOR COMMON MENTAL DISORDERS: A RANDOMIZED CONTROLLED TRIAL

4.2.1 Methods

4.2.1.1 Procedure and inclusion

Study II ran parallel to Study I. Consecutively recruited adult patients with CMDs, but not on sick leave, from the four primary clinics were included. Patients with sub-threshold disorder severity were also included (i.e., patients with symptoms within, but not fulfilling full diagnostic criteria for, a CMD). All patients ($N = 396$) received guided self-help CBT in step 1. Patients not in remission after step 1 were randomized to continued self-help CBT or face-to-face CBT. Patients with post-traumatic stress disorder were not included as the support for the efficacy of self-help treatments for this disorder was limited at the time of study start ¹⁶⁹.

4.2.1.2 Primary outcomes

The primary outcome was remission status, which was operationalized as scoring below a predefined cut-off on a validated disorder-specific self-rated symptom scale (type of scale was chosen in accordance with the patient's principal disorder). The scales were rated by patients at baseline, after step 1, and after step 2.

4.2.1.3 Treatments

In step 1, patients received a disorder-specific self-help book according to principal disorder. The self-help books ^{135,170-174} were based on evidence-based treatments, except the one for adjustment and exhaustion disorder that was developed by the research group (the same content as the face-to-face treatment described in the background of this thesis). For all patients, guidance consisted of two sessions with a psychologist, one at the start of treatment, and one approximately four weeks into treatment. In step 2, face-to-face CBT protocols were identical to those in Study I. For self-help CBT, the patient continued with the same book as in step 1, and received one additional guidance session.

4.2.1.4 Statistical analyses

Number of patients in remission after step 1 was reported as percentages. After step 2, the chi-squared test was used to estimate difference between conditions in remission status.

4.2.2 Results

At baseline, 333 patients (84%) rated above the pre-established cut-off on their primary disorder. After step 1, 134 patients (40%) of these patients were considered in remission. Among patients randomized in step 2 ($n = 161$), face-to-face CBT was significantly more

effective than continued self-help CBT, with 39% and 19% of patients in remission, respectively.

4.2.3 Conclusion

The investigated stepped care model yielded promising results. For patients not in remission after guided self-help CBT, stepping up treatment intensity to face-to-face CBT seems to be logic. Overall, the program resulted in high remission rates (63%), using limited therapist time, suggesting effective resource utilization.

4.3 STUDY III: MEDIATORS OF CHANGE IN COGNITIVE BEHAVIOR THERAPY FOR CLINICAL BURNOUT

4.3.1 Methods

4.3.1.1 Procedure and inclusion

This investigation of mediators of change included patients from Study I with exhaustion disorder as their primary disorder, randomized to CBT ($n = 40$) or RTW-I ($n = 42$).

4.3.1.2 Primary outcomes and assessments

Alongside the primary outcomes in Study I, patients were also assessed weekly on self-rated disorder-specific outcomes and potential mediators, that were used for mediational analyses. For exhaustion disorder, the outcome was symptoms of burnout/exhaustion (Shirom-Melamed Burnout Questionnaire ¹⁷⁵), and the mediators were sleep quality (Insomnia Severity Index ^{166,176}), valued activation (Behavioral Activation for Depression Scale, Activation subscale ¹⁷⁷), perceived competence (Perceived Competence Scale ^{178,179}) and therapeutic alliance (Working Alliance Inventory ¹⁸⁰).

4.3.1.3 Treatments

The treatments are described under Study I. Briefly, the CBT consisted of a protocol developed by the research group, with several traditional CBT components included, such as behavioral activation (with additional focus on recuperating activities), functional analyses, exposure, and optional modules (e.g., focusing disturbed sleep). The CBT was scheduled for 9 to 13 individual sessions. The CBT is further described in the background of this thesis (see Table 2). The RTW-I was scheduled for 10 individual sessions and functioned as a control condition in this study.

4.3.1.4 Statistical analyses

Mixed-effects models were used to analyze change over time in outcome (the c-path) and mediators (the a-path). To model the effect of change in mediators on subsequent weeks' change in outcome (the b-path), time-lagged mixed-effects models were used. The indirect effect was computed by multiplying the a-path with the b-path.

4.3.2 Results

CBT led to larger effects on symptoms of exhaustion than RTW-I, and this difference in effects was mediated by improvements in sleep quality and perceived competence. Valued activation and therapeutic alliance were not found to mediate the difference in effects between treatments.

4.3.3 Conclusion

The results suggest that improved sleep and increased perceived competence may be important process goals related to symptom improvement in CBT for exhaustion disorder.

4.4 STUDY IV: PROCESSES IN COGNITIVE BEHAVIOR THERAPY FOR SOCIAL ANXIETY DISORDER: PREDICTING SUBSEQUENT SYMPTOM CHANGE

4.4.1 Methods

4.4.1.1 Procedure and inclusion

This process-study included patients with a primary social anxiety disorder (SAD, $N = 61$) from Study II (among the 64 patients with primary social anxiety in Study II, three did not fulfill full diagnostic criteria and were thus omitted from analyses). Step 1 (i.e., the guided self-help CBT in the first phase of the Study II) was analyzed, consequently, this study used a within-group design.

4.4.1.2 Primary outcomes and assessments

Patients were assessed weekly on outcome and the proposed change processes according to the cognitive model of SAD⁵². The self-rated outcome was symptoms of social anxiety (Liebowitz Social Anxiety Scale self-report version^{181,182}) and the processes were estimated probability and cost of negative social events (Social Probability and Cost Questionnaire^{136,137}), anticipatory processing, post-event processing, self-focused attention and avoidance (Social Phobia Weekly Summary Scale⁵⁷), and safety behaviors (Safety Behaviour Questionnaire, unpublished scale).

4.4.1.3 Treatment

The self-help book used in this trial¹³⁵ is described in the background of this thesis (see Table 3). In brief, it consists of components typically included in CBT protocols for SAD, such as monitoring of negative automatic thoughts (NATs) and challenging them, behavioral experiments, exposure, and practice in shift of attention. The self-help book was worked through in nine weeks, and included two guidance sessions with a psychologist.

4.4.1.4 Statistical analyses

Time-lagged mixed-effects models were used to (a) estimate the effect of the presumed processes on subsequent weeks' outcome, and (b) estimate the effect of the outcome on

subsequent weeks' processes. This was done to analyze the temporal relations between changes in processes and outcome. Thus, this study focused on the b-path in a traditional mediational analysis. Magnitude of effects were analyzed by explained variance, pseudo-R².

4.4.2 Results

Decreased avoidance predicted subsequent improvements in social anxiety, and the reversed direction of change (the impact reduced social anxiety on subsequent avoidance) was non-significant. Estimated probability and cost, self-focused attention, and safety behaviors were bidirectionally related to social anxiety, i.e., these processes predicted subsequent social anxiety, but were also predicted by prior reductions in social anxiety. Effects were generally stronger in the presumed direction of change (compared to the reversed direction).

Anticipatory and post-event processing did not predict subsequent social anxiety, but were predicted by prior symptom reduction.

4.4.3 Conclusion

The results indicate that several of the proposed change processes according to the cognitive model of SAD (except for worry and post-mortem rumination) are related to subsequent improvements in social anxiety. However, only avoidance showed a unidirectional relation to subsequent social anxiety, which suggests that this process might be of specific clinical relevance. The remaining processes seem to be part of reciprocal positive cycles, that is, improvements in processes and symptoms affect each other.

4.5 STUDY V: INFLAMMATORY CYTOKINES IN PATIENTS WITH COMMON MENTAL DISORDERS TREATED WITH COGNITIVE BEHAVIORAL THERAPY

4.5.1 Methods

4.5.1.1 Procedure and inclusion

This study of inflammatory correlates of change included patients ($N = 367$) from Study I and II. Patients included in either of these clinical trials were asked for participation. The study used a within-group design.

4.5.1.2 Primary outcomes and assessments

Self-rated psychiatric symptoms and inflammatory markers were assessed at pre- and post-treatment. Symptom domains were depression (Montgomery Åsberg Depression Rating Scale Self-rated¹⁸³), stress (Perceived Stress Scale¹⁸⁴), and anxiety (Hospital Anxiety and Depression Scale, Anxiety subscale¹⁸⁵). Inflammatory markers analyzed were pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and IL-8.

4.5.1.3 *Treatments*

Treatments are described under Study I and Study II. In sum, they consisted of one of the following conditions: CBT, RTW-I, COMBO, guided self-help CBT, guided self-help CBT + continued guided self-help CBT, or guided self-help CBT + face-to-face CBT.

4.5.1.4 *Statistical analyses*

Baseline correlations between psychiatric symptom severity and level of pro-inflammatory cytokines were analyzed using linear regression. Changes in symptoms and cytokines over time (pre-to-post) were analyzed using mixed-effects models. Both these analyses included potential moderators and confounders. Finally, Spearman rank correlation was used to analyze the association between changes in symptoms and changes in cytokines.

4.5.2 **Results**

At baseline, levels of symptoms and cytokines were significantly associated in subgroups (e.g., levels of TNF- α were related to levels of all symptom measures in men, but not in women), but no robust associations across the study sample were found. Symptom severity decreased markedly between pre- and post-treatment, but cytokine levels were unchanged. There was no association between changes in symptoms and changes in cytokines.

4.5.3 **Conclusion**

Pro-inflammatory cytokines were related to psychiatric symptom severity only in subgroups. Although symptoms were substantially reduced after treatment, cytokine levels did not track this improvement, suggesting a limited role of these inflammatory processes in CBT for CMDs.

4.6 **ETHICAL CONSIDERATIONS**

All studies were approved by the regional ethics committee in Stockholm, Sweden. First, the clinical trials (Study I and II, including analyses for Study III and IV in the present thesis) were approved. Subsequently, by an amendment to the approved application, the study of inflammatory markers (Study V) was granted. All patients provided written informed consent and were free to terminate study participation at any time. An additional informed consent was provided for Study V. If participation in either clinical trial was declined, patients were offered treatment according to the clinics' routine care. All parts of the studies were conducted in line with the Declaration of Helsinki Ethical Principles¹⁸⁶. The trials were preregistered at ClinicalTrials.gov (identifiers NCT01636791 and NCT01667822).

In Study I, one of the conditions to which patients were randomized was the RTW-I. This constitutes an ethical consideration because RTW-I is not an evidence-based treatment. However, only a minority of patients with CMDs that present in primary care (and specialist care) in Stockholm receive evidence-based treatments. The structured format of the RTW-I condition, as well as the CBT-based psychoeducation, makes this a tolerable treatment in this

regard. In retrospect, effects on symptoms were substantial in RTW-I (although larger in CBT).

In Study II, non-responders to guided self-help CBT were randomized to face-to-face CBT or continued guided self-help CBT. The latter condition served as a control condition to examine the potential additive effects of stepping up treatment intensity. Thus, some patients received treatment where therapeutic effects were expected to be limited. However, the potentially additive effects of face-to-face CBT in this second step of treatment were uncertain before the study, and the potential benefits of this research were seen as large.

Regarding the self-rated measures of mediators/processes and outcome, patients spent approximately 20 minutes weekly to rate 60-75 items (depending on primary disorder). This constituted an extra burden for some patients already suffering from stress-related problems. However, the experience of treating some of these patients was that most of them found the weekly measures not too demanding, but rather appreciated the carefulness given to monitoring changes in symptoms and processes over time. Generally, ratings were used jointly to monitor progress, that is, both patient and psychologist benefitted from the weekly provided information.

After patients had accepted participation in the either clinical trial (Study I or II) they were asked about additional participation in the study of inflammatory markers (Study V). Participation was voluntary and did not affect participation in the clinical trials. Thus, patients were free to participate in the treatment studies without contributing with blood samples before and after treatment. If participation was accepted, blood samples were collected by trained personnel at certified laboratories at the respective primary care clinic. The risk of nerve damage associated with venipuncture was assessed as very limited.

5 DISCUSSION

The aim of this thesis was to investigate processes of change in CBT for CMDs. Specifically, focus was placed on psychological change processes in CBT for exhaustion disorder (ED) and social anxiety disorder (SAD), and inflammatory processes in a broad sample of patients with CMDs. These process studies were based on two large clinical trials of CBT for CMDs set in primary care.

5.1 MAIN FINDINGS

In Study I and II, the clinical trials, CBT was found to produce favorable effects on psychiatric symptoms. In Study I, CBT was superior to a strong comparison condition (RTW-I). In Study II, a stepped care model resulted in high overall remission rates. Thus, the clinical trials constituted a beneficial base for further investigation of processes involved in therapeutic improvement. In Study III, patients with a primary ED from Study I were investigated regarding mediators of change. Sleep quality and perceived competence were found to mediate the favorable effects of CBT compared to RTW-I, while behavioral activation and therapeutic alliance were not significant mediators. In Study IV, processes of change were investigated in patients from Study II with a principal diagnosis of SAD who received guided self-help CBT. Reductions in the following processes were found to predict subsequent reduction in social anxiety: estimated probability and cost of negative social events, self-focused attention, avoidance, and safety behaviors. Notably, all these processes, except avoidance, were also found predicted by prior symptom reduction. Only worry and post-mortem rumination were not found predictive of subsequent social anxiety. In Study V, patients from both Study I and II were analyzed regarding inflammatory markers related to psychiatric symptoms. Results showed that inflammation and symptoms were only associated in subgroups at baseline, and the large symptom improvements over the treatment period were not correlated to reductions in inflammation. In the following, results of the clinical trials (Study I and II) will be discussed briefly, followed by a more extensive discussion of the process studies (Study III-V).

5.2 EFFECTIVENESS OF CBT FOR COMMON MENTAL DISORDERS IN PRIMARY CARE

The results of Study I support that disorder-specific face-to-face CBT is a suitable treatment option for CMDs in primary care, as showed by superior effects on psychiatric symptoms compared to another comprehensive psychological treatment (i.e., RTW-I). These results are in line with a large body of evidence supporting that CBT is efficacious for a wide range of disorders¹⁸⁷, for a review of meta-analyses^{113,188}, and also that CBT is effective in the primary care context^{113,188}. In contrast to our hypothesis, the results of Study I do not support that an intervention that primarily focuses on work issues (RTW-I) has beneficial effects on sick leave, as compared to disorder-specific CBT. Recent systematic reviews and meta-analyses investigating the effect of interventions on sick leave in CMDs have produced inconsistent results and effects seem to be small^{100,110,189,190}. The combined intervention (COMBO) in

Study I was not superior to any of the other treatments, either on symptoms or sick leave. In speculation, the COMBO treatment was too extensive for both therapists and patients.

In Study II, results support that a stepped care model could be a viable solution to increase access to evidence-based treatments for patients with CMDs in primary care. Some recent studies have shown promising results of stepped care models for obsessive-compulsive disorder¹⁰⁵; panic disorder and social anxiety disorder¹⁰⁶; panic disorder and generalized anxiety disorder¹⁰⁸; and anxiety disorders, adjustment disorder and depression¹⁰⁹. The results of Study II add to existing knowledge, particularly by showing that non-responders to guided self-help CBT can benefit from being stepped up to face-to-face CBT. This way, high remission rates can be achieved with limited therapist resources.

5.3 WHAT CAN WE LEARN FROM INVESTIGATING MEDIATORS OF CHANGE IN CBT FOR EXHAUSTION DISORDER?

As of today, no evidence-based treatments exist for exhaustion disorder (ED). CBT seems effective for work-related stress⁹⁹, but results for clinical populations are more uncertain¹⁰⁰⁻¹⁰³. Moreover, process studies of CBT for ED are lacking. A vital step in developing effective treatment for this patient group is to investigate mediators of change in the context of clinical trials.

An important finding in Study III was that sleep quality mediated the effect on symptoms of exhaustion: sleep improved more in CBT than RTW-I (a-path), sleep improvements predicted subsequent reductions in exhaustion (b-path), and the mediated effect (a*b product) was significant. Thus, sleep seems to be an interesting construct for further investigation in CBT for ED. If replicated, it implicates that sleep disturbance should be targeted in treatment. Clearly, one way to modify the present CBT protocol is to include evidence-based sleep strategies (e.g., sleep restriction and stimulus control⁹⁴) earlier in treatment. Further, if future research finds moderated mediation (i.e., that higher levels of sleep disturbance at baseline is associated with a stronger mediated effect on exhaustion through sleep improvements), sleep strategies should be especially emphasized for patients with higher levels of insomnia at treatment start.

What do these results tell us about the actual mechanisms of change? Although sleep quality can be viewed as a mediator (a variable that statistically explains the relationship between an independent and a dependent variable¹¹⁴), it does not give information of the steps and processes connecting the investigated CBT protocol, sleep improvements and reduced exhaustion. Increase in recuperating behaviors and reduction in perseverative cognitions could be intermediate steps involved in fostering improved sleep in the context of stress^{43,45}. Longitudinal investigation of the interrelations between these processes and their effect on exhaustion in future treatment trials is warranted.

Further, it should be noted that sleep quality in Study III was operationalized by the Insomnia Severity Index^{166,176}. Although this scale includes items concerning sleep disturbance (i.e., difficulties falling asleep, maintaining sleep and early awakening), it also includes items

regarding consequences of disturbed sleep (e.g., worry about the sleeping pattern). Some important aspects of sleep quality are however not included (e.g., sleep duration and sleep efficiency). Other scales (such as the Pittsburgh Sleep Quality Index ¹⁹¹), as well as sleep diary data and objective sleep assessment, could contribute with more detailed information of the role of sleep in improvements from exhaustion.

The other significant mediator in Study III was perceived competence, a concept close in meaning to self-efficacy ¹⁹². In this context, the construct refers to an individual's belief in the ability to cope with ED. Thus, some of the superior effects of CBT compared to RTW-I on symptoms of exhaustion were mediated by increased confidence in coping abilities. Further elucidation of these relations is, of course, of interest. For example, what components of the investigated CBT protocol (e.g., psychoeducation about stress, self-observation, functional analysis of emotion-provoking situations, planning recuperating activities etc.) lead to increased perceived competence (e.g., "I feel confident in my ability to manage my exhaustion disorder")? And what additional processes (e.g., cognitive and behavioral) are involved in the subsequent effect on exhaustion? Relatedly, how does perceived competence interplay with behavioral changes to promote changes in well-being? Recovery-related self-efficacy ¹⁹³ might, for example, increase the probability of engaging in recuperating activities.

Although the present CBT protocol leans heavily on behavioral activation, valued activation was not found a significant mediator in Study III. In this context, it should be noted that we analyzed the presumed mediators in relation to the difference in effects between treatments. Thus, behavioral activation could be a mediator in both treatments, if analyzed separately. Indeed, the b-path in the present analysis was significant (i.e., increased behavioral activation predicted subsequent symptom level across treatments). Further, although the a-path was non-significant (i.e., no difference in effects in valued activation between treatments), they both produced substantial within-group changes in valued activation (estimated Cohen's $d = 1.23$ and 1.28 at post-treatment, respectively, found in supplement Table S5 in the article). One interpretation of this finding is that psychoeducation, as well work-related strategies, in the RTW-I resulted in marked behavioral activation, comparable to the one found in CBT. Behavioral activation could therefore be further examined as a possible mediator of change in CBT against a comparator that does not involve similar treatment components.

Of note, we did not measure recovery explicit in Study III, which is unfortunate. By the start of the present studies, I was not aware of valid measures of recovery. Valued activation, as measured by the Behavioral Activation for Depression Scale, Activation subscale (that includes variety and structure in daily activity) was used in part as a proxy. However, explicit measure of recovery would have been preferably. Some recent recovery-focused programs for stress have examined both recovery activities (e.g., physical activities) and recovery experiences (e.g., psychological detachment from work) ¹⁹⁴ with promising results ^{35,43,193}. One suitable measure is the Recovery Experience Questionnaire ¹⁹⁵, covering different facets of recovery (e.g., both psychological detachment and relaxation). Noteworthy, previous research has mainly focused on (a) occupational stress and not clinical populations, and (b)

recovery in relation to work. Consequently, investigation of the mediating role of recovery in CBT for ED is still needed.

Therapeutic alliance was not found a significant mediator in Study III. However, null-findings concerning alliance as a mediator does not, of course, mean that it lacks importance in treatment. Rather, several other perspectives on therapeutic alliance (not investigated in the present study) are possible. For instance, initial level of alliance could be a predictor of treatment outcome or alliance could facilitate changes induced by specific treatment ingredients^{114,196}. Also, as argued regarding behavioral activation, it should be noted that the potential role of therapeutic alliance as a mediator of change was analyzed in relation to the difference in effects between treatments. However, the b-path (the effect of therapeutic alliance on subsequent symptoms of exhaustion across treatments) was non-significant (see Table 2 in the article), which limits motivation for further investigation.

5.4 HOW DOES CHANGE UNFOLD IN SOCIAL ANXIETY DISORDER?

In contrast to the evidence base of CBT for exhaustion disorder, there is strong support for the effectiveness of CBT for social anxiety disorder (SAD), in both face-to-face treatment and guided self-help⁸⁸. Nevertheless, not all patients benefit from treatment. About 25% of patients do not achieve clinically significant improvement even following the most efficacious face-to-face protocol (cognitive therapy)¹⁹⁷. Further, the theoretical basis for treatment concerning the maintaining processes has been studied widely⁵³. However, one limitation in previous research is the timeline of events in CBT for SAD. Do the presumed processes really precede change in outcome?

In Study IV, several of the investigated processes (i.e., estimated probability and cost of negative social events, self-focused attention, and safety behaviors) were found to have reciprocal relations with social anxiety, which has also been found in previous studies using repeated measures of processes and outcome^{145,147-149}. Thus, we were not able to provide insight into the order of change between these proposed processes and outcome, although effects pointed to more variance being explained by processes on subsequent symptoms, than the reversed relation. One interpretation of these bidirectional relations is that reductions in a process affects social anxiety, which in turn has beneficial effects on the process. Conversely, the results could also mean that a third, unmeasured, variable caused effects in both processes and social anxiety. In that case, important treatment targets are yet to be discovered.

Avoidance unidirectionally predicted subsequent social anxiety, while worry and post-mortem rumination were unidirectionally predicted by prior reduction in social anxiety. These results could implicate that to achieve reductions in social anxiety, it is important to target avoidance in treatment, while worry and post-mortem rumination should not hold such position in treatment. Importantly, Study IV was not randomized. Consequently, changes in processes could have been caused by other factors than treatment. In other words, avoidance seems to be important for symptom reduction, but the cause of decreased avoidance in Study IV was not necessarily the guided self-help CBT.

Further, given the number of presumed change processes in CBT for SAD, an interesting line of future research is the interplay between key processes. A recent review proposed an extended model of maintenance of SAD that take etiological factors, as well as the sequential development of different maintaining processes, into account⁵³. In such a model, primary maintaining processes (i.e., attentional biases directed toward detection of threat and avoidance/escape behaviors that are intended to eliminate threat) are viewed as predictive of later development of secondary maintaining processes (i.e., anticipatory- and post-event processing and safety behaviors). For example, avoidance as an initial strategy to eliminate exposure to social threat/evaluation is proposed to lead to later development of more subtle strategies, i.e., safety behaviors, serving the same function. Correspondingly, process change in CBT for SAD might unfold sequentially, so that relieve in one process affects another, that eventually has impact on symptoms. In Study IV, each process was investigated in isolation in relation to the outcome. Single-case designs might offer advantages in this regard, including isolating active components in treatment packages¹⁹⁸. Ultimately, ordering of treatment components may be optimized. For example, self-focused attention is targeted in chapter 6 in the present self-help book¹³⁵, while earlier implementation might be beneficial for outcome.

A central part of the cognitive model of SAD is the ‘processing of self as social object’, including self-focused attention and images/impressions of how one appears to others⁵². In Study IV, self-focused attention was measured, as in previous studies¹⁴⁵⁻¹⁴⁷. However, assessment of the occurrence of negative self-images would have added important information. Relatedly, self-images might be influenced by memories of socially traumatic events^{59,60}, and treatment development would benefit from more knowledge about this potential process.

An important limitation of Study IV is the within-group design. Nevertheless, an important gap in existing knowledge is the investigated temporal relations between processes and outcome (the b-path in a traditional mediational analysis), while the a-path (i.e., the effect of treatment on mediators) and the c-path (i.e., the effect of treatment on outcome) have received more attention in previous research.

5.5 WHAT IS THE ROLE OF INFLAMMATION IN COMMON MENTAL DISORDERS?

In Study V, measures of inflammation were not associated with psychiatric symptom severity across the study sample; significant associations between inflammatory cytokines and symptom severity were only found in subgroups. Further, inflammatory markers were not reduced after CBT, and the substantial symptom improvements were not correlated to cytokine reductions.

One caveat concerning our results of the baseline associations is that inflammation might not be relevant to psychiatric symptoms in all patients. For example, there might be a depressive subtype where elevated inflammation is involved (i.e., for some individuals’ immune

processes might be particularly relevant for depression development), whereas for other depressed individuals it is not ¹⁹⁹. This notion might apply across CMDs. Further, how should our null-findings concerning change over time in cytokines be interpreted? One way is to infer a true absence of effects of CBT on inflammatory markers in the studied population. Given the large sample size (largest to date), the gold-standard method of cytokine assessment (manual enzyme-linked immunosorbent assays) ²⁰⁰, and the structured and protocol-based treatments used, it might be argued that undetected true changes are improbable. On the other hand, there are aspects of Study V that could have masked effects. Some important confounders were not measured (e.g., use of medication during treatment), blood samples were not drawn at specific times (i.e., permitting circadian variations in inflammatory levels ²⁰¹ to possibly influence the results), and there was a mix of CBT treatments (e.g., the RTW-I included CBT psychoeducation, but did not aim primarily at symptom reduction). These factors hinder firm conclusions from the study. Moreover, analyses of change over time in cytokines might be relevant only for patients with elevated inflammatory markers at baseline (which could be a proxy for the inflammatory-related subtype of patients). In Study V, the within-group design and associated issue of regression to the mean unfortunately precluded such analyses.

There are also points to be made concerning assessments of inflammatory markers in Study V. Blood samples were drawn twice, at pre- and post-treatment, as in the vast majority of previous studies ¹⁶⁰. This carries some limitation. First, low-grade *chronic* inflammation is assumed to contribute to CMDs. Consequently, multiple baseline assessment of inflammatory markers would have been informative. Second, and maybe more important for the process focus of the present thesis, we did not measure cytokines repeatedly during treatment. To investigate the possibility of a mediating role of reduced inflammation on subsequent outcomes, frequent assessments are vital. One of few studies using repeated measures of inflammatory markers investigated the effects of a CBT stress management program for coronary heart disease patients ²⁰², and inflammatory markers were assessed at five timepoints. However, although a solid design, the biomarkers were not reduced over time, and mediational analyses were therefore not conducted. Further, although markers of inflammation in peripheral blood can serve as proxies for central inflammation ²⁰³, we did not measure immune processes relevant for CMDs in the brain.

Moreover, there are alternatives to the suggested role of inflammation in relation to CBT in the Study V. This study hypothesized that CBT could have anti-inflammatory effects. However, inflammation can also be viewed as a moderator of treatment effect. A recent meta-analysis suggests that baseline inflammation might predict non-response to anti-depressant pharmacological treatment for depression ²⁰⁴. This moderating role of inflammation might also be true for psychological treatments. The cytokine-induced sickness response has been described as a motivational state ⁶³. In learning theory terms, this could be translated to “establishing operations”, that is, circumstances that influence the strength of reinforcers and thus operant behaviors. Just as thirst can increase behaviors directed towards acquiring something to drink, the sickness response could decrease the tendency to try new behaviors

inherent in CBT (such as exposure or valued activation). Elevated inflammation could in this sense obstruct treatment outcome, which has been indicated in some studies²⁰⁵⁻²⁰⁷. This is an interesting line of research that could help in decisions regarding for which patient anti-inflammatory pharmacological treatment might be considered as an adjunct to behavioral treatment.

Given the uncertainty in current research, inflammation in relation to CBT could be posited as a correlate of change (e.g., a physiological observational level of symptom change), a consequence of symptomatic change (e.g., emotional improvements leading to reduced inflammation), a potential process of change (i.e., preceding symptom reduction), a moderator of treatment effect (i.e., predicting response to treatment), or largely unrelated to treatment effect. Moreover, if CBT has anti-inflammatory effects, how does such changes unfold? Decreased HPA-axis and sympathetic activity could be one pathway¹⁵¹, but improvements in important health-promoting behaviors associated with inflammatory processes (e.g., regarding physical activity, diet and smoking)^{67,208} are also possible routes. Of note in this respect, CBT for CMDs generally does not directly target such behaviors.

In sum, inflammation was not related to improvements in this heterogenous sample of patients with CMDs. The results suggest that if CBT has anti-inflammatory effects²⁰⁹, they are likely of limited importance for clinical improvement.

5.6 CLINICAL IMPLICATIONS

The clinical studies showed that implementing structured and protocol-based CBT in primary care yields substantial treatment effects and that a stepped care model could be a viable solution to increase access to evidence-based treatments. Further, although tentative, the results of the present process studies might have some implications for treatment improvements. First, targeting disturbed sleep could be important for symptom improvement in CBT for exhaustion disorder. Early and structured implementation of sleep enhancing strategies might hold promise. Second, the maintaining processes according to the cognitive model of social anxiety disorder⁵² were largely supported, and, speculatively, targeting avoidance might be of particular relevance to reduce social anxiety. Further, worry and post-mortem rumination might only be consequences of symptom improvement, and may therefore be of less clinical importance. Concerning inflammation, the present results mainly have implications for future research.

5.7 GENERAL METHODOLOGICAL ISSUES AND FUTURE DIRECTIONS

Studies of processes of change in clinical trials has the potential to ultimately produce better patient outcomes. However, there are several issues regarding these kinds of investigations that should be mentioned.

Bringing clarity to mechanisms of change in CBT for a particular disorder is a vast project, and the results of one study can only contribute with limited answers¹¹⁴. For example, the present finding concerning the role of sleep improvements in ED is, although interesting,

merely a starting point for future research. What CBT components, given the broad treatment package, lead to sleep improvement? Are there redundant components that could be omitted from the protocol? What intermediate process were involved? Relatedly, the b-path in mediational analyses (i.e., the effect of the mediator on outcome) is correlational by nature. The experimental manipulation (i.e., treatment allocation) controls for confounders in the c-path (i.e., the effect of treatment on outcome) and a-path (i.e., the effect of treatment on mediator), but not in the b-path. To claim that changes in the mediator *causes* changes in the outcome, the mediator needs to be manipulated (i.e., randomizing patients to different levels of the putative mediator, which is difficult in many cases)²¹⁰. Thus, to say that sleep improvements cause improvements in symptoms of exhaustion, one would essentially need to allocate patients with ED to different levels of sleep quality and analyze the effects on exhaustion.

Concerning investigation of the timeline (i.e., whether changes in processes precede changes in outcome), it is widely acknowledged that both processes and outcome should to be measured repeatedly during treatment. However, although a progress from previous pre-to-post analyses, weekly assessments might not be enough. As seen in Study IV, reciprocal relations between most of the investigated processes and outcome indicate that improved resolution is warranted. Theoretically, one could assume that some therapeutic changes (e.g., cognitive changes after a successful behavioral experiment) are almost instant. Tracking such changes in relation to changes in outcome (e.g., social anxiety) on tighter than weekly schedules would be informative. Conversely, changes could also unfold over longer time periods, and examination of process-outcome relations could benefit from analyses with different time-lags.

Further, although the time-lagged mixed-effects analyses (i.e., investigating the subsequent effect of one variable on another, in the present studies with a one week time-lag) used in Study III and IV have many advantages, there are also limitations. One is that effect sizes are not easily calculated or interpreted. Few would today find it sufficient to know that the difference in outcome between two treatments was statistically significant – the clinical significance/magnitude of difference is vital information. Likewise, a mediator may be related to outcome, but knowing the effect size of the relation has important implications. In Study IV, we calculated explained variance as a measure of the magnitude of effect. However, as evident in that paper, some of these calculations yielded uninterpretable results as to the size of effects.

Another issue concerning statistical analyses is that relations between processes and outcome need to capture what unfolds within individuals²¹¹. Therapeutically, the focus is to attain changes in processes believed to help the specific patients on some valued outcome. In research, analyses of process-outcome relations on a group level can confuse relations that occur between individuals (e.g., individuals with higher self-focused attention have more severe social anxiety) and within individuals (e.g., an individual that reduces self-focused

attention subsequently improve on social anxiety). In Study IV we explicitly modeled change over time with regard to this issue, which has been a limitation in previous research ¹⁴⁵.

On a broader note, knowledge on mediators of change is important for treatment development. Moreover, understanding of potential mechanism can help to discover moderators of treatment outcome (i.e., characteristics that affect the relation between an intervention and outcome), which concerns matching patients with treatment to improve benefit ^{20,117}. For example, attention training in SAD may only be an effective treatment component for patients with tangible attentional biases at treatment start ²¹². As of today, treatment packages are often implemented on basis of the patient's primary disorder. Process-informed decisions of treatment, or treatment components, may be an important way to increase the effectiveness of psychological treatments and alleviate suffering in the many persons affected by CMDs.

5.8 CONCLUSIONS

Implementing structured and protocol-based CBT for CMDs in primary can yield substantial treatment effects and stepped care CBT could be a way to increase accessibility. However, there is considerable room for improvement in outcomes and the present process studies gives some clues, although tentatively, to treatment development. Targeting disturbed sleep seems to be important in CBT for exhaustion disorder. Also, improving perceived competence, the belief in one's ability to cope, seems to be of value. In social anxiety disorder, reducing avoidance might be of particular relevance to attain symptom reduction, although several other processes seem to be involved. As to immune system dysregulation, inflammatory processes seem to play a limited role in CBT for CMDs.

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