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# SICKNESS & BEHAVIOR IN ME/CFS (CHRONIC FATIGUE SYNDROME)

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# Sickness & behavior in ME/CFS (Chronic Fatigue Syndrome)

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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# ABSTRACT

**Background:** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic debilitating condition characterized by physical and mental fatigue with a heightened sensitivity to exertion. To date, the causes are unknown. However, recently the condition has been implicated as a chronic sickness behavior state. That is, the adaptive changes in brain and behavior commonly following acute infection (experiences of malaise, fatigue, brain fog and so forth) seem to have become chronic and thus maladaptive, since no infectious agent is present. The condition is often debilitating, but no effective treatments are available, which implies that interventions are normally aimed at reducing symptoms and/or restoring or improving functioning. Furthermore, classifications are multiple and not empirically based. As such, there is a need for: (1) empirical investigations of how symptoms present and relate to each other and other measures of clinical importance; (2) evaluations of behavior medicine treatment approaches aimed at improving functioning and quality of life, and; (3) studies investigating sickness behavior processes in ME/CFS on both subjective and objective levels.

**Aims:** The overarching aims of the present thesis were to: (a) investigate factors of importance in ME/CFS, including; (b) symptom patterns and their relationships to health and functioning (Study I); (c) inflammatory markers implicated in sickness behavior and fatigue and their associations with common symptoms (Study III); (d) the level of subjective sickness behavior in ME/CFS, compared to chronic pain, primary care patients and the general population (Study IV), and; (e) evaluate the acceptability, safety and preliminary efficacy of an Acceptance and Commitment Therapy(ACT)-based behavior medicine treatment protocol aimed at increasing functioning and quality of life in ME/CFS (Study II).

**Methods:** All ME/CFS patients in the four studies were included after referral and diagnostic assessment (CDC and CCC or ICC criteria) at a tertiary specialist clinic. In Study I ($n$=106), a total of 14 common ME/CFS symptoms were quantified and latent symptom subgroups were explored. The relationship between latent symptom subgroups and measures of health and functioning were investigated. In Study II ($n$=40), the effects of the ACT treatment on measures of disability, symptoms and health-related functioning were investigated. In Study III ($n$=53), associations between inflammatory markers and common symptoms in ME/CFS were investigated. In Study IV, levels of subjective sickness behavior were investigated in, and compared between: patients with ME/CFS ($n$=40); patients with chronic pain ($n$=193); patients in primary care ($n$=168), and; individuals from the general population ($n$=163). The

associations between sickness behavior and self-rated health, mental and physical health-related functioning were also explored.

**Results:** The results in Study I showed four distinct subgroups in which differentiated symptoms gathered representing inflammatory, pain, neurocognitive and autonomic symptoms respectively. The symptom subgroups overall showed significant correlations with important clinical measures, although rarely exceeding .50, indicating the importance of other factors. ACT-based behavior medicine treatment can be considered acceptable, safe and preliminary effective for patients with ME/CFS (Study II). In Study III, several inflammatory markers (β-NGF; CCL11; CXCL10; IL-7; TGF-β-1 and; TNF-α) showed significant associations with common symptoms (post-exertional fatigue; impaired cognitive processing; musculoskeletal pain, and; recurrent flu-like symptoms). The level of sickness behavior was similar between ME/CFS and chronic pain patients, and significantly higher than in patients from primary care and individuals from the general population (*p*'s <.001).

**Conclusions:** Symptoms in ME/CFS seem to present in distinct patterns, underlining the importance of the further study of symptom but also illness subtypes. However, factors other than criteria symptoms, such as experiential avoidance and cognitive fusion, are likely more accessible targets in behavior medicine treatment. The results from the ACT-based feasibility study indicate the utility of conceptualizing disability in ME/CFS from a modern learning theory perspective, and the ACT-based behavior medicine treatment format should be further investigated in randomized controlled studies. Finally, sickness behavior processes may guide future research in the differentiation of ME/CFS illness subtypes, as indicated by the level of subjective sickness behavior reported in ME/CFS which is equal to the level found when healthy human subjects are injected with bacterial endotoxin to cause transient sickness behavior in an experimental setting.

# LIST OF SCIENTIFIC PAPERS

I. Jonsjö MA, Wicksell RK, Holmström L, Andreasson A, Bileviciute-Ljungar I, Olsson GL. Identifying symptom subgroups in patients with ME/CFS – relationships to functioning and quality of life. Fatigue: Biomedicine, Health & Behavior. 2017;5(1):33-42.

II. Jonsjö MA, Wicksell RK, Holmström L, Andreasson A, Olsson GL. Acceptance & Commitment Therapy for ME/CFS (Chronic Fatigue Syndrome) – A feasibility study. Journal of Contextual Behavioral Science. 2019;12:89-97.

III. Jonsjö MA, Olsson GL, Wicksell RK, Alving K Holmström L, Andreasson A. The role of low-grade inflammation in ME/CFS (Chronic Fatigue Syndrome) – associations with symptoms (manuscript in revision).

IV. Jonsjö MA, Åström J, Jones MP, Holmström L, Lodin K, Agréus L, Wicksell RK, Lekander M, Olsson GL, Kemani M, Andreasson A. Sickness behavior, self-rated health and functioning – differences in ME/CFS and chronic pain compared to primary care patients and the general population (manuscript in preparation).

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACT | Acceptance and Commitment Therapy |
| CBT | Cognitive Behavior Therapy |
| CCC | Canadian Consensus Criteria |
| CDC | (US) Centers for Disease Control and Prevention |
| EQ-5D | Euroqol EQ-5D |
| FMS | Fibromyalgia (Syndrome) |
| HADS | The Hospital Anxiety and Depression Scale |
| HPA | Hypothalamic-Pituitary-Adrenal(-axis) |
| IBS | Irritable Bowel Syndrome |
| ICC | International Consensus Criteria |
| ME/CFS | Myalgic Encephalomyelitis/Chronic Fatigue Syndrome |
| MFI-20 | The Multidimensional Fatigue Inventory |
| PCA | Principal Component Analysis |
| PEM | Post-exertional malaise |
| PNI | Psychoneuroimmunology |
| RFT | Relational Frame Theory |
| SF-36/SF-12 | The Medical Outcomes Study Short-Form Health Survey |
| SicknessQ | The Sickness Questionnaire |

# 1 INTRODUCTION

We all know how it feels to be sick. You have a headache, you feel tired and drained, your body aches, you definitely feel less smart and quick, you don't really want to see or hang out with anybody. Basically, your body tells you to do nothing, except maybe lie down and watch some semi-engaging tv-series until the symptoms have receded. Picture yourself for a second, the last time you were sick, and all the symptoms you had and how you felt and what you did. And now imagine that the symptoms stay the same, basically every day, for years to come.

This thesis concerns one of the most debilitating and yet unsolved conditions in healthcare – Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). For many with the diagnosis, the above description is their everyday reality. I will discuss the history of the condition (it is not new but has had many names), how it presents, factors affecting functioning and quality of life, how the life's of the sufferers can be improved, and how the intricate interplay between the central nervous system, the immune system and behavior could be the key to understand what gives rise to the condition, how it is maintained and how, hopefully in the future, it can be resolved.

*Stockholm, August 2019.*

# 2 BACKGROUND

## 2.1 MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME (ME/CFS)

### 2.1.1 Definition, classification and symptoms

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is classified as a neurological disorder by the World Health Organization (1). However, etiology and pathophysiological mechanisms are still unclear and multiple definitions and classification systems exist. The condition has been documented in the medical literature since the 1800's, it was described and termed "benign Myalgic Encephalomyelitis" in an anonymous editorial in The Lancet in 1956 (2). Historically, phenomenological descriptions of the conditions we now classify as either ME/CFS or clinical burnout/stress-related exhaustion are analogous to the condition termed *Neurasthenia*, or *Nervous Exhaustion*, by George Beard in 1869 (3). Interestingly, since then, ME/CFS and stress-related exhaustion have been researched and clinically treated as two separate phenomena depending on their assumed etiologies (immunological vs. psychological stressors), despite the many similarities as discussed below (4, 5). However, while attempting to differentiate the condition, the name Myalgic (muscle pain) Encephalomyelitis (inflammation of the brain and spinal cord) somewhat obscures the difficulties in finding a distinct marker, as the prevalence of muscle pain related to inflammation in the brain and the spinal cord in this condition is still in need of research support (6). Although numerous studies show abnormalities or differences in levels of immune and inflammatory markers in individuals diagnosed with ME/CFS compared to healthy controls, results are often unspecific and differences are only seen in some individuals (7). Muscle pain is highly prevalent, but not a required symptom for making a diagnosis, and thus misleading in describing the whole illness population (1, 8-11). Focusing solely on fatigue in naming the condition may also be too narrow, given the broad array of symptoms commonly occurring (10-15).

Longstanding unexplained physical and mental fatigue that is not substantially alleviated by rest, resulting in significant reductions in functioning is a key feature of most diagnostic criteria of the illness. However, patients normally present with a range of additional symptoms and diagnostic systems differ in which symptoms should be considered mandatory for diagnosis (9). Recently, a systematic review by Brurberg et al. identified 20 different classification systems used for making the diagnosis of ME/CFS (9). Although

new definitions have been developed since, the Centers for Disease Control and Prevention (CDC) diagnostic criteria from 1994 (1) (also called the Fukuda criteria) is still the most commonly used system in research and clinical settings (9). In contrast, clinicians and researchers more recently have suggested the use of the 2003 clinical working case definition (11) (also known as the Canadian consensus criteria) and the revised version known as the International Consensus Criteria (ICC) from 2011 (10) over the CDC criteria. Furthermore, in 2015 the Institute of Medicine suggested a new definition/new name, *Systemic exertion intolerance disease* (*SEID*) (8).

The cardinal symptom in these more recent classification systems is the systemic hypersensitivity to exertion (termed *post-exertional malaise* (*PEM*) or *post-exertional neuroimmune exhaustion* (*PENE*)) and a prolonged recovery time after exertion. PEM is described as the distinct increase of fatigue and/or other symptoms in concurrence with a rapid and marked loss of muscular and/or mental energy after even mild or moderate physical, cognitive or emotional effort with a prolonged recovery period lasting up to days (8, 10, 11). Many researchers and clinicians argue that this feature, rather than longstanding fatigue, should be the main and mandatory symptom for diagnosis (8, 10, 11). Although this might be a reasonable argument, and highlighting its importance seems adequate, there is a need for more research investigating for whom and in what way this feature presents, varies and relates to quality of life and functioning (16-19). Importantly, in my opinion, this is not a symptom in itself but rather a hypersensitivity to stimuli and/or effort resulting in symptom flare that varies broadly in its presentation in patients. As such, multiple definitions of this feature exist (20). The evident variability in definitions and symptoms gives rise to larger questions, namely, the need for the investigation of illness subtypes, and how the condition overlaps and/or distinguishes itself from similar conditions.

For perspective, it is of value to briefly return to the similarities between ME/CFS and *clinical burnout*/*stress-related exhaustion*, where clinical features overlap to a large extent (4, 21). Individuals with stress-related exhaustion normally present with longstanding mental and physical fatigue, cognitive difficulties and hypersensitivities to sensory stimuli (21). Roughly, the distinguishing differences are (a) how the etiology and pathophysiology are conceptualized and; (b) the general trajectory and treatment response of the illness (4, 21-23). In ME/CFS, since the 1980's, a viral infection has been described as the common specific mark of onset, while in clinical burnout/stress-related exhaustion, longstanding work-related psychosocial stress is highlighted as the main contributor to symptom debut (4, 5, 23-26). However, a viral infection at the time of illness debut is not a requirement for

making a diagnosis of ME/CFS (1, 10, 11). Importantly, not all ME/CFS patients describe their illness debut as a direct effect of an infection and many patients describe longstanding stressors or stressful life events as precipitating factors (27).

In summary, illness definitions of ME/CFS are multiple and most notably, none are based on empirical data of vulnerability factors, biological markers, comorbidities and/or overlap with similar conditions, symptom prevalence, intensity or relation to disability but on consensus. Hence, there is an evident need for studies investigating which and how biological and psychological markers and symptoms co-occur, how they relate to each other, and how they relate to disability and the course of the condition. Such steps seem crucial in order to develop definitions that allows for a systematic investigation of the mechanisms underlying the debilitating symptomatology in ME/CFS, but also in similar conditions such as fibromyalgia (FMS), chronic pain, irritable bowel syndrome (IBS) and stress-related exhaustion.

### 2.1.2 Epidemiology – prevalence, incidence and natural course

ME/CFS affects approximately 0.76-3.28 % of the adult population (28-32). In a comprehensive meta-analysis by Johnston et al (33), it is noted that the variation in prevalence across studies is plausibly due to differences regarding geographical area, method (self-report vs. clinical) and diagnostic criteria. However, to date there are no epidemiological studies based on the more recent definitions of the illness. On the basis of the small number of cross-cultural studies that exist, prevalence numbers appear to be similar across countries and cultures (31-36).

The illness prevalence differs vastly between the sexes, approximately 70-83 % of individuals in clinical and community samples are women (30, 31, 36-38). The largest and most robust population-based incidence study by Bakken et al. (39) found that age, with two separate incidence peaks (10-19 years of age and 30-39 respectively) and sex (female to male rate ratio of 3,2:1) were associated with elevated incidence risk. A recent retrospective cohort study showed that gastro-intestinal infection and previous psychological disorder independently were related to an elevated risk of subsequent IBS and ME/CFS (40). Notably, the sex prevalence characteristics of ME/CFS are similar to conditions such as chronic pain, FMS, IBS and most auto-immune illnesses (41-44). However, it is not known if women and men are differently affected in ME/CFS, regarding for example biological and psychological factors.

Studies of the natural course of the illness report small variations in symptoms and disability over time if the condition is untreated (29, 45-49). A small proportion of individuals seem to improve somewhat in symptom burden, while only a few percent demonstrate recovery (27). However, the use of different diagnostic criteria, context (community vs. primary or specialist care) and methods of sampling (self-report vs. clinician assessed) vary and thus make comparisons of results between studies difficult (45).

The condition often has detrimental effects on daily functioning and quality of life. Recent research suggests that health-related quality of life in individuals with ME/CFS is lower than other illness populations with well-documented disability (e.g. Multiple Sclerosis, cancer, stroke) (50). Furthermore, the high prevalence of mood and anxiety conditions (17.2 % and 24.0 % respectively) compared to the general population (5.2 % and 8.8 % respectively) is indicative of a severely affected group (51, 52).

## 2.2 ETIOLOGY AND PATHOPHYSIOLOGICAL MECHANISMS

Numerous etiological and pathophysiological factors have been suggested since the 1956 description of the condition in The Lancet (2, 7, 53). Ranging from suggestions of re-activated viruses and bacteria to arguments for psychological/psychosocial factors, no conclusive findings have emerged despite a marked increase in research into illness mechanisms during the last 30 years (54). Again, the heterogeneity in patient history of stressors before debut, type of illness debut, symptomatology, comorbidities, course and disability/severity are plausible explanatory factors for the variability in findings.

Given the symptomatology and classification, research into potential illness mechanisms have mainly focused on the brain and central nervous system and the potential involvement of the immune and endocrine systems (7, 55-57).

As in conditions with a similar symptom presentation like chronic pain, IBS and FMS, *central sensitization* has been suggested as one pathophysiological mechanism. In brief, central sensitization refers to a maladaptive lowered threshold for (potentially) noxious stimulation (pressure, warmth, cold and so forth) with a heightened excitatory mode in neurons conveying such signals from the body to the brain (58). Simplified, the body is telling the brain that it is in danger (via pain), although no infectious agent, wound or nerve damage is present. Such processes are worthy of further investigation in ME/CFS,

especially in light of the high prevalence of chronic widespread pain and hyperalgesia in ME/CFS, and the principal similarities between central sensitization and the hypersensitivity to stimuli and effort characteristic in ME/CFS (PEM) (57, 58). However, not all ME/CFS patients presents with pain symptoms, limiting the full explanatory value of this theory. Studies investigating potential abnormalities in the function of the *hypothalamic-pituitary-adrenal (HPA)-axis* have not found any evident dysfunction that would explain the clinical presentation (59). While some results indicate differences between patients and healthy controls, for example a mild hypocortisolism in some patient populations, other studies do not find such differences (60). Also, subtle changes in the HPA function may be secondary to the illness state itself (59). This is echoed in the field of immune research on ME/CFS, where findings of differences in immunological and inflammatory markers are as prevalent as results showing no differences (7, 54, 61). However, this would be less confounding if the illness drivers are differentially distributed, where brain-immune interactions play an important role for symptom development in a subset of patients.

### 2.2.1 Psychoneuroimmunology and sickness behavior

The interactions between the immune, endocrine and central nervous system might provide some keys to the understanding of ME/CFS. With immune system activation, *inflammatory mediators* (*cytokines*) are released (62). These small proteins act both locally and globally in the body and are important factors in the initiation, maintenance and resolution of inflammation. However, these proteins can also affect the brain via multiple signaling pathways, mainly via afferent nerves (most importantly the *vagus nerve*) or via locations where the *blood-brain-barrier* is weaker (63-66).

Following the acute release of cytokines, for example due to a viral infection, the individual soon presents with *sickness behavior* which includes fatigue, malaise, anxiety, anhedonia, worsened mood, reduced social interaction and increased pain sensitivity (67). Within this field of research, the sickness behavior response is not viewed as a sign of weakness, but a motivational state intended to promote energy conservation in order to facilitate the immune response to pathogens. As such, the sickness behavior state is assumed to be an evolutionary response to threats against homeostasis. That is, the experiences (e.g. fatigue) and overt behaviors (e.g. social withdrawal) that constitute the sickness behavior response are thought to have evolved to promote rest and recovery. In the prototypical situation then, sickness behavior is viewed an adaptive response in the short-term by increasing survival

from infections. However, these changes are also suggested to contribute to ill-health and disability in the long-term, when persisting after recovery or where recovery has not been completed (68, 69).

In the field of *psychoneuroimmunology* (*PNI*), these effects of pro- and anti-inflammatory mediators on the brain and behavior, and the vice versa effects, are the main foci of research (63, 70-72). Although it is beyond the scope of the present thesis, future research investigating how and which areas in the brain that may elicit, respond to or forward the sickness signals in the sickness behavior circuitry will be of utmost value for the development of our understanding of ME/CFS.

However, there is evident merit in investigating peripheral aspects of sickness behavior as they are more easily accessible, for example by investigating inflammatory marker levels in blood and subjective experiences. The relationship between cytokine-mediated inflammation and the development of fatigue and neurocognitive symptoms have been explored in for example cancer-related fatigue (73-75). Although preliminary, the results from such studies indicate an association between the variation of inflammatory markers and the development of longstanding fatigue and cognitive dysfunction. In Gulf War Illness, with a symptom profile similar to ME/CFS and unknown etiology, inflammatory markers may be related to the course of fatigue (76).

The association between inflammatory markers and symptoms has also received support in for example mood disorders (77-80), psychosis (81), seasonal allergy (82) and in relation to subjective health without demonstrable disease (83). It follows then, that the sickness behavior processes can be initiated without an ongoing infection, through administration of bacterial endotoxin (with a structure found on the surface of bacteria with highly potent immune-stimulatory capacity) or typhoid vaccine (79, 84, 85), by conditioning (86) or by stress (87). As such, sickness behavior is of importance also in situations besides the prototypical (when due to an ongoing infection). Notably, the increasing body of research on the relations between the sickness behavior circuitry and psychological/behavioral factors has led to some preliminary but interesting results within the ME/CFS field (88). Recent studies investigating the relationships between objective and subjective markers of stress and inflammation, depression, stress management skills and symptoms in ME/CFS indicate the importance of taking such interactions into account (88-90). Results indicate that levels of perceived stress management skills were related to less fatigue and distress but also to decreased levels of inflammatory cytokines (90).

As previously mentioned, there has been some debate as to which extent psychological factors play a role in the illness etiology and/or maintenance. The inherent mind-body-dualism perspective is an evident problem. Importantly, the developments within the field of psychoneuroimmunology makes debate regarding the mind or the body as the "cause" of symptoms and disability obsolete, with a growing body of research showing that psychological factors, stress, inflammation, the brain and behavior affect each other in complex ways (91). More so, the importance of psychological factors for how the illness affects functioning and quality of life is presumably as important as in other longstanding somatic conditions (92-97). That is, developing adaptive and long-term effective approaches and strategies for illness-related symptoms, emotions and thoughts should be crucial in minimizing the illness impact and alleviating suffering. In for example cancer, Multiple Sclerosis, *Rheumatoid Arthritis*, chronic pain, IBS and FMS, addressing psychological and behavioral factors beyond the levels of symptoms or inflammation has been shown to lead to better health outcomes (97-102).

## 2.3 TREATMENT – BIOLOGICAL AND BEHAVIORAL PERSPECTIVES

### 2.3.1 Treatments for ME/CFS

In ME/CFS, no pharmacological or biological treatments aimed at symptom alleviation show evidence of efficacy (103, 104). Studies of B-cell depletion with Rituximab initially showed promising results for subsets of patients with ME/CFS, however results from the most recent multicenter placebo-controlled trial suggest no evident long-term benefits (105-108). Importantly, heterogeneity in the patient population could explain such results, and future studies should investigate why, how and for whom such immunosuppressive strategies may be effective and safe in the long term. Plausibly, auto-immune and/or other inflammatory processes are important in some but not all cases of ME/CFS.
To date however, given the absent conclusive results in medical treatment trials, studies investigating the effects of cognitive behavior therapy (*CBT*) have accumulated the most evidence of efficacy (109, 110). Generalizing, CBT-based treatments conceptualize disability as related to a non-helpful fear-avoidance cycle, where fear about unwanted outcomes (for example symptom exacerbation) give rise to avoidance behaviors (for example avoiding situations and activities that may worsen symptoms) that maintain symptom levels. The target then, is to break this cycle. Although it has given rise to much

debate and critique from patient organizations, the to-date largest trial comparing CBT to graded exercise, adaptive pacing and standard medical treatment showed moderate but evident improvements in functioning (111). Importantly, as the authors also highlight, the modest number of strongly improved patients may reflect the heterogeneity of the population (112). One possible explanation is that treatment responders represent a subtype analogous to stress-related exhaustion, where improvements in somatic symptoms following multimodal treatment including CBT are more commonly seen (21, 113). Overall, CBT-based treatments for ME/CFS vary in foci and scope as well as in underlying assumptions of disabling mechanisms. Also, the variation in diagnostic criteria used makes conclusions about the efficacy of CBT-based (and biological/pharmacological) treatments harder. Some CBT treatment formats focus on symptom alleviation by ways of changing illness beliefs and behaviors and thus increasing activity and functioning, while others are aimed at managing the symptoms by using skills such as relaxation (110). Hence, central targets and outcomes vary, from symptom decrease to increases in quality of life. As long as the etiology and pathophysiology of the condition remain unknown, it is equally hard to argue for, for example solely immunological **or** solely psychological mechanisms of symptom maintenance in this condition. Importantly, as the sickness behavior circuitry can be active even in the absence of pathogens or verifiable disease, behavior medicine approaches to longstanding somatic conditions with unknown pathophysiology may also be directed at other targets than symptom decrease. Novel developments within the field of behavior medicine highlights the importance of developing approaches to symptoms and discomfort based on a generic sickness behavior and learning theory model (114).

### 2.3.2 Analyzing disability from a learning theory perspective

The clinical application of learning theory, functional analysis, may add to the understanding of any illness condition, as the analysis focuses on the most accessible variables, experiences and behavior (115). From a functional analytic perspective, experiences and behaviors should always be analyzed and understood in a context. This includes identifying relevant antecedents (for example, perceived signals from the body as potential triggers for a behavior), and consequences following the behavior (for example, a perceived change in the signal from the body as a potential reinforcer for a behavior). As such, by applying operant conditioning principles (learning by consequences), one can investigate which antecedents and consequences that are most relevant in influencing target behaviors, in the short and long-term (116). This in turn, may guide the evaluation of the

efficacy of behaviors/strategies aimed at for example reducing symptoms or improving quality of life. Importantly, the model makes sense of avoidance approaches to symptoms/discomfort, as the immediate alleviation of such experiences is a most powerful, and plausibly inherent evolutionary, reinforcer for behaviors (117). The analysis of long-term effects of such strategies is then applied for evaluating the efficacy or inefficacy of the alleviation of discomfort or improvement of life quality over time. As such, the functional analysis gives an overview of central (experienced) problems and contrasts them to long-term wanted consequences/goals, and guides the formation of treatment target behaviors connected to those goals.

In a learning theory-based behavior medicine treatment approach, educating the patient about the evolutionary but unhelpful function of prolonged non-malignant symptoms and the behavioral repertoire it triggers is a core intervention. Hence, a shift in perspective, from symptom reduction to a valued life, could be a more accessible and effective approach in behaviorally oriented treatments for a chronic illness like ME/CFS. In recent years, such perspectives in behavior medicine treatment approaches to longstanding somatic conditions has received increased attention and support, especially in treatment studies evaluating Acceptance and Commitment Therapy (*ACT*) (114, 118).

As such, there is evident value in further investigations of the importance of psychological factors for the illness severity in ME/CFS, especially in the context of plausible subtypes (for example ME/CFS and stress-related exhaustion) on a spectrum where differential aspects of psychological factors play a role. Furthermore, the importance of psychological and behavioral factors for ME/CFS is clear in the context of the general human processes suggested to contribute to suffering and disability as they are defined by novel developments within learning theory and its clinical application - *Relational Frame Theory* (*RFT*) and ACT (118, 119).

### 2.3.3 A contextual behavioral approach to human suffering – Relational Frame Theory and Acceptance & Commitment Therapy

#### *2.3.3.1 Relational Frame Theory – a functional analytic account of human language and cognition*

RFT is a functional analytic theory of human cognition, language and behavior developed within the broader research field of contextual behavioral science (115). It is beyond the scope of this thesis to give an in-depth description of RFT (and ACT), and the interested reader is recommended the excellent introductions by Törneke and Hayes et al. respectively

(118, 120). In short however, RFT suggests that the human capability to think abstractly – to analyze and solve problems, compare the present with an imagined future, evaluate a novel experience based on prior experiences and so forth –is intertwined with the development of language and the ability to interpret and take actions that are not based only on the worlds formal characteristics (what it looks like, e.g. warm/cold; light/dark etc.) but rather on what it means in the given context based on arbitrary symbolic, or language-derived, characteristics. For example, "life has no meaning" is a statement we all can understand as meaning something, and may make us behave in certain ways if we believe the statement, even though we cannot observe it in the same way we observe and react to warm temperature.

Building on respondent and operant learning theory, what RFT adds is a model to help understand how this complex human behavior – cognition – affects how conditioning fundamentally works for humans. Our language provides an ability to relate anything to anything along all imaginable dimensions (for example "better", "worse", "nicer" and so forth - try to come up with arguments for why a banana is "better" than a car - you will succeed!). This ability becomes more advanced as a function of age, learning and brain development (119). Through learning, it is developed via multiple exemplar training from once we become able to use language, where the reinforcer for the behavior is basically that it makes sense, that we are understood. The perhaps most important effect of this ability is the constant process of transformations of stimulus functions that follows.
Simplified, the stimulus functions are the cues and qualities we consciously and non-consciously act on to choose behavior in a given situation. That is, our ability to evaluate and respond in a certain situation are not only based on the formal characteristics of the situation (warm weather, blue skies) but dependent on the arbitrary, language-derived characteristics based on our knowledge and previous experience of, to us, related situations ("but winter is coming").

With the ability to understand the world based on arbitrary symbolic (language) meaning, this ability and the processes it entails are always going to affect how we experience and act in the present situation. A simplified example to clarify: The first time I play tennis, what shows up in my mind and body and how I behave will be very different from the ten thousandth time I play. It will be different, even though the weather, time of day, my shoes, the court, racquet, balls and opponent have the exact same formal characteristics as the first time. When I hit the ball the ten thousandth time, it is not only the velocity and angle of the

ball coming towards me (and my rising fear) that affects how I hit it back, but also my history of all similar angles and velocities as well as my evaluation of my opponents earlier and current status via multiple dimensions ("it's been a **long** game, he's **more tired** now and I know he sprained his ankle last month so **he'll be cautious** – I'll try a drop shot!" and so forth and so on). Such complex behavior is not explained solely by respondent or operant principles (this is the first time I've played somebody with a sprained ankle). The stimulus functions and cues for behavior in the situation are derived through the situations relationship to all things related to such situation in the network that is my unique learning history.

This ability is certainly crucial for the excellence of human development in all domains of life. Not in the least, it simplifies everyday behavior, as we as humans through language can develop and follow general rules (e.g. "being kind is good!") to adapt our behavior instead of behaving as a two-year-old across the whole lifespan (121). The possibility of acting on the present situation in the light of one's experience and ability to "see" possible consequences in the future has been and is an evident evolutionary advantage for the human race (122). The dark side however, is the potential for humans to be in contact with experiences that elicits discomfort and avoidance behaviors, without long-term discomfort resolution, at every waking moment.
This, since everything (situations, objects, sights, sounds, smells, thoughts, memories, feelings, bodily sensations) can (/will) be related to, and evaluated in relation to, everything else in my learning history and the present situation. For example, even the word "pain", or the thought of pain, shares some qualities with the actual experience of pain, and will then more likely be avoided through the same rule-governance that has helped me avoid real pain (123). Things we experience in our mind however, do not seem to go away by trying to avoid them, but rather quite the opposite. Try, for 30 seconds, actively with focus, not to think about something painful you've experienced in your life. It's not that easy.

As language-able humans, we do not only learn through respondent (association) or operant (by consequences) processes, but mainly by this derived conditioning. That is, we don't have to have experienced something first-hand as horrible, we can expertly start to avoid it for the rest of our lives through language-based derivation and the following transformation of stimulus functions. According to RFT, behaviors in everyday life are almost exclusively dependent on this symbolic logical system where we explicitly and implicitly consider experiences (for example symptoms, feelings and thoughts) to be causes for behaviors. This

in turn, may result in behavioral patterns defined by avoidance observable on the "outside" (for example avoiding close relationships) because of the "inside" (for example "I could never stand the hurt of being left"). RFT gives an account of how and why we as humans seem prone to act based on these indirect, language-created functions of a stimulus, instead of looking for other more adaptive ways to approach, for example, discomfort. Simply put, we do it because it is logically coherent in our symbolic world – it makes perfect sense.

These processes become highly relevant when internal bodily signals from the evolutionary older homeostatic systems (stress/fear and sickness behavior responses for example) are processed through our newer symbolic interpretation system (for example the thought "something is wrong and needs to be fixed!"). In the presence of discomfort of symptoms, the interpretation of these signals may give rise to thoughts and behaviors aimed at resolving this discomfort as an evolutionary function (122). However, focusing solely on symptom resolution in a condition where no pathophysiological process is known and hence without evident markers and mechanisms to target, could potentially establish rules and behaviors that paradoxically only will produce more discomfort and suffering. The thought/rule "I can't continue to live my life until I get well" is an understandable one from a sickness behavior motivational state, but totally unhelpful in a longstanding condition where no effective resolving treatment exists. Rather, it presumably results in a life that is put on hold, which then only adds to the discomfort, since struggling with aversive experiences (symptoms, feelings, thoughts) rarely is part of the valued life for most humans. As an alternative to struggling with symptoms and related thoughts and feelings that cannot be avoided in the long-term, the clinical extension of RFT – ACT, takes a different stance.

#### *2.3.3.2 Acceptance & Commitment Therapy*

In ACT treatment, the overarching aims do not entail symptom or discomfort removal. Rather, the aim in treatment is to increase functioning and quality of life by increasing the individual's *psychological flexibility*. Psychological flexibility in short, is the ability to act in line with long-term values (regarding for example relationships, interests, health and so forth) even in the presence of discomfort (symptoms, emotions, thoughts) (124). Hence, the target in ACT treatment is also to decrease the unwillingness to experience negative private events, broadly defined as *experiential avoidance*. Experiential avoidance is considered to predict behaviors aimed at alleviating distress in the short-term. Conceptually this is similar

to the sickness behavior motivational state where an avoidance behavioral repertoire is activated and evolutionarily adaptive in the acute phase of illness. In chronic conditions however, the outcome of such strategies in the long-term is seldom symptom or discomfort alleviation. Rather, the effect of experiential avoidance over time is the narrowing of life while symptoms and discomfort remain present.

The overall aim in ACT then, is to identify such processes (derived rule-governed behavior that continues because of logic coherence despite not resulting in what the rule "says" it should) as unhelpful. This identification is termed *cognitive defusion*. The purpose of this analysis is to enable a shift in perspective and behaviors towards a broad and meaningful life while making space for the discomfort (*acceptance*) one cannot remove (118). As such, by approaching situations and experiences in new more workable ways, the process of transformation of stimulus functions is used in the service of something good. Through values-directed behavior change and exposure to stimuli that previously elicited only discomfort and avoidance, the qualities of these stimuli are widened and added to. In parallel, the individual's behavioral repertoire is widened and added to, resulting in an increase of available ways to act in the presence of discomfort. In essence, psychological flexibility is increased.

In similar conditions like chronic pain, IBS and FMS, psychological flexibility seems to be a factor of central importance for the relationship between illness factors and functioning and quality of life (98, 125, 126). Consistent with this, treatments aimed at increasing psychological flexibility show promising results in these conditions (98, 100, 126-128) Although only a few studies exist, acceptance and psychological flexibility seem to be of similar importance also in ME/CFS (129-132). However, there is a lack of clinical trials investigating if an ACT-based behavior medicine treatment could be of benefit for individuals with ME/CFS.

## 2.4 SUMMARY

In a chronic illness with unknown pathogenesis and multiple definitions like ME/CFS, one main task at-hand should be to identify factors that can effectively be addressed in treatment in order to alleviate suffering. Traditionally, in the field of ME/CFS, research has to an important extent addressed biological and psychological mechanisms as separate domains. From a joint PNI/sickness behavior and behavior medicine perspective, these should be bridged in order to develop the knowledge about the mechanisms establishing

and maintaining the condition and its effects on behavior and everyday life. Most importantly, it is plausible that the symptom complex that constitutes ME/CFS is driven by differential factors across the illness population. The identification of illness subtypes may be the most promising way to move forward. To investigate how symptom development relates to both biological and psychological factors, in which subsets of individuals, and how all of the above relate to functioning and quality of life is critical for further development of treatments and the understanding of this complex and debilitating condition.

# 3 AIMS OF THE THESIS

The specific aims of this thesis were to:

1. Investigate symptom prevalence and latent symptom patterns in adult patients with ME/CFS referred to a tertiary specialist clinic, and examine the relations between latent symptom subgroups and: dimensions of fatigue; depression; anxiety; physical and mental health-related functioning, and; quality of life. (Study I)

2. Evaluate the feasibility, including acceptability, safety and preliminary efficacy, of an ACT-based behavior medicine treatment protocol for adult patients with ME/CFS referred to a tertiary specialist clinic. (Study II)

3. Investigate the associations between levels of inflammatory markers previously related to: (a) sickness behavior, and; (b) fatigue severity in ME/CFS respectively, and (c) levels of common symptoms in adult patients with ME/CFS referred to a tertiary specialist clinic. (Study III)

4. Investigate: (a) the level of subjective sickness behavior, assessed with a validated instrument, in patients with ME/CFS referred to a tertiary specialist clinic; (b) differences and similarities in levels of sickness behavior in patients with ME/CFS and patients with chronic pain referred to a tertiary specialist clinic compared to patients in primary care and individuals from the general population, and; (c) the relationship between sickness behavior and self-rated health, physical and mental functioning respectively in patients with ME/CFS, patients with chronic pain and individuals from the general population (Study IV)

# 4 EMPIRICAL STUDIES

The studies included in the present thesis are all conducted on clinical samples of adult patients with ME/CFS. First, I describe how we explored and identified the presence of latent subgroups of symptoms in ME/CFS, and the associations between these symptom subgroups and different aspects of health and functioning (Study I). Second, I delineate how we developed and evaluated an ACT-based behavior medicine treatment protocol for ME/CFS (Study II). Third, I depict how we explored the associations between inflammatory markers, measured in peripheral blood, and common/sickness behavior-related symptoms in ME/CFS (Study III). Finally, I outline how we investigated and compared the subjective level of sickness behavior in ME/CFS with the level in patients with chronic pain, patients from primary care and individuals from the general population (Study IV).

As the methods and results are thoroughly described in the respective paper, I will present them here in a briefer format.

## 4.1 STUDY I: IDENTIFYING SYMPTOM SUBGROUPS IN PATIENTS WITH ME/CFS – RELATIONSHIPS TO FUNCTIONING AND QUALITY OF LIFE

Symptoms required for diagnosis differ across the different consensus-based diagnostic criteria used for diagnosing ME/CFS. Hence there is a need for empirical studies investigating if and how commonly reported symptoms present and relate to each other and clinically important factors.

### 4.1.1 Methods

Recruitment of patients was part of the diagnostic assessment at an out-patient ME/CFS specialist clinic between 2011 and 2013. After diagnostic evaluations by a physician and psychologist respectively, a total of 106 adult patients were included in the study after fulfilling the 1994 CDC and 2003 Canadian criteria for ME/CFS (1, 11). Dimensions of fatigue (MFI-20), depression/anxiety (HADS), health-related functioning (SF-36) and quality of life (EQ-5D) were assessed with validated questionnaires (133-136). For the exploration of latent symptom subgroups, patients reported the prevalence and intensity (from “not present” to “unbearable”) of 14 commonly reported symptoms chosen based on the 2003 Canadian criteria and our clinical experience of commonly occurring symptoms (11). Principal component analyses (PCA) were utilized to explore how symptoms were related in subgroups, bivariate correlation analyses were used to investigate the relationships between

symptom subgroups and: dimensions of fatigue; depression; anxiety; health-related physical and mental functioning and; quality of life respectively.

### 4.1.2 Results

Main findings include the identification of four distinct and clinically meaningful subgroups of symptoms, termed “Inflammatory”, “Pain”, “Neurocognitive” and “Autonomic” based on the included symptoms in each group. Furthermore, symptom subgroups were consistently related to measures of fatigue, anxiety, health-related functioning and quality of life. Notably, the strength of the correlations seldom exceeded .50, which indicates that factors besides the common symptoms are important for functioning and health in ME/CFS.

## 4.2 STUDY II: ACCEPTANCE & COMMITMENT THERAPY FOR ME/CFS (CHRONIC FATIGUE SYNDROME) – A FEASIBILITY STUDY

Based on the findings from Study I, and our clinical and research experience of the chronic pain patient population, we sought to adapt and develop our ACT-based behavior medicine treatment protocol, developed originally for chronic pain, for patients with ME/CFS. The aim was to preliminarily evaluate if the treatment was feasible, accepted as safe and relevant for patients, and effective in improving subjective functioning and quality of life. A secondary aim was to preliminarily explore the importance of psychological flexibility for the treatment outcome.

### 4.2.1 Methods

Adult patients were consecutively recruited after diagnostic assessment at a tertiary specialist clinic. Besides fulfilling the 1994 CDC and 2003 Canadian criteria for ME/CFS (1, 11), inclusion criteria included no present primary condition (psychiatric or somatic) in need of treatment and no other planned treatment in the coming six months. A total of 40 patients were included in the study and started treatment consecutively, consisting of 13 sessions (45 min) weekly to bi-weekly, delivered by a psychologist (10 sessions) and a physician (3 sessions). The ACT treatment format was developed as an adapted version of a treatment protocol developed and evaluated for chronic pain by our group during the last 15 years (98, 126, 127, 137-144). The treatment is described in more detail in the paper, a brief overview will follow here.

The initial phase of treatment included education in plausible physiological mechanisms and learning theory principles. This in order to validate the symptoms as real and at the same time

non-malignant, and to shift focus to the function (what do you do in the presence of symptoms/discomfort and is it effective?) and not the shape/form/logic of experiences (symptoms, thoughts, feelings) and behaviors. In this phase, a functional contextual analysis of the present life situation was carried out, identifying all forms of discomfort the patient currently struggled with. In the next phase, the "struggle" behaviors and accompanying rules/thoughts were operationalized and analyzed based on their workability, i.e. what effects they had on either symptom resolution or quality of life. All such strategies and outcomes were evaluated in relation to the life the individual valued, concerning for example relationships, interests and so forth. The main targets of treatment then, were to increase contact with such values as consequences, through increasing values-directed behaviors. The practice in identifying and reducing unhelpful rules and behaviors (cognitive defusion) and the letting go of the struggle with discomfort that cannot be avoided (exposure and acceptance in order to allow a shift in focus towards values) were central parts of sessions throughout treatment following the initial education phase.

Measures of symptoms (measured as in Study I), dimensions of fatigue (MFI-20), depression/anxiety (HADS), psychological flexibility (an adapted version of the Psychological Inflexibility in Pain Scale replacing Pain with Fatigue), disability (an adapted version of the Pain Disability Index replacing Pain with ME/CFS symptoms), health-related functioning (SF-36) and quality of life (EQ-5D) were assessed at baseline, post-treatment and at 3- and 6-month follow-ups. Additionally, psychological flexibility and disability were assessed at mid-treatment in order to enable a preliminary investigation of the importance of changes in psychological flexibility for treatment outcome. Changes in all above measures across time were analyzed with piecewise (pre-post; post-FU) linear mixed-effects models. Furthermore, the participants experience of the treatment format, content, and potential side-effects, were assessed with a brief questionnaire, developed for the study, after completion of treatment.

### 4.2.2 Results

32 patients (80%) completed treatment. Results showed that the ACT-based behavior medicine protocol could be considered safe, acceptable and preliminarily effective with improvements in multiple outcomes including disability ($d$=.80) and psychological flexibility ($d$=1.07). In addition, the results indicate that changes in psychological flexibility added to the treatment effect on disability in a significant way ($p$<.001).

## 4.3 STUDY III: THE ROLE OF LOW-GRADE INFLAMMATION IN ME/CFS (CHRONIC FATIGUE SYNDROME) – ASSOCIATIONS WITH SYMPTOMS

As demonstrated in Study I and II, ME/CFS patients present with several symptoms besides fatigue, that are consequently related to functioning and health. The symptomatology shows great similarities with sickness behavior, the motivational state accompanying innate immune activation. In addition, recent research results indicate an association between fatigue severity and levels of inflammatory markers. However, there is a lack of studies investigating the associations between; (a) sickness behavior-related symptoms; (b) common ME/CFS symptoms besides fatigue, and; (c) inflammatory markers previously shown to be related to sickness behavior and fatigue respectively.

### 4.3.1 Methods

Adult patients were recruited consecutively after diagnostic assessment a tertiary specialist clinic as in Study II. In total, 53 patients were included in this study. Patients rated the average severity of symptoms (0-10) during a structured clinical interview. Symptoms (recurrent flu-like symptoms; musculoskeletal pain; impaired cognitive processing; post-exertional fatigue) were chosen based on previous research of sickness behavior and ME/CFS respectively and our clinical experience of patient-reported commonly occurring debilitating symptoms. Blood was collected in the morning (participants were instructed not to eat before blood sampling on this day), plasma was analyzed using the Olink Proseek Multiplex Inflammation Panel and the BioRad Human Cytokine Type 1 assay. The Olink panel includes 92 inflammation-related biomarkers. The BioRad assay was used to measure tumor necrosis factor (TNF)-α as this marker was not detectable in approximately 50% of samples using the Olink panel. In total, 13 inflammatory markers were chosen for subsequent analyses based on previous research of sickness behavior (TNF-α, interleukins (IL)-6 and (IL)-8) and ME/CFS (IL-7, IL-10, IL-18, Eotaxin (CCL11), C-X-C motif chemokine (CXCL)1, CXCL10, Latency-associated peptide transforming growth factor beta (LAP-TGF-β)-1, Transforming growth factor (TGF)-α, Stem cell factor (SCF) and Beta-nerve growth factor (β-NGF)). Associations between symptoms and inflammatory markers were investigated with bivariate correlations and moderated regression analyses with biological sex as moderator.

### 4.3.2 Results

Several inflammatory markers (β-NGF, CCL11, CXCL10, IL-7, TGF-β-1) showed significant associations with post-exertional fatigue, musculoskeletal pain and impaired

cognitive processing, and the sickness behavior-related marker TNF-α showed a significant association with recurrent flu-like symptoms. Furthermore, biological sex moderated some of these associations.

## 4.4 STUDY IV: SICKNESS BEHAVIOR, SELF-RATED HEALTH AND FUNCTIONING – DIFFERENCES IN ME/CFS AND CHRONIC PAIN COMPARED TO PRIMARY CARE PATIENTS AND THE GENERAL POPULATION

The overarching context for this thesis is the investigation of ME/CFS from a joint sickness behavior and behavior medicine perspective. Notably, the level of sickness behavior, assessed with a validated instrument, has not been investigated in patients with ME/CFS nor in patients with chronic pain, despite the similarities in symptomatology. Furthermore, we wanted to compare the level of sickness behavior in these patient groups with the level in patients in primary care and in individuals from the general population, in order to provide context for the results. In addition, we sought to investigate the associations between sickness behavior, self-rated health and health-related mental and physical functioning in patients with ME/CFS, patients with chronic pain and in individuals from the general population.

### 4.4.1 Methods

Patients with ME/CFS (*n*=40) were recruited as described in Study II and III. Patients with chronic pain (*n*=193) were also recruited at a tertiary specialist clinic, exclusion criteria included primary psychiatric comorbidity (high risk of suicide; severe depression; psychotic symptoms). Patients at a primary care drop-in clinic (*n*=168) were recruited consecutively as described in detail previously (145, 146). The three most common causes of visit in this group were muscle/joint pain, acute infection and airway symptoms (allergy/asthma). Data from individuals from the general population (*n*=163) was collected as part of the LongGERD study, investigating abdominal symptoms in a random sample of the general population, described previously in detail (147). Sickness behavior was assessed using the Sickness Questionnaire (SicknessQ), a 10-item questionnaire developed to assess subjective sickness behavior in humans (146). Self-rated health and health-related mental and physical functioning were assessed with the RAND SF-36 (ME/CFS and general population)/SF-12 (chronic pain) Health Survey (134, 148). The first question in the instrument (SF-36/SF-12) assesses self-rated health, the mental (MCS) and physical (MCS) composite scores were used to assess health-related mental and physical functioning respectively. Linear regression was utilized to compare differences in level of sickness behavior between the groups, including

item-by-item comparisons. Bivariate correlations and moderated regression analyses were used to investigate the associations between sickness behavior, self-rated health and health-related mental and physical functioning.

### 4.4.2 Results

Patients with ME/CFS and chronic pain reported similar and high levels of sickness behavior. The level of sickness behavior was significantly higher in these patients compared to primary care patients and individuals from the general population. Significant associations between sickness behavior and self-rated health, mental and physical health-related functioning were repeatedly shown.

## 4.5 ETHICAL CONSIDERATIONS

All studies in the present thesis have been reviewed by the regional research ethics committees in Stockholm or Uppsala. Study 2, 3 and 4 were approved by the board. Study I was reviewed but considered a clinical development project which does not fall under the law of ethical assessment of research in humans. However, the committee stated no ethical conflicts. All participants were given written and oral information and provided informed consent. Importantly, all research in the present thesis was conducted in accordance with the World Medical Association Declaration of Helsinki (149). The ACT trial was registered in the ClinicalTrials.gov registry. All ME/CFS participants in all included studies were referred for specialist care, where instructions were that the patient as well as the referring physician explicitly stated a request of assessment of ME/CFS and/or ACT-based behavior medicine treatment for ME/CFS (if diagnosis had been made by a specialist before referral).

The present thesis entails an ACT-based behavior medicine treatment study encompassing approximately 15 visits á 45 minutes weekly to bi-weekly. Questionnaire data was sampled before, during and after treatment as well as at follow-ups. Questionnaire data from ME/CFS patients not included in the treatment study was sampled as part of the diagnostic assessment visits. The project also includes blood sampling through standard procedure at the hospital by trained health-care professionals.

First, regarding the treatment program, no negative or harmful side effects were considered to appear in the short or the long-term. Notably, at the time of study inclusion, ACT had, to our knowledge, not been tested for ME/CFS. However, numerous studies investigating the acceptability of CBT have not shown any short or long-term negative effects of treatment. Furthermore, ACT-based treatment is considered safe and effective for similar conditions

(chronic pain, FMS, IBS). More so, the ACT treatment protocol did not entail systematic increase in physical activity nor did it by rule encourage participants to systematically push their physical limits as a way to improve. Finally, to date there are no empirically evaluated or evidence-based treatment programs for patients with ME/CFS in Sweden. Potential negative side-effects were continuously monitored throughout the trial. Hence, when balancing the risk of negative events with the opportunity of developing evidence-based treatments for this severely affected group without any other effective treatment at-hand, the treatment program part of the project could be considered ethical as is could potentially lead to benefits for the participants, their families and society at-large.

Second, sampling of blood data was not considered to entail any adverse events for the participant in the short or long-term besides the potential momentary discomfort of blood drawing. More so, participants were informed that participation in the treatment part of the research project was not conditioned on participation in the sampling above and vice versa. Furthermore, analyses of the individual data sampled was presented and available to the individual participant, which includes tests that are not part of the standard laboratory tests in healthcare and hence directly informative for the individual participant. We considered this as ethical as the etiology and pathophysiology of the condition is unknown, and discovering as well as discarding potential illness mechanisms through this data collection would benefit participants both in the short and long-term.

The identification of a subgroup of patients in which a malfunctioning sickness behavior circuitry is a factor in the development of these symptoms has important clinical implications. First, this would be a small but important step towards the discovery of disease mechanisms. This would also generate specific hypotheses to guide future treatment studies. Furthering the knowledge of the diagnosis in this manner would entail the future identification of other clinically important subgroups within the patient population. Especially since heterogeneity within the patient group is a clear factor that prevents the development of knowledge regarding etiology/pathophysiology, reflected in the numerous classifications and lack of effective treatment. The results are also expected to significantly contribute to new hypotheses regarding the importance of sickness behavior in other long-term intractable conditions, such as stress-related exhaustion, chronic pain, fibromyalgia and irritable bowel syndrome. Finally, the present research project will generate new hypotheses regarding the relationships between sickness behavior and mental health. Etiology and pathophysiology are still unknown for many psychiatric conditions, but an increasing number of studies point to the link between depression and neuro-immune interactions for example.

The questionnaires and data from the studies included in this thesis were coded for anonymity and kept safe in locked facilities and secure servers to minimize the risk of violation of integrity. Through developing shorter and still valid and reliable instruments, and through achieving more effective assessment overall, the patient burden of assessment may ultimately be reduced. For the overall project, several parties can be identified for whom the benefits differ. For the participants, increased knowledge about ME/CFS and possible comorbidity will potentially lead to better care, and possibly fewer unnecessary assessments. Most importantly, the level of knowledge of ME/CFS and how it affects health and disability is in general low in the Swedish healthcare and health insurance system. Thus, the study participation in research on ME/CFS in Swedish samples of patients should also be of value for the participant as it will communicate empirically based information about the condition to decision-makers in the proximity of the patient as well as to policy makers. For the next-of-kin, increased knowledge about ME/CFS may likely lead to less concern (or more adequate concern) in family members and important others. Moreover, effective treatments and better assessments will probably also mean less time spent in hospitals or clinics for family members and important others. For the healthcare system, effective assessment and treatment of patients with ME/CFS probably entails improved management of resources e.g. through fewer healthcare contacts and more satisfied patients. For the community, savings in terms of reduced costs of healthcare as a result of improved assessment and treatment are plausible.

In summary, it may be concluded that the benefits outweigh the risks associated with the research in the present thesis.

# 5 DISCUSSION

## 5.1 MAIN FINDINGS

Symptoms other than fatigue that are commonly present in ME/CFS form distinct subgroups. That is, symptoms follow patterns where the level of one symptom is related to the level of another specific symptom. The symptom subgroups are in turn differentially associated with levels of health and functioning in patients with ME/CFS. This might guide future research towards the further study of patient subgroups and the identification of accessible treatment targets (Study I). Considering the moderate sizes of the correlations it is plausible that other factors beyond symptoms, plausibly experiential avoidance and cognitive fusion, are of importance for subjective health and functioning in ME/CFS and in need of further study (Study I). Consistent with this, targeting these general human processes thought to contribute

to suffering and disability as they are conceptualized in ACT treatment was found to be feasible, safe, relevant and preliminary effective for ME/CFS patients seeking tertiary specialist care (Study II). Sickness behavior-related inflammatory processes may be related to symptom intensity in ME/CFS, although larger longitudinal studies are needed to investigate causality. The results also indicate the potential importance of investigating biological sex as a moderator when studying how inflammatory markers are related to symptoms in ME/CFS, where women outnumber men 3:1 approximately (39), as mechanisms may differ between the sexes (Study III). The level of sickness behavior as measured subjectively with the SicknessQ is remarkably high in ME/CFS, with levels similar to those reported by individuals after experimentally induced inflammation (Study IV). This, and the similarity in sickness behavior level between ME/CFS and chronic pain patients, clearly indicates the merit of the further study of sickness behavior processes in these populations, where both etiological factors and important treatment targets could be overlapping.

## 5.2 CONCLUSIONS AND LIMITATIONS

### 5.2.1 Symptom presentation, variation and heterogeneity in ME/CFS

The results from Study I expands previous research on symptom patterns in ME/CFS, where studies show similarities in findings of latent symptom subgroups pertaining to inflammatory (e.g. feverishness), pain (e.g. musculoskeletal pain) and neurocognitive (e.g. difficulties with concentration) symptoms respectively (150-152). Notably, we also found a fourth distinct subgroup (autonomic) consisting of headache, irritable bowel symptoms and orthostatic intolerance (dizziness when standing up). The spectrum of symptoms prevalent in ME/CFS is vast, echoed in the multiple illness definitions that have been developed to date (9). Hence, it is probable that also other symptoms than those measured in Study I are of importance, which is an evident limitation of the study. All of the subgroups found in Study I showed significant but differential associations to dimensions of fatigue, depression, anxiety, health-related mental and physical functioning and quality of life. The identification of symptom subgroups and the variation of the strength of the relationships between these subgroups and important clinical measures indicate the importance of the further investigation of: (a) other factors important for functioning and quality of life, and; (b) potential illness subtypes. Furthermore, my clinical experience of working with this condition is that symptoms, in many cases, vary across time not only between but also within patients. This variation is described both in terms of the level and type of symptoms. Also, the results from Study IV, where ME/CFS and chronic pain patients show great similarities in levels of sickness behavior, indicate potential similarities between these groups also with regards to general symptomatology. As such,

there is a need for larger longitudinal studies investigating symptom prevalence, intensity and variation in ME/CFS, as the cross-sectional design in Study I is a limitation that prevents investigation of causality. It would be of evident value to include assessment of similar conditions such as chronic pain, fibromyalgia, irritable bowel syndrome and stress-related exhaustion in such a longitudinal design, in order to improve classification systems and perhaps find better distinguishing features than solely symptomatology and/or perceived causes. I think such research is of paramount importance in conditions where etiology and pathophysiological mechanisms are unknown, there is a high level of comorbidity (one condition may in some cases increase the probability of another), and psychological factors/stressors and neuro-immune interactions are plausibly involved.

### 5.2.2 The value of ACT for patients with ME/CFS – not a one size fits all model

ACT for ME/CFS (Study II) as described in the study treatment protocol can preliminarily be considered safe, with no reported negative effects in the short or long-term, lending further support to previous research showing the importance of promoting psychological flexibility for lessening the illness impact on functioning and quality of life in ME/CFS (129-132). However, there is a need for randomized controlled trials in order to evaluate efficacy. Although the drop-out could be considered reasonable (20%), a personal reflection from the trial is that ACT for ME/CFS requires therapists that are up-to-date regarding the current body of research on ME/CFS in order to maintain the face validity of an ACT approach to symptoms and discomfort. Patients with ME/CFS seeking specialist care oftentimes have a distinct and coherent story of what their illness is and is caused by, including both school medicine and alternative medicine explanatory models. As such, the initial physiological and learning theory education part of the treatment (described in detail in the article) making the conceptualization of the illness and its impact on life coherent despite unavoidable uncertainties, is of crucial importance for enabling the shift in perspective from struggling with symptoms to a valued life. This is the case in all ACT treatment, but for clinicians and researchers planning similar treatments or studies, it seems even more important to stress in ACT for ME/CFS patients, as they have often tried all accessible treatment options. Furthermore, the variability in symptom intensity, and most importantly, the hypersensitivity to exertion in ME/CFS brings its own set of challenges when conducting an out-patient protocol-based trial requiring a certain frequency of face-to-face sessions in the clinic. Namely, sometimes patients are too disabled to attend sessions. This is also an evident limitation in Study II, where included patients in general had a level of functioning allowing the completion of such a format. Patient ratings and our clinical experience from the trial

indicate that a more expanded treatment format could be more advantageous for ME/CFS patients (in comparison with chronic pain patients for whom the original protocol was developed), with a treatment duration of at least 6 months and a lower frequency than the common once a week-session. A hybrid treatment format with live video sessions and online treatment content should be investigated in future studies, especially in order to make treatment available for those too disabled or too distant from specialist clinics. With regards to the conceptualization of human suffering in ACT discussed in the Introduction, the results also lend preliminary support for psychological flexibility as an important mediating factor for improvements in disability also in ACT for ME/CFS. In a longstanding condition like ME/CFS, it may be more workable to: (a) analyze and interpret symptoms and experiences in the context of a malfunctioning sickness behavior circuitry that will not shut down even though it should, since; (b) the assumed inherent evolutionary functions of sickness behavior and derived rules there-of ("my body is telling me there is something wrong!"), which in the prototypical situation prompts behaviors that resolve the sickness state, does not result in resolution in this condition. Still, limitations such as the non-controlled design and the lack of competing measured constructs during treatment makes conclusions about efficacy and the importance of psychological flexibility very tentative, and future randomized studies with relevant competing factors known to affect change are needed to confirm psychological flexibility as a significant mediator of effects in ACT for ME/CFS, and if so, for whom.

### 5.2.3 ME/CFS as a chronic sickness behavior condition – from inflammatory molecules to subjective experience

Although several significant associations between inflammatory markers and symptoms were found in Study III, the results should be interpreted cautiously given the cross-sectional design and small sample size. Interestingly, biological sex moderated several associations, and future larger studies should include this aspect as inflammatory processes may differ in their relationships to symptom development between women and men in ME/CFS. Another aspect that could be considered both a limitation and a strength, is the measurement of symptoms, which could have affected the strength of the associations. Patients rated their average (trait) and not the present moment (state) severity of symptoms. An evident limitation in that levels of inflammatory markers on the day of measurement could not be related to the levels of symptoms as they presented at the same time-point. A strength, as although symptoms vary, the most commonly elevated symptoms across time should plausibly be related to pathophysiological mechanisms. However, cytokines in peripheral blood is a noisy, fluctuating variable that changes depending on a large number of other factors such as body mass index, smoking, recent food intake, previous night's sleep,

menstrual phase, and so forth. Cytokines change in circadian and ultradian rhythms - the same person under the same conditions will show different cytokine levels from hour to hour (6). Furthermore, experimental studies show that the association between inflammation and subjective experience does not necessarily depend on the absolute level of inflammatory markers, making the significant vs non-significant associations between inflammatory markers in periphery and subjective symptom ratings in Study III more difficult to interpret (85). Nevertheless, as the symptomatology in ME/CFS is analogous to a chronic sickness behavior state, it is plausible that illness drivers are related to a malfunctioning sickness behavior circuitry in a subset of patients. Longitudinal studies with multiple assessments including neural correlates are needed to investigate the importance of inflammatory markers for symptom variation in ME/CFS. Another most interesting finding, in Study IV, was that the level of sickness behavior assessed with the SicknessQ were similar between ME/CFS and chronic pain patients. Furthermore, the level of sickness behavior reported in these conditions is equivalent to the level reported at peak immune response in experimental studies (146, 153). As such, the results point to the importance of the further study of objective and subjective markers of sickness behavior in these groups, where malfunctioning sickness behavior-related mechanisms may be part of the pathophysiology in subgroups of patients.

### 5.2.4 Concluding remarks and future directions

For readers familiarizing themselves with ME/CFS just now, as part of reading the present thesis, it may seem perplexing that etiology and pathophysiological mechanisms are still unknown and no effective treatment choices exist, despite a considerable amount of research studies since the rather precise description of the condition already in the 1800's (3). Based on this fact, and the results from the studies in the present thesis, I would suggest that: (a) ME/CFS is not ONE illness entity, but consists of several subsets of patients with differentiated illness mechanisms, and; (b) contextualizing ME/CFS from an ACT-based behavior medicine perspective and; (c) understanding it from a sickness behavior perspective is of evident value in order to: (d) alleviate suffering and promote quality of life; (e) guide further research in search of mechanisms accessible for targeted treatment, and; (f) identify vulnerability factors in order to develop effective preventive strategies. Most importantly, future research should be guided by empirically based definitions of the condition(s). As such, a more workable view would be to look beyond the topographical features of stressors (for example viral infection vs. long-term stress) or symptoms and instead consider how multiple "hits" on the homeostatic systems in some individuals lead to the chronic symptoms

seen in conditions with longstanding debilitating unclear fatigue and comorbid symptoms. Plausibly, it is not necessarily the type of hit in itself nor the absolute levels of immune mediators that cause or maintain the symptoms. Rather, research investigating ME/CFS should explore: (a) predictors and vulnerability factors, including biological and psychological/behavioral; (b) the activity and reactivity of brain areas related to interoceptive communication of body state; (c) the activity and reactivity of the stress and immune systems; (d) responses and behaviors on the psychological level; (e) how these factors are related and; (f) relates to disability. Such approach potentially holds the best promise of discovering the etiological and pathophysiological mechanisms in these conditions. In the wait of such discoveries, approaches effective in alleviating suffering and increasing contact with the valued life should be available to all sufferers.

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# 7 REFERENCES


1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Annals of internal medicine. 1994;121(12):953-9.

2. A New Clinical Entity? The Lancet. 1956;267(6926):789-90.

3. Beard G. Neurasthenia, or Nervous Exhaustion. The Boston Medical and Surgical Journal. 1869;80(13):217-21.

4. Leone SS, Wessely S, Huibers MJ, Knottnerus JA, Kant I. Two sides of the same coin? On the history and phenomenology of chronic fatigue and burnout. Psychol Health. 2011;26(4):449-64.

5. Grossi G, Perski A, Osika W, Savic I. Stress-related exhaustion disorder--clinical manifestation of burnout? A review of assessment methods, sleep impairments, cognitive disturbances, and neuro-biological and physiological changes in clinical burnout. Scand J Psychol. 2015;56(6):626-36.

6. VanElzakker MB, Brumfield SA, Lara Mejia PS. Neuroinflammation and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Critical Review of Research Methods. Front Neurol. 2019;9(1033).

7. Natelson BH, Haghighi MH, Ponzio NM. Evidence for the presence of immune dysfunction in chronic fatigue syndrome. Clinical and diagnostic laboratory immunology. 2002;9(4):747-52.

8. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington DC: 2015 by the National Academy of Sciences; 2015 Feb 10.

9. Brurberg KG, Fonhus MS, Larun L, Flottorp S, Malterud K. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. BMJ open. 2014;4(2):e003973.

10. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al. Myalgic encephalomyelitis: International Consensus Criteria. Journal of internal medicine. 2011;270(4):327-38.

11. Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Journal of Chronic Fatigue Syndrome. 2003;11(1):7-115.

12. Jason L, Corradi K, Torres-Harding S, Taylor R, King C. Chronic Fatigue Syndrome: The Need for Subtypes. Neuropsychol Rev. 2005;15(1):29-58.

13. Jonsjö MA, Wicksell RK, Holmström L, Andreasson A, Bileviciute-Ljungar I, Olsson GL. Identifying symptom subgroups in patients with ME/CFS – relationships to functioning and quality of life. Fatigue: Biomedicine, Health & Behavior. 2017;5(1):33-42.

14. Vollmer-Conna U, Aslakson E, White PD. An empirical delineation of the heterogeneity of chronic unexplained fatigue in women. Pharmacogenomics. 2006;7(3):355-64.

15. Wilson A, Hickie I, Wilson A, Hickie I, Hadzi-Pavlovic D, Wakefield D, et al. What is Chronic Fatigue Syndrome? Heterogeneity Within an International Multicentre Study. Aust N Z J Psychiatry. 2001;35(4):520-7.

16. Jason LA, Kot B, Sunnquist M, Brown A, Evans M, Jantke R, et al. Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: Toward An Empirical Case Definition. Health psychology and behavioral medicine. 2015;3(1):82-93.

17. Nijs J, Lundberg M. Avoidance behavior towards physical activity in chronic fatigue syndrome and fibromyalgia: the fear for post-exertional malaise. Clinical rheumatology. 2014;33(1):151-2.

18. Nijs J, Van Oosterwijck J, Meeus M, Lambrecht L, Metzger K, Frémont M, et al. Unravelling the nature of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1β. J Intern Med. 2010;267(4):418-35.

19. Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. Medicine and science in sports and exercise. 2012;44(6):1186-93.

20. Jason LA, Evans M, So S, Scott J, Brown A. Problems in defining post-exertional malaise. Journal of prevention & intervention in the community. 2015;43(1):20-31.

21. Glise K, Ahlborg G, Jr., Jonsdottir IH. Prevalence and course of somatic symptoms in patients with stress-related exhaustion: does sex or age matter. BMC Psychiatry. 2014;14:118.

22. Huibers MJH, Beurskens AJHM, Prins JB, Kant IJ, Bazelmans E, Van Schayck CP, et al. Fatigue, burnout, and chronic fatigue syndrome among employees on sick leave: do attributions make the difference? Occup Environ Med. 2003;60 Suppl 1:i26.

23. Leone SS, Huibers MJH, Knottnerus JA, Kant I. A comparison of the course of burnout and prolonged fatigue: A 4-year prospective cohort study. J Psychosom Res. 2008;65(1):31-8.

24. Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, et al. Chronic fatigue syndrome: a working case definition. Annals of internal medicine. 1988;108(3):387-9.

25. Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, et al. A report--chronic fatigue syndrome: guidelines for research. Journal of the Royal Society of Medicine. 1991;84(2):118-21.

26. Shirom A. Reflections on the study of burnout. Work Stress. 2005;19(3):263-70.

27. Chu L, Valencia IJ, Garvert DW, Montoya JG. Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Frontiers in pediatrics. 2019;7:12.

28. Nacul LC, Lacerda EM, Pheby D, Campion P, Molokhia M, Fayyaz S, et al. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. BMC medicine. 2011;9:91.

29. Jason LA, Porter N, Hunnell J, Rademaker A, Richman JA. CFS prevalence and risk factors over time. J Health Psychol. 2011;16(3):445-56.

30. Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, et al. A community-based study of chronic fatigue syndrome. Arch Intern Med. 1999;159(18):2129-37.

31. Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, et al. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003;163(13):1530-6.

32. Lindal E, Stefansson JG, Bergmann S. The prevalence of chronic fatigue syndrome in Iceland - a national comparison by gender drawing on four different criteria. Nordic journal of psychiatry. 2002;56(4):273-7.

33. Johnston S, Brenu EW, Staines D, Marshall-Gradisnik S. The prevalence of chronic fatigue syndrome/ myalgic encephalomyelitis: a meta-analysis. Clinical epidemiology. 2013;5:105-10.

34. Cho HJ, Menezes PR, Hotopf M, Bhugra D, Wessely S. Comparative epidemiology of chronic fatigue syndrome in Brazilian and British primary care: prevalence and recognition. The British journal of psychiatry : the journal of mental science. 2009;194(2):117-22.

35. Hickie I, Davenport T, Vernon SD, Nisenbaum R, Reeves WC, Hadzi-Pavlovic D, et al. Are chronic fatigue and chronic fatigue syndrome valid clinical entities across countries and health-care settings? The Australian and New Zealand journal of psychiatry. 2009;43(1):25-35.

36. Lloyd AR, Hickie I, Boughton CR, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. The Medical journal of Australia. 1990;153(9):522-8.

37. Johnston SC, Staines DR, Marshall-Gradisnik SM. Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. Clinical epidemiology. 2016;8:97-107.

38. Lawrie SM, Pelosi AJ. Chronic fatigue syndrome in the community. Prevalence and associations. The British journal of psychiatry : the journal of mental science. 1995;166(6):793-7.

39. Bakken IJ, Tveito K, Gunnes N, Ghaderi S, Stoltenberg C, Trogstad L, et al. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008-2012. BMC medicine. 2014;12:167.

40. Donnachie E, Schneider A, Mehring M, Enck P. Incidence of irritable bowel syndrome and chronic fatigue following GI infection: a population-level study using routinely collected claims data. Gut. 2018;67(6):1078-86.

41. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347-69.

42. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European journal of pain. 2006;10(4):287-333.

43. Hauser W, Ablin J, Fitzcharles MA, Littlejohn G, Luciano JV, Usui C, et al. Fibromyalgia. Nature reviews Disease primers. 2015;1:15022.

44. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. Nature reviews Disease primers. 2016;2:16014.

45. Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. Occupational medicine. 2005;55(1):20-31.

46. Jason LA. Natural History of Chronic Fatigue Syndrome. Rehabil Psychol. 2011;56(1):32-42.

47. Jason LA, Porter N, Brown M, Anderson V, Brown A, Hunnell J, et al. CFS: A Review of Epidemiology and Natural History Studies. Bulletin of the IACFS/ME. 2009;17(3):88-106.

48. van der Werf SP, de Vree B, Alberts M, van der Meer JW, Bleijenberg G. Natural course and predicting self-reported improvement in patients with chronic fatigue syndrome with a relatively short illness duration. Journal of psychosomatic research. 2002;53(3):749-53.

49. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Prognosis in chronic fatigue syndrome: a prospective study on the natural course. Journal of neurology, neurosurgery, and psychiatry. 1996;60(5):489-94.

50. Falk Hvidberg M, Brinth LS, Olesen AV, Petersen KD, Ehlers L. The Health-Related Quality of Life for Patients with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS). PloS one. 2015;10(7):e0132421.

51. Janssens KA, Zijlema WL, Joustra ML, Rosmalen JG. Mood and Anxiety Disorders in Chronic Fatigue Syndrome, Fibromyalgia, and Irritable Bowel Syndrome: Results From the LifeLines Cohort Study. Psychosomatic medicine. 2015;77(4):449-57.

52. Johansson R, Carlbring P, Heedman A, Paxling B, Andersson G. Depression, anxiety and their comorbidity in the Swedish general population: point prevalence and the effect on health-related quality of life. PeerJ. 2013;1:e98.

53. Swartz MN. The chronic fatigue syndrome--one entity or many? The New England journal of medicine. 1988;319(26):1726-8.

54. Klimas NG, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. Brain Behav Immun. 2012;26(8):1202-10.

55. Arnett SV, Clark IA. Inflammatory fatigue and sickness behaviour - lessons for the diagnosis and management of chronic fatigue syndrome. Journal of affective disorders. 2012;141(2-3):130-42.

56. Maloney EM, Boneva R, Nater UM, Reeves WC. Chronic fatigue syndrome and high allostatic load: results from a population-based case-control study in Georgia. Psychosomatic medicine. 2009;71(5):549-56.

57. Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, et al. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. European journal of clinical investigation. 2012;42(2):203-12.

58. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.

59. Papadopoulos AS, Cleare AJ. Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. Nature reviews Endocrinology. 2011;8(1):22-32.

60. Tomas C, Newton J, Watson S. A review of hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. ISRN neuroscience. 2013;2013:784520.

61. Blundell S, Ray KK, Buckland M, White PD. Chronic fatigue syndrome and circulating cytokines: A systematic review. Brain Behav Immun. 2015;50:186-95.

62. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46-56.

63. Dantzer R. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. European journal of pharmacology. 2004;500(1-3):399-411.

64. Vitkovic L, Konsman JP, Bockaert J, Dantzer R, Homburger V, Jacque C. Cytokine signals propagate through the brain. Mol Psychiatry. 2000;5(6):604-15.

65. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. 2002;25(3):154-9.

66. Quan N, Banks WA. Brain-immune communication pathways. Brain Behav Immun. 2007;21(6):727-35.

67. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature Reviews Neuroscience. 2008;9(1):46-56.

68. Brydon L, Walker C, Wawrzyniak A, Whitehead D, Okamura H, Yajima J, et al. Synergistic effects of psychological and immune stressors on inflammatory cytokine and sickness responses in humans. Brain, Behavior, and Immunity. 2009;23(2):217-24.

69. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007;21(2):153-60.

70. Hart BL. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev. 1988;12(2):123-37.

71. Hart BL. Behavioral adaptations to pathogens and parasites: five strategies. Neurosci Biobehav Rev. 1990;14(3):273-94.

72. Dantzer R, Cohen S, Russo SJ, Dinan TG. Resilience and immunity. Brain, Behavior, and Immunity. 2018;74:28-42.

73. Lyon DE, Cohen R, Chen H, Kelly DL, McCain NL, Starkweather A, et al. Relationship of systemic cytokine concentrations to cognitive function over two years in women with early stage breast cancer. J Neuroimmunol. 2016;301:74-82.

74. Wang XS, Williams LA, Krishnan S, Liao Z, Liu P, Mao L, et al. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain, Behavior, and Immunity. 2012;26(5):699-705.

75. Lacourt TE, Vichaya EG, Chiu GS, Dantzer R, Heijnen CJ. The High Costs of Low-Grade Inflammation: Persistent Fatigue as a Consequence of Reduced Cellular-Energy Availability and Non-adaptive Energy Expenditure. Front Behav Neurosci. 2018;12:78.

76. Parkitny L, Middleton S, Baker K, Younger J. Evidence for abnormal cytokine expression in Gulf War Illness: A preliminary analysis of daily immune monitoring data. BMC immunology. 2015;16:57.

77. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends in Immunology. 2006;27(1):24-31.

78. Savitz J, Harrison NA. Interoception and Inflammation in Psychiatric Disorders. Biological psychiatry Cognitive neuroscience and neuroimaging. 2018;3(6):514-24.

79. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biological psychiatry. 2009;66(5):407-14.

80. Harrison NA. Brain Structures Implicated in Inflammation-Associated Depression. Curr Top Behav Neurosci. 2017;31:221-48.

81. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. The Journal of clinical psychiatry. 2010;71(2):138-49.

82. Marshall PS, O'Hara C, Steinberg P. Effects of seasonal allergic rhinitis on fatigue levels and mood. Psychosomatic medicine. 2002;64(4):684-91.

83. Andreasson AN, Szulkin R, Unden AL, von Essen J, Nilsson LG, Lekander M. Inflammation and positive affect are associated with subjective health in women of the general population. Journal of Health Psychology. 2012;18(3):311-20.

84. Schedlowski M, Engler H, Grigoleit JS. Endotoxin-induced experimental systemic inflammation in humans: a model to disentangle immune-to-brain communication. Brain Behav Immun. 2014;35:1-8.

85. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ, et al. Neural origins of human sickness in interoceptive responses to inflammation. Biological psychiatry. 2009;66(5):415-22.

86. Schedlowski M, Pacheco-López G. The learned immune response: Pavlov and beyond. Brain, Behavior, and Immunity. 2010;24(2):176-85.

87. Dickerson SS, Gable SL, Irwin MR, Aziz N, Kemeny ME. Social-evaluative threat and proinflammatory cytokine regulation: an experimental laboratory investigation. Psychol Sci. 2009;20(10):1237-44.

88. Milrad SF, Hall DL, Jutagir DR, Lattie EG, Czaja SJ, Perdomo DM, et al. Depression, evening salivary cortisol and inflammation in chronic fatigue syndrome: A psychoneuroendocrinological structural regression model. Int J Psychophysiol. 2017.

89. Hall DL, Lattie EG, Antoni MH, Fletcher MA, Czaja S, Perdomo D, et al. Stress management skills, cortisol awakening response, and post-exertional malaise in Chronic Fatigue Syndrome. Psychoneuroendocrinology. 2014;49C:26-31.

90. Lattie EG, Antoni MH, Fletcher MA, Penedo F, Czaja S, Lopez C, et al. Stress management skills, neuroimmune processes and fatigue levels in persons with chronic fatigue syndrome. Brain Behav Immun. 2012;26(6):849-58.

91. Karshikoff B, Sundelin T, Lasselin J. Role of Inflammation in Human Fatigue: Relevance of Multidimensional Assessments and Potential Neuronal Mechanisms. Front Immunol. 2017;8:21.

92. Brenner P, Piehl F. Fatigue and depression in multiple sclerosis: pharmacological and non-pharmacological interventions. Acta Neurol Scand. 2016;134 Suppl 200:47-54.

93. Orji F. The Influence of Psychological Factors in Meniere's Disease. Annals of Medical and Health Sciences Research. 2014;4(1):3-7.

94. Syrjala KL, Jensen MP, Mendoza ME, Yi JC, Fisher HM, Keefe FJ. Psychological and Behavioral Approaches to Cancer Pain Management. Journal of clinical

oncology : official journal of the American Society of Clinical Oncology. 2014;32(16):1703-11.

95. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004;5(10):617-25.

96. Crofford LJ. Psychological aspects of chronic musculoskeletal pain. Best practice & research Clinical rheumatology. 2015;29(1):147-55.

97. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology. 2013;52(12):2136-48.

98. Wicksell RK, Kemani M, Jensen K, Kosek E, Kadetoff D, Sorjonen K, et al. Acceptance and commitment therapy for fibromyalgia: A randomized controlled trial. European journal of pain. 2012.

99. Kemani MK, Olsson GL, Lekander M, Hesser H, Andersson E, Wicksell RK. Efficacy and Cost-effectiveness of Acceptance and Commitment Therapy and Applied Relaxation for Longstanding Pain: A Randomized Controlled Trial. The Clinical journal of pain. 2015.

100. Ljotsson B, Falk L, Vesterlund AW, Hedman E, Lindfors P, Ruck C, et al. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome--a randomized controlled trial. Behaviour research and therapy. 2010;48(6):531-9.

101. Hind D, Cotter J, Thake A, Bradburn M, Cooper C, Isaac C, et al. Cognitive behavioural therapy for the treatment of depression in people with multiple sclerosis: a systematic review and meta-analysis. BMC Psychiatry. 2014;14:5.

102. Tatrow K, Montgomery GH. Cognitive behavioral therapy techniques for distress and pain in breast cancer patients: a meta-analysis. Journal of behavioral medicine. 2006;29(1):17-27.

103. Collatz A, Johnston SC, Staines DR, Marshall-Gradisnik SM. A Systematic Review of Drug Therapies for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. Clin Ther. 2016.

104. Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, et al. Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Annals of internal medicine. 2015;162(12):841-50.

105. Fluge O, Risa K, Lunde S, Alme K, Rekeland IG, Sapkota D, et al. B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment. PloS one. 2015;10(7):e0129898.

106. Fluge O, Bruland O, Risa K, Storstein A, Kristoffersen EK, Sapkota D, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PloS one. 2011;6(10):e26358.

107. Fluge O, Mella O. Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series. BMC neurology. 2009;9:28.

108. Fluge O, Rekeland IG, Lien K, Thurmer H, Borchgrevink PC, Schafer C, et al. B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Annals of internal medicine. 2019.

109. Reid S, Chalder T, Cleare A, Hotopf M, Wessely S. Chronic fatigue syndrome. Clinical evidence. 2011;2011.

110. Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008(3):CD001027.

111. White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823-36.

112. White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychological medicine. 2013:1-9.

113. Glise K, Ahlborg G, Jr., Jonsdottir IH. Course of mental symptoms in patients with stress-related exhaustion: does sex or age make a difference? BMC Psychiatry. 2012;12:18.

114. Graham CD, Gouick J, Krahe C, Gillanders D. A systematic review of the use of Acceptance and Commitment Therapy (ACT) in chronic disease and long-term conditions. Clinical psychology review. 2016;46:46-58.

115. Vilardaga R, Hayes SC, Levin ME, Muto T. Creating a Strategy for Progress: A Contextual Behavioral Science Approach. Behav Analyst. 2009;32(1):105-33.

116. Ramnerö J. The ABCs of human behavior behavioral principles for the practicing clinician. Electronic version. ed. Törneke N, editor. Oakland, Calif.: Oakland, Calif. : New Harbinger Publications; 2008.

117. Craig AD. A new view of pain as a homeostatic emotion. Trends Neurosci. 2003;26(6):303-7.

118. Hayes SC, Strosahl K, Wilson KG. Acceptance and commitment therapy : an experiential approach to behavior change. New York: Guilford Press; 1999. xvi, 304 p. p.

119. Hayes SC, Barnes-Holmes D, Roche B. Relational frame theory : a post-Skinnerian account of human language and cognition. New York: Kluwer Academic/Plenum Publishers; 2001. xvii, 285 p. p.

120. Törneke N. Learning RFT an introduction to relational frame theory and its clinical applications. Oakland, Calif.: Oakland, Calif. : New Harbinger Publications; 2010.

121. Hayes SC. Rule-governed behavior : cognition, contingencies, and instructional control. Reno, NV: Context Press; 2004. xix, 391 p. p.

122. Wilson DS, Hayes SC, Biglan A, Embry DD. Evolving the future: Toward a science of intentional change. 2014;37(4):395-416.

123. Blackledge JT. AN INTRODUCTION TO RELATIONAL FRAME THEORY: BASICS AND APPLICATIONS. The Behavior Analyst Today. 2003;3(4):421-33.

124. Hayes SC. Acceptance and Commitment Therapy, Relational Frame Theory, and the third wave of behavioral and cognitive therapies. Behav Ther. 2004;35(4):639-65.

125. Ferreira NB, Eugenicos MP, Morris PG, Gillanders DT. Measuring acceptance in irritable bowel syndrome: preliminary validation of an adapted scale and construct utility. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2013;22(7):1761-6.

126. Kemani MK, Olsson GL, Lekander M, Hesser H, Andersson E, Wicksell RK. Efficacy and Cost-effectiveness of Acceptance and Commitment Therapy and Applied Relaxation for Longstanding Pain: A Randomized Controlled Trial. The Clinical journal of pain. 2015;31(11):1004-16.

127. Ljotsson B, Atterlof E, Lagerlof M, Andersson E, Jernelov S, Hedman E, et al. Internet-delivered acceptance and values-based exposure treatment for fibromyalgia: a pilot study. Cognitive behaviour therapy. 2014;43(2):93-104.

128. Wicksell RK, Vowles KE. The role and function of acceptance and commitment therapy and behavioral flexibility in pain management. Pain management. 2015;5(5):319-22.

129. Brooks SK, Rimes KA, Chalder T. The role of acceptance in chronic fatigue syndrome. Journal of psychosomatic research. 2011;71(6):411-5.

130. Densham S, Williams D, Johnson A, Turner-Cobb JM. Enhanced psychological flexibility and improved quality of life in chronic fatigue syndrome/myalgic encephalomyelitis. Journal of psychosomatic research. 2016;88:42-7.

131. Van Damme S, Crombez G, Van Houdenhove B, Mariman A, Michielsen W. Well-being in patients with chronic fatigue syndrome: the role of acceptance. Journal of psychosomatic research. 2006;61(5):595-9.

132. Jacobsen HB, Kallestad H, Landrø NI, Borchgrevink PC, Stiles TC. Processes in acceptance and commitment therapy and the rehabilitation of chronic fatigue. Scand J Psychol. 2017;58(3):211-20.

133. Myers C, Wilks D. Comparison of Euroqol EQ-5D and SF-36 in patients with chronic fatigue syndrome. Qual Life Res. 1999;8(1-2):9-16.

134. Sullivan M, Karlsson J. The Swedish SF-36 Health Survey III. Evaluation of criterion-based validity: results from normative population. J Clin Epidemiol. 1998;51(11):1105-13.

135. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. Journal of psychosomatic research. 1995;39(3):315-25.

136. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica Scandinavica. 1983;67(6):361-70.

137. Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, et al. Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. Pain. 2012;153(7):1495-503.

138. Kemani MK, Hesser H, Olsson GL, Lekander M, Wicksell RK. Processes of change in Acceptance and Commitment Therapy and Applied Relaxation for long-standing pain. European journal of pain. 2016;20(4):521-31.

139. Lasselin J, Kemani MK, Kanstrup M, Olsson GL, Axelsson J, Andreasson A, et al. Low-grade inflammation may moderate the effect of behavioral treatment for chronic pain in adults. Journal of behavioral medicine. 2016;39(5):916-24.

140. Wicksell RK, Ahlqvist J, Bring A, Melin L, Olsson GL. Can exposure and acceptance strategies improve functioning and life satisfaction in people with chronic pain and whiplash-associated disorders (WAD)? A randomized controlled trial. Cognitive behaviour therapy. 2008;37(3):169-82.

141. Wicksell RK, Melin L, Lekander M, Olsson GL. Evaluating the effectiveness of exposure and acceptance strategies to improve functioning and quality of life in longstanding pediatric pain--a randomized controlled trial. Pain. 2009;141(3):248-57.

142. Wicksell RK, Melin L, Olsson GL. Exposure and acceptance in the rehabilitation of adolescents with idiopathic chronic pain - a pilot study. European journal of pain. 2007;11(3):267-74.

143. Wicksell RK, Olsson GL, Hayes SC. Psychological flexibility as a mediator of improvement in Acceptance and Commitment Therapy for patients with chronic pain following whiplash. European journal of pain. 2010;14(10):1059 e1- e11.

144. Wicksell RK, Olsson GL, Hayes SC. Mediators of change in acceptance and commitment therapy for pediatric chronic pain. Pain. 2011;152(12):2792-801.

145. Karin L, Mats L, Predrag P, Gustav N, Erik H-L, Anna A. Cross-sectional associations between inflammation, sickness behaviour, health anxiety and self-rated health in a Swedish primary care population. European Journal of Inflammation. 2019;17.

146. Andreasson A, Wicksell RK, Lodin K, Karshikoff B, Axelsson J, Lekander M. A global measure of sickness behaviour: Development of the Sickness Questionnaire. J Health Psychol. 2018;23(11):1452-63.

147. Agreus L, Hellstrom PM, Talley NJ, Wallner B, Forsberg A, Vieth M, et al. Towards a healthy stomach? Helicobacter pylori prevalence has dramatically decreased over 23 years in adults in a Swedish community. United European gastroenterology journal. 2016;4(5):686-96.

148. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33.

149. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4.

150. Friedberg F, Dechene L, McKenzie MJ, 2nd, Fontanetta R. Symptom patterns in long-duration chronic fatigue syndrome. Journal of psychosomatic research. 2000;48(1):59-68.

151. Janal MN, Ciccone DS, Natelson BH. Sub-typing CFS patients on the basis of 'minor' symptoms. Biol Psychol. 2006;73(2):124-31.

152. Nisenbaum R, Reyes M, Unger ER, Reeves WC. Factor analysis of symptoms among subjects with unexplained chronic fatigue: What can we learn about chronic fatigue syndrome? J Psychosom Res. 2004;56(2):171-8.

153. Andreasson A, Karshikoff B, Lidberg L, Akerstedt T, Ingvar M, Olgart Hoglund C, et al. The effect of a transient immune activation on subjective health perception in two placebo controlled randomised experiments. PloS one. 2019;14(3):e0212313.