Fatigue, Cortisol and ACT: A pre-post study on the effects of work related rehabilitation

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Abbreviations

CFS – Chronic fatigue syndrome

ACT – Acceptance and commitment therapy

CATS – Cognitive activation theory of stress

HPA axis – Hypothalamic pituitary adrenal axis

PVN – Paraventricular nucleus

CRH – Corticotropin releasing hormone

AVP- Arginine Vasopressin

ACTH – Adrenocorticotropic hormone

BDNF – Brain derived neurotrophic factor

CBT – Cognitive and behavioral therapy

TSST – Trier social stress test

TSST-G – Trier social stress test for groups

T1 – Test 1

T2 – Test 2

HADS – Hospital anxiety and depression scale

Abstract

Objective: There is evidence that chronic stress leads to sustained levels of arousal, causing a dysregulation of the stress response. Patients with chronic fatigue often suffer from hypocortisolism. This study aimed to find out whether a 3.5 week long work-focused acceptance and commitment therapy (ACT) could change acute salivary cortisol response in patients with subjective chronic fatigue.

Methods: Participants (n=42) were consecutively recruited from the Hysnes outpatient clinic at St. Olavs Hospital, Trondheim. We used the Trier Social Stress Test for Groups to measure the effect of acute psychosocial stress in a laboratory setting before and after treatment of ACT. Saliva samples were used to measure neuroendocrine responses to stress. 31 patients with fatigue (fatigue group) and 11 patients without fatigue (non-fatigue group) were included in the study.

Results: The results showed no significant differences in cortisol output post treatment in the fatigue group or the non-fatigue group. A significant reduction of symptoms of anxiety, depression and fatigue was found in the fatigue group but not in the non-fatigue group.

Conclusion: ACT did not have a direct effect on cortisol output in this study. However the results imply that it lead to a reduction of symptoms of patients with subjectively reported chronic fatigue.

Contents

1. Introduction

Western countries have seen a marked increase in sick leave during the last decades (1). Norway spends far more than neighboring countries on sick leave related benefits, and this has led to the increased attention on causes and rehabilitation of long-term sick leave (2). Since the 90s, reduced work ability is acknowledged to be a common and serious consequence of psychiatric disorders (3). In 2011, 15.3 % of Norwegians on sick leave was due to psychiatric illnesses (4). A high prevalence of anxiety and depression (affecting 20-25% of the adult population), as well as fatigue, is contributing to the increasing rate of people on long-term sick leave (1, 5). Van't Leven et al. found that one-third of the adult population had complaints of fatigue, and among them 1% reported complaints similar to chronic fatigue syndrome (CFS) (6). Further, the duration of the absence period of people with psychological diagnoses is usually longer that of people with e.g. muscle- and/or skeletal disorders (7). A primary physician will in most cases treat patients on long-term sick leave. However, those deemed in need for extended treatment by their primary physician can be referred to vocational rehabilitation centers, such as Hysnes Rehabilitation Center (HRC), which offers more specialized health care.

Norwegian rehabilitation institutions offer a variety of therapeutic interventions to patients with psychiatric illnesses. HRC has chosen to use work-targeted Acceptance and commitment therapy (ACT), a third-wave cognitive therapy based on clinical behavior analysis. Its theoretical foundation lies in Relational frame theory (RFT) which is a behavioral therapy of language and cognition. ACT focus on how language creates pain and useless methods of dealing with it, and RFT offers an explanation to why this happens. Metaphors, logical paradox, and experimental exercises are used in the therapeutic components of ACT. This is a way to undermine excessive literal language, and instead use an experience-based approach. ACT encourages the patient to increase acceptance of the full range of subjective experiences. This includes distressing thoughts, beliefs, sensations, and feelings, in order to promote a behavior change that can result in improved life quality. In ACT, the patients are encouraged to defuse from distressing psychological experiences, and further have an accepting attitude toward their experience as it develops in real time. Personal values are turned into specific behavioral goals for the patient, and promote the concept of committed action as movement towards these goals (8). Evidence related to the effectiveness of ACT is reported in studies regarding the treatment of workplace stress (9), psychosis (10), depression (11), social anxiety

disorder (12), and chronic non-malignant pain (13). Not much research exists on the effect of ACT in symptoms of chronic fatigue, and this present study is among the first doing so.

CFS is recognized by symptoms as unexplained, profound disabling and long-lasting fatigue (14). The onset of the symptoms is new or definite, and is not a result from ongoing exertion that is not "fixed" by rest. In addition to feelings of fatigue, the patient must also experience at least four of the following symptoms over a six month period of illness: sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, postexertional malaise, unrefreshing sleep, headaches and impaired memory or concentration (14).

1.1 The human stress response

Chronic fatigue has been associated with long-term sickness absence in the last years (15, 16). Sickness absence can be a reaction to symptoms of stress (17), which is an important factor in several psychiatric diagnoses. Dysregulation of the body's stress system is common in major diagnostic categories (18) such as in depression where dysregulations may affect sleep and appetite functions (19).

The term stress is widely used today, but often with some ambiguity in its definition. Hans Selye originally described stress as the non-specific adaptive response of an organism to *any kind* of stressors, whether the stressor is of physical or emotional nature. This concept is referred to as the general adaptation syndrome (20). However, in more recent years it has been more common to talk about stressors as events or experiences that threaten our ability to adapt and cope in stressful situations (21). This view indicates a greater role of psychological factors as the most powerful stressors for human beings. Having a scientific view and definition of stress is necessary in order to understand the physiological effects stress has on the body. Such an approach involves the central nervous system and viewing stressors as alterations in psychological homeostatic processes (22).

As described by Walter Canon, a stressful situation can be experienced as "good," "tolerable" or "toxic", all depending on the degree to which a person feels he or she has control over the given stressor (21). An adaptive response that is activated during stress will show specificity towards the stressor, and try to destabilize its potential (23). If successful, this can result in growth, adaptation, and beneficial types of learning, which will further have positive effect on our health. However, if the attempt to meet the demands caused by the stressor fails, it can

lead to neural, physiological, behavioral, cognitive, and emotional changes that will make an individual more vulnerable to both physiological and mental illness (24).

Several aspects are of importance in the subjective experiences of stress. There is a huge variation in how each individual responds to stress, and it can depend on either early and/or adult life experiences. In our everyday life we experience small daily hassles with no serious harm. These stressors can be related to poor health, economic insecurity, or interpersonal conflicts. But during our lifetime we may also experience stressors of a more serious life-threatening kind that activate the classical "fight or flight" response, such as natural disasters, violence, or accidents, but these occur more rarely. Daily life stressors are those that operate more chronically and often at a low level. If we are feeling "stressed out", we are more vulnerable to anxiety and depression (25), sleep problems (26), and/or negative health behaviors such as increased smoking and drinking (27).

The human brain is the key organ of our adaptation to physical and social environmental changes, as it controls both the behavioral and physiological responses to a stressful situation, whether health-promoting or health-damaging. How we determine a threat, and how we perceive and interpret stressful situations is controlled by perception involving both higher cognitive functions, but also faster and more reflexive cognitions (28). In order to respond and change under acute and chronic stress, the brain is in control of several bodily systems. The metabolic, cardiovascular- and immune system are all involved in the short- and long term consequences of stress (27).

A widespread theory that describes how cognitive functions are used as frameworks to understand stress and how a stimulus is translated into a physiologic response is The Cognitive Activation Theory of Stress (CATS) by Ursin and Eriksen (29). Whenever there is a discrepancy between what we expect (set value) and what really exists (actual value), stress occurs. This indicates that there is always a comparison between present sensory information and stored brain information. The evaluation an individual makes when facing a challenge is based on expectancies related to the situation, and to the possible responses that are available to this particular individual. This means that the resulting stress response depends on previous learning.

The response outcome expectancies to the available responses are defined as positive, negative or none. This can also be referred to as coping, hopelessness or helplessness. Coping is related to positive response outcome expectancies. A lack of success will produce

expectancies of failure. When there is no relationship between acts and results, the brain will store this as expectancies referred to as helplessness. On the other hand, when an individual learns that all acts/responses lead to a negative result it is referred to as hopelessness. The normal arousal response we experience when facing a stressful situation is adaptive and health promoting. So if an individual is coping successfully, the threat only has a short training effect on the body. But if this individual experiences a state of hopelessness or helplessness, this could lead to sustained activation and a catabolic strain effect on the body, or a lack of adequate response (29). Cardiovascular and thermoregulatory regulations can lead to sustained arousal observed in chronic fatigue patients. Sustained arousal have further been thought to explain some of the neuroendocrine changes observed in the hypothalamic-pituitary-adrenal (HPA) axis (30).

Stress adaptation involves activation of neurotransmitters and modulators, in addition to several hormones, cytokines, and chemokines of the immune system. Adaptation is meant to promote survival and maintain homeostasis, and does this through activation of these systems (31). An example of how our bodily system responds during a stressful situation is that the body will release certain chemical mediators, such as catecholamines, which will cause an increase in heart rate and blood pressure, making us able to handle the situation. The down side to this is however if these same mediators are activated over time, this will lead to a "wear and tear" on the on the body (27). These wear and tear experiences can also be related to patients with chronic fatigue. Their subjective feelings range from tiredness to exhaustion, which interferes with the normal energy capacity of an individual (32).

1.2 The HPA-axis

Biomedical approaches usually refer to stress as situations where adrenal glucocorticoids and catecholamines are elevated due to an experience. This happens through activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. The HPA axis is a critical endocrine system, and the end product, cortisol, plays an important role in metabolism by mobilizing resources that will provide energy. The HPA axis is involved in maintaining the daily energy balance and functions as important to the endocrine stress response.

Three serially arranged elements connected by vascular links constitute the elements of this axis. The key elements in the HPA-axis involve the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal cortex. In the HPA-

axis, tissues from the hypothalamus, pituitary, adrenal cortex, and the associated regulatory inputs, releasing factors, and hormones are comprised. PVN is the brain structure that is responsible for regulating the stress response of the HPA-axis. Neurosecretory neurons in the medial parvocellular zone of the PVN mediate the activation of the axis. These neurons further project to blood vessels in the external lamina of the median eminecence. Here, adrenocorticotropin "secretagogues" are synthesized and secreted into the microportal circulatory system of the pituitary stalk, and the most important of these are corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). Further, CRH and AVP stimulate the release of adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary, and ACTH enters the circulating blood and stimulates release of glucocorticoid hormones, mainly cortisol, from the cortex of the adrenal glands (33, 34). As stress leads to CRH secretion, there is a "compensatory" increase in CRH mRNA expressing in the PVN, and this compensatory enhancement will further be suppressed by glucocorticoids in the PVN. The stress response will be shut down, and the person will return to his/hers level of homeostasis. This process primarily involves activation of glucocorticoid receptors in PVN (35).

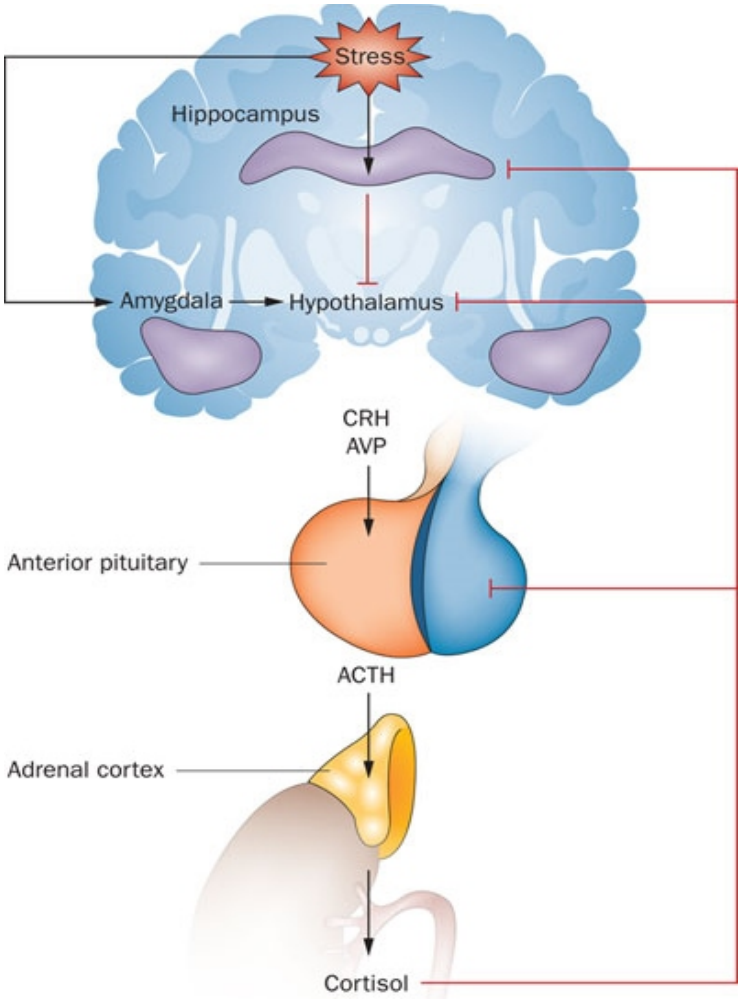

Figure 1 A simplified illustration of the HPA-axis. Neurosecretory neurons from the parvocellular zone in the paraventricular nucleus of the hypothalamus (PVN) mediate the activation of the HPA axis. Adrenocorticotropic secretagogues are synthesized in the external lamina of the median eminecence in the hypothalamus. The most important adrenocorticotropic secretagogues are corticotropin-releasing hormone (CRH) and arginine vasopression (AVP), and these will stimulate the release of adrenocorticotropic hormone (ACTH) from the anterior lobe. ACTH will further stimulate the release of glucocorticoid hormones, mainly cortisol. Illustration adapted from Papadopoulos, 2011 (36).

1.3 Saliva cortisol

In humans, cortisol excerts a variety of effects on several systems, ranging from impact on our sleep/wake cycle, food intake, stress adaptation and stress recovery, to promotion of learning and memory processes. Cortisol binds mainly (90-95%) to binding proteins in the blood, and only 5-10% of the total plasma cortisol is circulating as biologically active, unbound, "free" cortisol (37). A common, robust and feasible way of measuring free cortisol is by sampling saliva, which can be stored at 5˚C for up to 3 months, or at -20˚C or -80˚C for at least one year. Salivary cortisol has proven to be stable through changes of temperature, storage, and is used extensively as a biomarker (38).

Cortisol has a clear circadian rhythm, and show typically low secretion during the first half of night time sleep, followed by a sudden elevation during the second half of night time sleep. Shortly after morning awakening the levels peak and will continue to decrease during the rest of the day. Normal circadian rhythm is disturbed by stress related cortisol secretion (39).

The circadian signal that is generated by the circadian pacemaker is located in the suprachiasmatic nucleus of the hypothalamus, and controls overall diurnal cortisol variation (39). When an individual is in a non-stressful situation, both CRH and AVP are secreted in a circadian rhythm that shows a frequency secretion that includes about two or three episodes per hour (40). During rest, CRH and AVP pulses increase early in the morning, and will later result in bursts of ACTH and cortisol secretion in the general circulation (41). Environmental changes such as eating, lighting changes, and physical activity perturb these diurnal variations, and they are, as mentioned, also disrupted by stress. If a person experiences acute stress, CRH and AVP pulsations in the hypophyseal system will increase, and this will lead to increased episodes of ACTH and cortisol secretion. Circulating ACTH is the main regulatory system of glucocorticoid secretion by the adrenal cortex (42).

However, even though salivary cortisol is a common biomarker used studying psychological mechanisms in stress research, it can only indirectly assess the level of free cortisol. Several variables affect salivary cortisol, such as adrenal sensitivity, capacity, cortisol binding etc. So due to the complexity of the HPA axis, perceived stress should only be expected to have moderate associations with salivary cortisol. Nevertheless, salivary cortisol is the method of choice in research of free cortisol on target tissue, and is the most valid parameter in this case. One should however have in mind variables such as estrogens and medical conditions that might affect HPA axis responses and binding of cortisol (43).

1.4 Stress and the hippocampus

Research regarding the stress response has a lot of focus around the role of the hypothalamus and the pituitary. But other brain structures, such as the hippocampus, are also related to both perception of stressors and the initiation of stress responses (44). The hippocampus is one of the most sensitive regions of the brain, and has an abundance of corticosteroid receptors. It is a brain structure that is highly involved in cognitive function, learning and memory. Hippocampal neurons also show a remarkable plasticity that involves both synaptic potentiation and synaptic depression, as well as dendritic remodeling and neurogenesis in the dentate gyrus (44). Among the large concentration of glucocorticoid receptors in the hippocampus, are type 1 (mineralcorticoid) and type 2 (glucocorticoid). Type 2 receptors play a more central role in modulating HPA functions during glucocorticoid release during acute stress, and they have a lower affinity for glucocorticoids than type 1 receptors. Type 1 receptors are more related to the regulation of the basal activity of the HPA system (45). The hippocampus also modulates the release of glucocorticoids as it has inhibitory effects on the HPA axis. This indicates an important role of the hippocampus related to the integration of neurohumoral and neurochemical responses to stress (46).

1.5 Homeostasis and allostasis

In life we depend on the ability to maintain a stable and a relatively constant equilibrium in several bodily properties, such as blood oxygen and pH. This state is constantly being challenged by either intrinsic or extrinsic factors, the stressors, and we need to make adjustments of a hormonal, behavioral and autonomic nature to maintain it (47). The parallel processing between sensory input from the environment and internal input from the body

enables the brain to control the adjustments needed to maintain homeostasis. An example of how the brain responds and adapts to a threatening situation (e.g. escape from predator) is by increasing cardiac output and peripheral vascular resistance. This is how hemodynamic and metabolic support is provided for large muscle groups that are needed for immediate or anticipated action. This adaptation process is related to the activation of systems at a more biological level, such as the HPA-axis, the autonomic nervous system, the gut, the kidneys, and the immune system. As mentioned, the main biological components of these systems are cortisol, sympathetic and parasympathetic transmitters, cytokines, and metabolic hormones. Mediators like these operate in an interactive network that is nonlinear and dynamic. Here, the mediators down- and upregulate each other, depending on different factors such as their concentration, location in the body and sequential temporal patterning (27). The active process by which these biological systems respond to daily events and challenges is often referred to as allostasis, and is essential in maintaining homeostasis (48).

Allostatic systems that are activated in response to a challenging situation are most useful when they are rapidly mobilized and ended. If they remain prolonged and are not ended within normal time, this can undermine mental and physical health, primarily due to their effect on brain plasticity. If the body is not able to activate allostatic systems when necessary, this may also cause a load on the body, as the protection it normally gets by these systems is lacking (28) . So, if mediators that show increased activity over time, e.g. chronic elevated levels of glucocorticoids in a flattened diurnal rhythm or as a result of chronic stress, the state is referred to as an "allostatic state". This is followed by a prolonged effect on target cells, which further lead to other consequences like receptor desensitization and tissue damage, a state referred to as "allostatic load"(27).

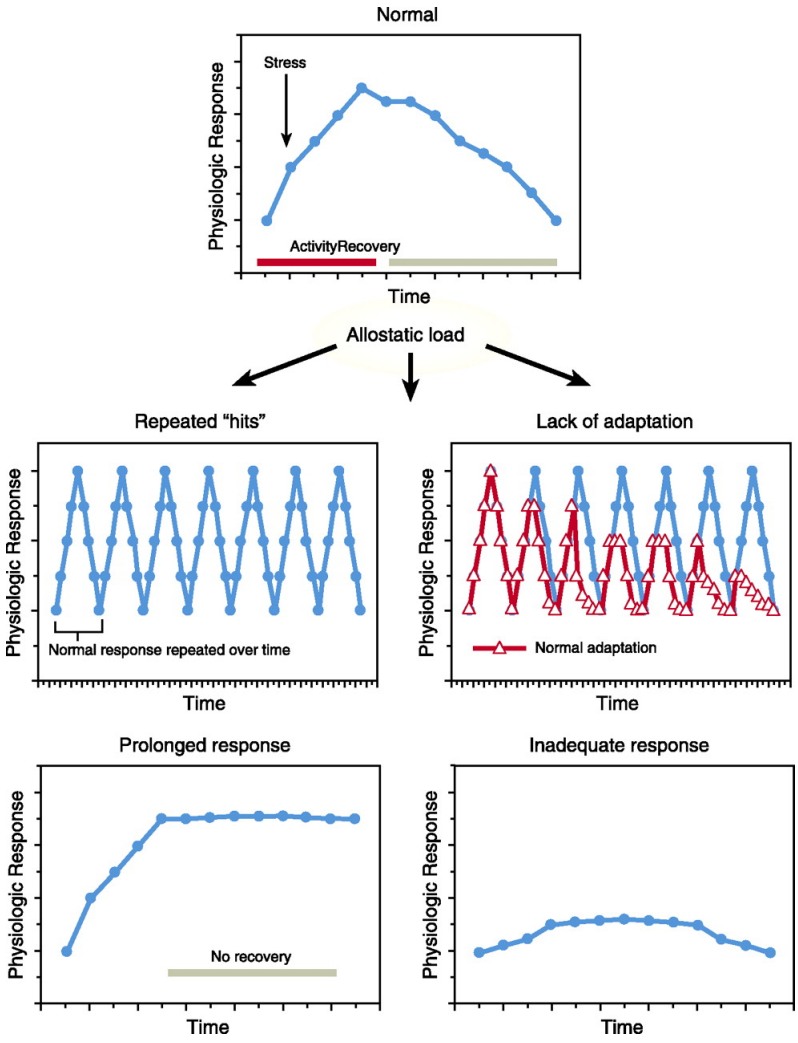

Figure 2 Four types of alllostatic load. "Top panel" illustrates normal allostatic response where the response caused by a stressor is sustained for an appropriate time, before being turned off. "Top left panel" shows repeated hits from multiple stressors. "Top right panel" show lack of adaptation, where and individual fails to habituate to a repetition of the same stressor. This leads to persistent elevation of mediators such as cortisol. "Bottom left panel" shows a prolonged response due to delayed shut down. "Bottom right panel" shows that inadequate response will lead to compensatory hyperactivity of other mediators. An example is inadequate glucocorticoid responses seen in chronic fatigue syndrome. Figure adapted from McEwen,2011 (28).

Several states contribute to allostatic load, and these can be repeated challenges, a failure to habituate with repeated challenges, failure to shut off the response after the challenges is past, and failure to mount an adequate response (49).

Being exposed to stress for a brief period is harmless for both physical and mental health. However, if a person experience lack of control and uncertainty over time, this can produce a chronic state of distress that is believed to make a person more vulnerable to stress-related disorders (46). Therefore, when a normal response to stress is by showing adaptation to a stressor which will lead to a short activation of the HPA axis, overproduction of stress

hormones can cause maladaptive responses that may lead to failure of terminating the HPA activation. In humans, chronic stress can cause sustained increases in cortisol (46).

1.6 Chronic fatigue and hypocortisolism

HPA axis abnormalities have been documented in patients with chronic fatigue during recent years. Compared to healthy individuals, patients with chronic fatigue display flatter cortisol awakening response, and a flatter diurnal slope of salivary cortisol output (50, 51). These findings are parallel to those of Heim, Ehlert, and Hellhammer (52) who also suggest hypocortisolism as an important factor in the pathogenesis of bodily disorders such as fatigue. This is recognized by a lack of cortisol availability that may cause an individual to be more vulnerable to bodily disorders.

Previous studies on hypocortisolism found that individuals exposed do daily work stress showed decreased basal plasma morning cortisol. They also reacted to increased work responsibilities by showing blunted cortisol responses (53). Also, a study of rats that were exposed to chronic morphine treatment for 16 days showed prolonged elevated levels of ACTH after withdrawal of morphine, followed by a continuous drop of corticosterone levels. The animals displayed signs of hypocortisolism eight days after ending the morphine treatment. These findings indicate a reduced corticosterone response to restraint stress (54).

The alterations that are present in the HPA axis in individuals with chronic fatigue are determined by several factors: i) different levels of the HPA axis (CRH/AVP from the hypothalamus, ACTH from the pituitary, or cortisol from the adrenal glands) will experience a decrease of the respective releasing hormone, followed by a subequent decreased stimulation of the respective target receptors, ii) a hypersecretion of one secretagouge will lead to a subsequent down-regulation of the respective target receptors, iii), glucocorticoids will have a greater negative feedback sensitivity iv), there will be a decreased availability of free coritsol, and or v) target tissues will experience reduced effect of cortisol, which further describes a relative cortisol resistance (52, 55).

1.7 Hippocampal plasticity

Plasticity is referred to the ability of the brain to adapt to various challenges. Neuronal plasticity is highly important for an individual to function normally in a changing

environment. The process of plasticity involve neuronal systems, brain nuclei, single neurons, synapses and receptors, and how these adapt to changes in the internal and/or external environment by modifying their structure and function (56).

Alterations in brain function due to chronic stress can have an effect on allostatic overload. In animal models, allostatic overload as a result of chronic stress lead to atrophy of hippocampal neurons and prefrontal cortex (57). Chronic elevation of corticosteroid levels may cause neurodegeneration or suppressed neurogenesis in the hippocampus (58). Direct exposure to glucocorticoid can also lead to decreased dendritic branching. CA3 pyramidal neurons in rats exposed to restraint stress for 21 days showed atrophy in apical dendrites (59). In addition, changes in the structure of synaptic terminals (60) as well as inhibition of neural regeneration in the dentate gyrus, is the result of prolonged exposure of glucocorticoids (61). Further, glutamate transmission can be enhanced in CA3 and dentate gyrus, and long-term potentiation can be impaired in hippocampal subareas. In addition, 5-HT1A receptor-mediated responses can be decreased after a period of chronic stress, or prolonged due to an overexposure of corticosterone. This could be a possible reason for the increased risk of mood disorders after a prolonged period of hypercortisolemia (31). There is evidence for a role of hippocampal atrophy in psychiatric disorders like Cushing's syndrome, major depression and post-traumatic stress disorder. All these illnesses display a loss of volume in the hippocampus (62).

One of the reasons hippocampus is of high relevance to the stress response is due to its importance in new learning and memory. An example is the ability to assess a potential threat in a dangerous situation, e.g. facing a predator. Alterations in memory play a central role in the clinical presentation of patients with stress-related psychopathology (63). Common complaints in patients with chronic fatigue are related to memory impairment (14). These patients have reported having trouble with remembering things, information processing is less efficient than normal, they struggle with their performances in demanding jobs, and complex tasks can be very tiring (64). An example is a study of patients with chronic fatigue that reported reduced attention among participants causing impaired performances in tasks that required memory responses (65).

Even though neurogenesis is challenging to study in humans, research has indicated that reduced neurogenesis is related to psychiatric disorders (66). In animal studies, stress has been found to result in a down-regulation of brain-derived neurotrophic factors (BDNF). BDNF is widely expressed in the hippocampus, and are neurotrophins involved in cell

survival and differentiation. Through its activation with the HPA axis, BDNF is indicated to play an important role in the pathophysiology of mood disorders (33). Studies to support this found decreased expression of BDNF mRNA in the hippocampus of a chronic fatigue murine model (67). The major symptoms of chronic fatigue, such as anxiety, depression, are also related to a reduction of BDNF mRNA expression in the hippocampus (68). In addition, reduced hippocampal BDNF was found in a study of sleep deprived rats (69). As BDNF supports survival and growth of several neuronal subtypes, a dysfunction of this structure can have an impact on neurogenesis, and therefore also on normal brain function.

As previously outlined, the use of ACT in the treatment of psychiatric illnesses is increasing (8). Another therapeutic approach related to disorders such as chronic fatigue is cognitive and behavioral therapy (CBT). This is a therapy where the treatment is based on cognitive formulation, as well as beliefs and behavioral strategies that address characteristics of a specific disorder. The focus is also on understanding the individual patient, including their specific beliefs and behavioral patterns. Cognitive changes is produced by modifying the patients thinking and belief systems, which will lead to emotional and behavioral change (70, 71). A popular approach related to cognitive therapy is mindfulness-based therapy. Mindfulness used in contemporary psychology involves having an individual to increase their awareness and respond skillfully to mental processes contributing to emotional distress and maladaptive behavior (72). Mindfulness Based Stress Reduction developed from Mindfulness is most used to reduce psychological morbidity that is associated with chronic illnesses. It further focuses on treating emotional and behavioral disorders (73). CBT is an established therapeutic approach in the treatment of chronic fatigue. Mindfulness based therapy and ACT are used in several psychiatric disorders, and more recently tried out on chronic fatigue patients (74).

1.8 Measuring psychosocial stress through cortisol

As previously outlined, a common tool used in measuring free cortisol as well as HPA axis activity is saliva samples. As cortisol enters saliva by passive diffusion or by other types of active transport mechanisms, the levels of cortisol in saliva are not affected by saliva flow rate. Proteins and protein-bound molecules are prevented from entering saliva by acinar cells arranged along the saliva glands. This is why saliva cortisol is a common method used in both the measure and assessment of unbound, free hormone fraction (75, 76).

Findings from a meta-analysis done by Dickerson and Kemeny (77) indicated that motivated performance tasks that combines elements of socio-evaluative threat and uncontrollability provides reliable and robust biological stress responses used for research. The Trier Social Stress Test for Groups (TSST-G) is an experimental test based on the original Trier Social Stress Test (TSST) (78). TSST-G is designed to trigger mental stress among participants under controlled conditions. Studies have shown that this experiment is a reliable stressor through increased secretion of saliva cortisol in approximately 80-85 % of healthy participants (79). A study by Kudielka and colleagues found impairment of normal habituation in response to repeated acute psychosocial stress among participants with vital exhaustion. Vital exhaustion is among other things recognized by unusual fatigue and loss of mental and physical energy. Higher exhaustion was associated with increased sensitization and reduced habituation (80, 81). These findings suggest that exhaustion is related to impaired habituation, rather than a lack of response to the experimental stressors.

Using TSST-G to measure saliva cortisol output among participants and in turn relate these findings to a possible role of ACT among patients with chronic fatigue would be of value for both researchers and therapists. Relating changes in cortisol patterns to an effect of ACT can contribute to existing knowledge especially in the area of therapy, as ACT is more commonly used in the treatment of many disorders causing disability and sick leave. Faster return to work has been shown in patients with stress and pain, demonstrating the important role of ACT in these groups (82).

Patients with chronic fatigue often display symptoms of anxiety and depression (83). Therefore, comparing results of a chronic fatigue group to results of a non-fatigue group that includes patients diagnosed with anxiety and depression could provide interesting insight to the role of chronic fatigue in response to ACT based on the experimental conditions of this study. To our knowledge, there is no existing research on ACT for cortisol output in chronic fatigue patients. More research exists on the effect of ACT on disorders like anxiety and depression, but the majority of the published literature in this field has more focus on factors such as improvement on life quality etc., and is not at a neuroendocrine level. As previous research has supported the effectiveness of ACT on patients with anxiety and depression, we expect the therapeutic intervention in this study to have an effect on cortisol in these participants.

1.9 Study aims

The aim of this study is to test the hypothesis that a 3.5 week long intervention of ACT will have an effect on cortisol output in patients with subjectively reported chronic fatigue using the TSST-G in a pre-post design. A significant change in cortisol secretion from T1 to T2 is expected in the fatigue group.

2. Methods

2.1 Overall sampling procedure

During a six month period from January to June 2012, patients on long term sick leave staying at HRC were requested to participate in this study. HRC offers occupational rehabilitation through a 3.5 week long treatment program to patients on long-term sick leave from musculo-skeletal disorders, psychiatric disorders, fatigue and combinations of these. The patients have been referred by their general practitioner to stay at HRC where they received work-focused ACT (8). To participate in the study, the patients had to be between 18-59 years, on sick leave or received work and disability benefits longer than eight weeks, referred by their primary physician for experiences of fatigue, or been diagnosed with mental and/or muscle and skeletal disorders. Patients with severe mental disorders, severe somatic disorders, pregnant women, or patients that were on medication that could affect secretion of cortisol were excluded from participation.

Participation in this study involved pretest (T1), ACT, and posttest (T2). All testing and intervention took place at Hysnes Rehabilitation Centre during a six month period (from January to June 2012).

The study was approved by The Regional Ethics Committee for Medical Research in Trondheim, Norway and conducted in line with the declaration of Helsinki. All patients received information about the experiment, and gave their written informed consent.

2.2 Procedure

2.2.1 TSST-G

We created an experimental situation as described in von Dawans et al. (79) to trigger moderate psychosocial stress among participants. Six participants were randomly chosen to participate in the experiment. The test was performed in a group format in order to investigate the effect of socio-evaluative threat and uncontrollability. Physiological measures were taken during the experiment session (cortisol). Due to diurnal variations in cortisol secretion, the timing of the experiment sessions at T1 and T2 was kept constant throughout the testing period (84). TSST-G has proven to be a reliable method when measuring psychobiological stress responses in a laboratory setting (79). Participants as well as test instructors had no

previous knowledge to each other. Neither of the participants had previous knowledge to stress experiments. Three people were in charge of the experiment; one person was responsible for the preparation phase, while two people were in the test panel (the test instructors). The participants were told not to eat or drink caffeine for two hours prior to the experiment.

The experiment consisted of i) a preparation phase (30 min), ii) an experimental phase (20 min), and iii) a debriefing phase (60 min). The experimental phase consisted of a job interview presentation and a mental arithmetic task. Both experimental sessions (T1 and T2) were equal and took place between 16:30 and 19:00.

In the preparation phase, the participants were told to prepare for a mock job interview, which would include a 2 minute long speech about their personal qualities. Further, they were told that the speech would be performed in front of a test panel. 10 minutes before the preparation phase was over, the first salivette was taken. During the experimental phase, the participants were told not to talk to each other. Mobile walls were used to separate the participants, and to avoid eye contact. The participants were introduced to the test instructors, and told that they were specialized in evaluating non-verbal behavior. The participants received no feedback during the experimental phase, besides instructions given by one person in the test panel. The other person would make notes based on the behavior of the participants throughout the experiment. Further, the participants were told that a video camera and a microphone would record their performance in order to analyze body language and verbal behavior respectively. The spokesman of the test panel could interrupt and ask new questions to a participant at any time throughout the experiment. The order of each presentation was randomly chosen by the test panel. Each presentation lasted two minutes, and no kind of feedback was given during this time. If the participant finished his/hers presentation within the prescribed time, the spokesman of the test panel would first wait several seconds, before stating that “You still have some time left”. Further follow-up questions could be “Which personal qualities would your friends and family use to describe you as a person?” or “Why do you think you are suitable for this job position?”. After all participants finished their presentation, the second salivette was taken.

The spokesman of the test panel further presented the next task. The participants were instructed to do a mental arithmetic task, and told to calculate as fast and correctly as possible. If they miscalculated, the test panel would notify this. The calculation task involved

subtracting the number 16 from a number given by the test panel (3330, 3314, 3298). If the calculation was correct, the test panel would not give any feedback and the participant would continue subtracting the number 16. Each participant spent 1 minute and 20 seconds on the arithmetic task. The third salivette was taken after the arithmetic task. During the debriefing phase, the participants were given the opportunity to share thoughts and reflections about their experience. A salivette was taken every 15 minutes of the debriefing period (in total 4 salivettes).

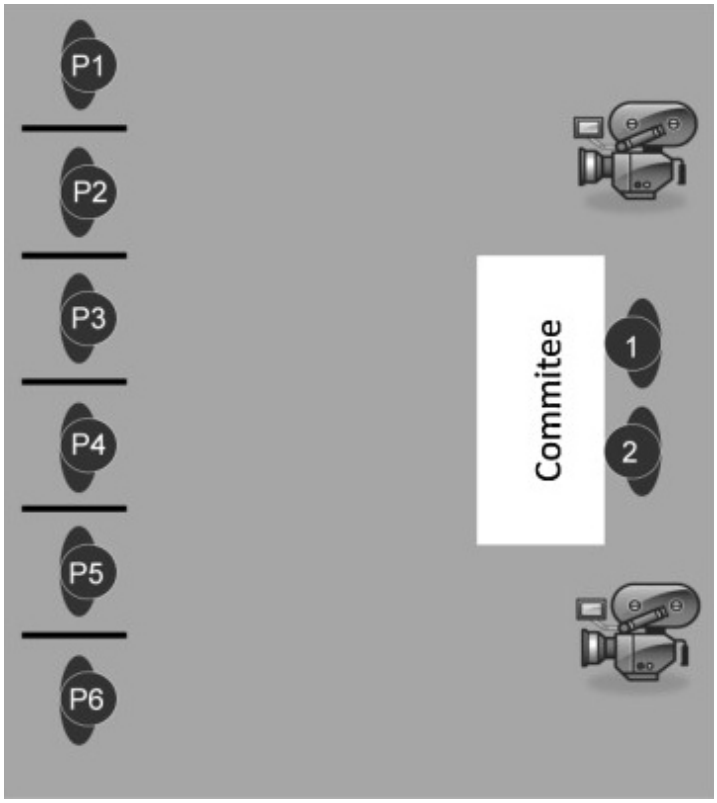

Figure 3. Study design in TSST-G as illusstrated in Von Dawans et al. (79)

2.3 Measures

2.3.1. Saliva cortisol

Saliva cortisol samples were used to measure adrenocortical activity in response to psychosocial stress. Measuring saliva cortisol by using cotton salivettes is considered a reliable and valid method when looking at unbound or free plasma cortisol levels (75). The salivette used for this experiment was produced by Sarstedt Inc., Rommelsdorf, Germany, and

has been used in several previous studies (85, 86). The salivette is a plastic tube containing a piece of polyester. Participants were instructed to chew on the salivette for 60 seconds in order to obtain 0.5-1 ml volume of saliva. In total 14 salivettes were collected from each participant. Seven salivettes were collected at T1 and T2, where one was taken during the preparation phase, two were taken during the experiment, and four were taken during the debriefing phase. The samples were stored in -20 ° C before being analyzed at the Department of Medical Biochemistry at St. Olavs Hospital, Trondheim. Analyses were carried out by using Siemens DPC (Diagnostic Products Corporation) Immulite 2000 with analytic variation 4.5 % at 7.6 pmol/L.

2.3.2 Chalder Fatigue

In order to assess individual symptoms of fatigue, all patients completed the Chalder Fatigue Scale. This scale measures both mental and physical fatigue (87). It is a 13 – item self-report questionnaire, where each item is rated on a 4-point scale scored bimodaly: 0 = Less than usual, 0 = Not more than usual, 1= More than usual, 1= Much more than usual. Cut off indicating fatigue =< 5 and a duration < 6 months (87). Higher scores indicated more mental and physical fatigue. The test has proven to have good reliability, and high internal consistency as measured by Cronbach's alfa (.89) (87).

Participants with fatigue "caseness" had a total dichotomized score higher score than 4 and with duration over 6 months were included in the "fatigue group". Participants scoring lower were included in the "non-fatigue group". Both groups had a prevalence of participants with anxiety and depression (table 3).

2.3.3 Hospital anxiety and depression scale

In order to measure symptoms of anxiety and depression we used the Hospital Anxiety and Depression Scale (HADS). This is a thirteen-item scale with each item raging from 0-3. The scale yields separate scores for anxiety and depression, which then are summed. A score ≥ 8 on either subscale was used to indicate caseness (88).

2.3.4 Acceptance and Commitment therapy

Total duration of the intervention period at HRC was 3.5 weeks, consisting of eight group sessions and five individual consultations. Each group session lasted 90 minutes, and each individual consultation lasted 45 minutes. Group sessions were mandatory. Individual consultations were voluntary with a focus on the individual needs of the patients. For further description of sessions and tools see Appendix.

Table 1. Topic of ACT sessions at HRC.

Session	Group sessions	Individual sessions
1	Socialization to the ACT model and motivation the patient for change	Building a working alliance and identifying the patient's goals and values
2	Barriers and the issue of control	Building a working alliance and identifying the patient's goals and values
3	The consequence of control and the difference between pain and suffering	Cooperation, planning and identifying goals in regards to values
4	Family and important supporters	Cooperation, planning and identifying goals in regards to values
5	You are not your thoughts	Cooperation, planning and identifying goals in regards to values
6	Communication and conflict	
7	Language	
8	Recap and staying committed to value-guided behavior	

Group session 1-8 seen in the left column. Individual session 1-2 and 3-5 seen in the right column.

2.4 Statistical analyses

Data analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows. In initial analyses the population was dichotomized into fatigue/non-fatigue and compared on salient characteristics. In secondary analyses, a student's paired t-test was performed to compare saliva cortisol means before and after treatment in the fatigue group and the non-fatigue group in response to TSST-G, and to measure reduction of symptoms after treatment of ACT in both groups. P-values below .05 were considered statistically significant. Data are presented as mean ± SD/SEM.

3. Results

42 people participated in this study, 33 women (1 missing) (M=40.94, SD=10.653) and 9 men (M=38.11, SD=7.88).

Table 2. Characteristics of the fatigue group and the non-fatiuge group.

	Fatigue group (*n=31*)	Non-fatigue group (*n=11*)	*P*-Value
Age	42 ± 10.94	37.45 ± 8.53	0.48
Gender	Men: 16.1 *(n=5)*	Men: 36.4 *(n=4)*	0.22
	Women: 80.6 *(n=25)*	Women: 63.6 *(n=7)*	
Marital status	Single: 19.4 %	Single: 36.4 %	0.62
	Married: 38.7 %	Married: 36.4 %	
	Cohabitant: 32.3 %	Cohabitant: 27.3 %	
Sick leave (100 %)	Yes: 32.3 %	Yes: 54.5 %	0.28
	No: 67.7 %	No: 45.5 %	
Sick leave (>100 %)	Yes: 22.6 %	Yes: 0 %	.016
	No: 77.4%	No: 100%	
Anxiety	58.1 %	54.5 %	1.0
Depression	41.9 %	72.7 %	0.16

All values except age and BMI are given in percent. Values on age and BMI are mean ± SD. To estimate P-values for continuous/ordinal variables a Student's independent t-test was used, for categorical/dichotomous variables a chi-square was used.

3.1 Effect of ACT on cortisol output

Measures of mean cortisol output from T1 and T2 were conducted using a paired t-test. No significant differences were observed in the non-fatigue group; t(9)=1.85, p=.09 and in the fatigue group t(23)=.05, p=.96. Mean cortisol levels decreased from 10.38 (SD=3.26) at T1 to 9.04 (SD=2.97) at T2 in the non-fatigue group and from 11.84 (SD=4.97) at T1 to 11.79 at T2 (SD=4.28) in the fatigue group (figure 4).

No significant differences were observed in cortisol output from T1 to T2 among participants with anxiety; t(18)=.19, p=.85 and depression; t(17)= -.26, p=.80.

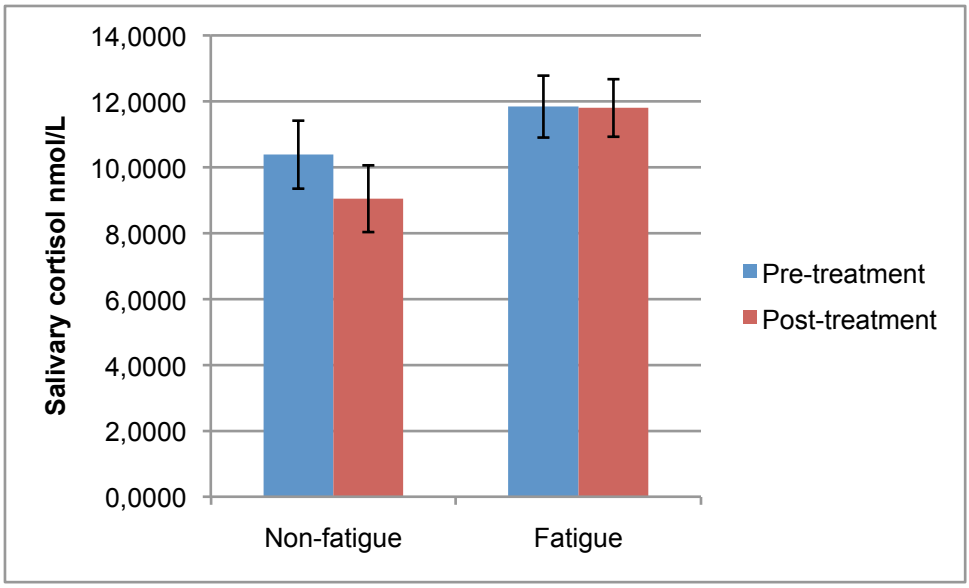

Figure 4 Average amount of cortisol output pre and post treatment with ACT in the non-fatigue group and the fatigue group is presented. Values are mean ± SEM.

3.2 Effect of ACT on symptoms of fatigue, anxiety and depression

The fatigue group showed significant reduction of symptoms on HADS and Chalder fatigue scale. No significant symptom reduction was found in the non-fatigue group (table 3).

Table 3. Results from Student's paired t-tests for symptom reduction.

	T1	T2	*P*-value
	Mean	Mean	
HADS			
Non-fatigue group	.94	.70	.11
Fatigue group	1.23	.79	.00
Chalder fatigue scale			
Non-fatigue group	1.68	1.57	.56
Fatigue group	2.29	1.53	.00

Mean levels from HADS and Chalder fatigue scale at T1 and T2 are presented.

4. Discussion

This pre-post analysis on 42 patients on long-term sick leave, investigated the effect of ACT on salivary cortisol in fatigue and non-fatigue patients. In contradiction to the hypothesis in this study, saliva cortisol output did not show a significant change in the fatigue group from T1 to T2 (p=.96). Paired t-tests were performed in order to investigate symptom reduction outside the main effect on cortisol. Scores on HADS showed significant differences after treatment; t(21)=4.21, p=.00, and mean levels decreased from T1 to T2. Scores from the Chalder fatigue scale also showed a significant difference after treatment; t(21)=5.21, p=.00, and mean levels decreased.

There were no significant changes in cortisol output at T2 in the non-fatigue group (p=.09). Further, *s*cores on HADS showed non-significant differences after treatment*;* t(7)=1.80, p=.11, mean levels decreased from T1 to T2. Scores from the Chalder fatigue scale also showed non-significant differences after treatment*;* t(7)=.61, p=.56, mean levels decreased.

As patients in the fatigue group reported decreased symptom reduction, a change in cortisol output at T2 could be expected. Neuroendocrine measures from TSST-G did not change in this group at T2. If these patients report that they are less tired, worried and depressed, there is also reason to expect cortisol output to change after the intervention. Several reasons might contribute to the explanation as to why there were no alterations in cortisol output even though patients reported significant reduction of symptoms.

First of all, there is no data to support whether the fatigue-group displayed low levels of cortisol output prior to their stay at HRC. Patients at HRC probably have fewer limitations than patients with severe cases of chronic fatigue syndrome. Considering that the dividing of participants into the fatigue group and non-fatigue group in this study was based on results from Chalder fatigue questionnaire (87), patients classified to the fatigue group have reported fatigue-like symptoms, but it is not certain that they fulfill the criteria for a diagnosis of chronic fatigue syndrome. In addition, the prevalence of participants with anxiety and depression in this group was high and could interfere with the treatment effects (table 3). Patients with anxiety and depression often suffer from hypercortisolism (19) which could be related to the small decrease seen in mean cortisol output.

Based on results outlined in section 3*, t*here is reason to indicate that ACT had a positive effect on symptom reduction in the fatigue group in terms of anxiety, depression and feelings

of fatigue. The treatment effect on cortisol was however rather low. A study by Roberts and colleagues from 2009 investigated the effect of CBT during a six month period on patients with chronic fatigue. They found that patients with a flattened diurnal cortisol profile responded less well to the therapeutic intervention (89), similar to the cortisol output in response to therapy in this study, although measuring diurnal variation and not acute response to psychosocial stress. The same authors have further suggested that CBT could increase cortisol output in fatigue patients, and found a significant rise in salivary cortisol output after six months of therapy in medication free patients with chronic fatigue (90). It has been difficult to say whether HPA axis dysfunction occur early or late in the course of chronic fatigue, as most patients that are studied have been ill for a long time. This makes it challenging to find out whether cortisol related disturbances are primary or secondary factors to inactivity, sleep disturbances, deconditioning or stress (91). CBT addresses several of these symptoms through its focus in changing unhelpful patterns of rest and activity, sleep improvement, increase exercise capacity, and stress reduction at an individual level, among other things (92). Roberts and colleagues have therefore suggested a possible role of CBT in increasing salivary output after treatment (90). The precise role of coping mechanisms in the fatigue group remains unclear.

Several studies supports the view of hypocortisolism as a central factor in chronic fatigue patients (50, 51). If, based on the suggestions in Cleare (91), factors such as sleep disturbances, reduced general condition, or stress are primary factors leading to chronic fatigue, and hypocortisolism is secondary, CBT could have successfully increased cortisol output by more specifically addressing the symptoms mentioned above. Perhaps hypocortisolism is a result of these symptoms that further leads to chronic stress, rather than playing the central role in chronic fatigue pathology.

Based on these suggestions, one could argue that the ACT treatment at HRC was not successful in targeting the primary symptoms of the fatigue patients, or that the treatment adherence was comprimized. However, this does not fully explain the significant reduction of symptoms reported after treatment. If these patients were feeling less tired, less worried and less stressed, a significant change in cortisol output should be expected. Other factors might have had implications for these results. Even though cortisol output did not change after intervention of ACT, this therapy for fatigue patients should not be rejected, as the results indicate that ACT successfully reduced symptoms in the fatigue group.

Further, the duration of the rehabilitation period at HVC is 3.5 weeks. As seen in other studies investigating the effect therapy on chronic fatigue, therapies often exceed over a longer period of time. Breast cancer survivors with chronic fatigue responded well to mindfulness-based cognitive therapy after a nine week intervention (93). Also, other chronic fatigue syndrome patients offered 16 weekly sessions of CBT throughout one year showed clinical improvement after treatment had ended (94). There is a possibility that the patterns of hypocortisolism seen in chronic fatigue patients are in need for therapy of a longer duration than 3.5 weeks. Intervention of CBT in Roberts et al. (90) that led to increased cortisol output had a duration of six months. An extended period of therapy for the fatigue patients might contribute to change cortisol levels.

Normally, prior experiences with psychosocial stress can habituate the stress related cortisol response of an individual (84). In this present study, the experience of participation in the first experiment (T1) could have affected the expectations of participation in the second experiment (T2). Reduced tension levels might have impact on the degree to which emotional distress during TSST-G is taken seriously. As outlined in the study by Kudielka and colleagues, patients with feelings of exhaustion and fatigue showed impaired habituation in response to repeated exposure to the same stressor (80). Patients with vital exhaustion are suggested to have subtle hypocortisolism (95). A reduced cortisol response was seen in the first experimental session of the study. An assumption to this could be due to a lack of response to the stressor. However, throughout three sessions of TSST, only two out of twenty-five subjects did not have a significant cortisol response, suggesting that participants with exhaustion failed to habituate rather than having a complete lack of response to the experimental stressor (80). These findings are in line with results from the fatigue group of this present study, where no changes in cortisol secretion were observed at T2, indicating that these patients might show reduced ability to learn during acute psychosocial stress. One should have in mind that neither of these patients has been in an extreme state of illness, which makes it difficult to generalize to patients with more severe illness conditions. Further research should include cardiac measures to be able to investigate whether fatigue patients show increased heart rate during the experimental sessions.

Research has indicated sex differences in cortisol output in response to psychological stress. Cortisol output has been reported to be higher in healthy men than in healthy women during a mental arithmetic task and public speaking (96). A review by Kudielka and Kirschbaum suggest that, based on previous research, adult men seem to have a greater increase in cortisol

compared to women. Further it is argued that the hyperreactivity of cortisol observed in men might be related to a risk for diseases like cardiovascular disease and diabetes, while the hyporeactivity observed in women is related to an increased risk for autoimmune diseases, where a common symptom is fatigue (97). The majority of the population in this present study are women, both in the in the chronic fatigue and non-chronic fatigue group (80.6% and 63.6%, table 1) (98). In addition, research in women using oral contraceptives have reported altered adrenocortical responses and low cortisol output during a mental and arithmetic speaking task (99). The number of oral contraceptive users was not excluded in this study, which further might have affected adrenal activity. As baseline measures are not presented, it is not known whether cortisol levels are high or low among participants in this study. If patients in the fatigue-group suffer from hypocortisolism, this is something that should be included in the interpretation of results.

If the decrease in mean cortisol levels from T1 to T2 in the non-fatigue group is related to an effect of ACT, a significant reduction of symptoms should also be likely. It is well established that hypercortisolism is common in patients with depression (19). Patients with depression often suffer from excessive amounts of released cortisol in response to stress. A study by Caroll et al. found increased ACTH secretion in depressed patients, confirming central HPA axis overdrive in severe depression (100). There have however been some inconsistent findings regarding HPA axis activity in patients with anxiety disorders. However, research exists that support the findings of elevated cortisol levels in patients with anxiety. Vreburg et al. found HPA axis hyperactivity in patients with complicated anxiety disorders, with comorbid depressive disorders or agoraphobia (101). Increased cortisol response has also been found in patients with social anxiety in response to the Trier Social Stress Test (102). Consistent with these findings are also those of Takahashi et al. from 2005 (103).

Several studies support the effect of ACT on disorders such as anxiety and depression (12, 104, 105). Results from cortisol measures in the non-fatigue group had a p-value of .09, and mean cortisol levels decreased. Based on this, there is reason to believe that ACT might have had a positive effect on cortisol by reducing levels at T2. However, *s*ince no symptoms of anxiety, depression and fatigue changed significantly, and mean symptom reduction was low for both HADS and Chalder fatigue scale, there is a possibility that the decreased mean cortisol output seen in this group is due to habituation to the test. Further, the sample size is in the non-fatigue group was low (n=11), so one should also be aware of the effect of Type-II error (106).

It is also difficult to know how long the patients in the non-fatigue group have been ill. Intervention during early phases of the illness has proven successful in individuals with symptoms of anxiety and also fatigue, and ACT has been found to play a role in reducing a broad spectrum of psychological distress (107). Such preventative interventions at an early stage of the illness could contribute to a larger reduction of symptoms. Further, individuals with anxiety and depression often report severe symptoms of feeling worried and sad. 3.5 weeks of therapy might not be enough for these patients to report improvement of symptoms.

As mentioned, TSST and TSST-G are common and well-established stress protocols used to achieve significant activation of the HPA axis (78, 79), and about 80-85% of individuals that are tested in TSST have shown typically moderate to large subjective and physiological responses from baseline to peak values (78). The non-significant change in cortisol secretion in the fatigue group in response to TSST-G are similar to those by Bower et al. who reported blunted cortisol output in response to TSST in breast cancer survivors with persistent fatigue compared to non-fatigued survivors (108). Previous studies have demonstrated that patients with panic disorder is recognized by increased cortisol output when exposed to new, threatening and uncontrollable conditions (109). In a study by Petrowski and colleagues (110) patients with panic disorder showed hyporeactivity of the HPA axis in response to TSST before and after treatment of psychotherapy. However, heart rate measures increased significantly at both experimental sessions of TSST, indicating that the subjects consciously participated in the tasks during the experiment. A habituated response to acute and uncontrollable psychosocial stress due to previous experiences of panic attacks was suggested to be related to the hyporeactive response to TSST (110). As this experiment usually elicits fear and increased cortisol levels, and these patients had a normal cortisol awakening response in the morning as well as normal heart rate measures, a significant response to TSST should be expected. The reason for these findings in patients with panic disorder is unclear. Subjects in the study by Kudielka and colleagues (37) showed impaired habituation when exposed to repeated acute psychosocial stress. These patients show reduced ability to learn when exposed to the acute experimental stressors in TSST. Petrowski and colleagues suggest habituation due to previous experiences with panic attacks as a possible explanation to the non-response in cortisol seen in patients with panic disorder during TSST. Further research on the HPA axis dysfunction might contribute to the explanation reduced cortisol response seen in these patients.

The results of this study are based on saliva cortisol samples collected from TSST-G pre and post treatment. As this is an experiment performed in a laboratory setting, and measures acute stress, it might not be representative for the diurnal variation in cortisol output among participants. Chronic fatigue patients often report impaired cortisol awakening responses (111). Also, normal diurnal cortisol patterns in healthy individuals display a rise of cortisol output in the morning, followed by a decreased output throughout the day and the afternoon (39). There is a possibility that measures from the cortisol awakening response could act as a better indicator for a possible effect of therapy treatment on cortisol output. No direct evidence exists in this present study that TSST-G was not successful in causing stress among the participants. As we have not compared base line cortisol measures to experimental cortisol measures, we cannot be certain that the experimental condition failed to trigger a stress response in the fatigue group.

Mindfulness training is another growing approach for the treatment of chronic fatigue patients. As outlined in the introduction, mindfulness therapy focuses on how an individual increases its awareness and responds skillfully to mental processes that contribute to emotional distress (72). Mindfulness based stress reduction has previously proven to be an effective intervention in the treatment of chronic pain, anxiety disorders, and mood and adjustment in cancer (112). A study by Surawy, Roberts and Silver investigated the effect of Mindfulness based stress reduction on chronic fatigue in three explorative studies and found that when this therapy is practiced in the framework of a clear cognitive rationale, patients can experience improved mood, quality of life and physical functioning (113). Similar findings also showed that participation in a Mindfulness stress reduction program led to an improvement of fatigue symptoms after the intervention (114). As ACT is a mindfulness-based approach, further research on these interventions for chronic fatigue patients could contribute to increase flexibility towards individuals as well as efficiency of treating symptoms at a neuroendocrine level.

4.1 Limitations

This study has several limitations, which will now be considered. First, the sample size of this study was relatively small, which makes generalization of these results to the population challenging, especially in the non-fatigue group. However, this study is one of the first of its kind and the patients were consequently recruited from a clinical setting, hence limiting the

sample opportunity. In addition, the number of participants should be more evenly distributed across gender. Also, the dividing of patients into the fatigue and non-fatigue group was based on subjective measures of fatigue from the Chalder fatigue scale. A clinical diagnosis of chronic fatigue was not given to any patients. Further, as we followed a detailed experiment protocol, the roles of the instructor/test panel should be kept similar at both experiment sessions (T1 and T2) for each group. After T1, the participants were not familiar of whether the experimental procedure would remain the same at T2. Therefore, if the participants in example experienced the spokesman of the test panel as uncomfortable or threatening at T1, and this person turned out not to be the spokesman of the test panel at T2, the participants could end up feeling more relaxed than if they knew that they were expecting an uncomfortable or threatening person. One should also have in mind the well established circadian rhythm of cortisol, which is highly synchronized with light-dark and sleep-wake cycles (39). The saliva cortisol samples were collected between Janary and June. Some patients participated in the experiment during dark winter months (January-March). One should have in mind that this can have an effect on saliva cortisol. It is however likely that if this was the case, the influence of seasonal effects would probably not be very high.

Strengths of this study involve a population of patients not on medication. This way we could exclude possible factors that could complicate HPA axis assessments. In addition, the patients acted as their own controls. For saliva cortisol sampling to be a reliable research tool, it is important that the experimental testing should be done with strict reference to timing (84). Timing of the experiment sessions in this study was set to the afternoon (between 16-18) throughout the whole testing period, which is important for reliable measures. Further, the participants were not informed about the structure of the second experiment (T2), and of whether they had to prepare for participation in a new experimental setting with new tasks. Also, we used saliva cortisol as a biological marker when measuring the effect of acute psychosocial stress, a common and reliable research tool in psychobiological research (76). Cortisol reflects physiological measures more accurate rather than written questionnaires and scales.

5. Conclusion

This study underlines the importance of work-focused rehabilitation in patients on long-term sick leave. Based on the results from this study we suggest that ACT had a positive effect on reducing symptoms of anxiety, depression, and feelings of fatigue in the fatigue group. Even though no direct neuroendocrine changes were observed in this group, the findings of reduced symptoms supports that therapy can be of great importance to an individual. If these patients continue to maintain their mental state after treatment at HRC, a faster return to work might be seen in these patients. This, together with intervention at an early stage of the disease might contribute to more effectively reducing the amount of patients on long-term sick leave.

Future research should aim to focus on the effect of therapeutic methods such as ACT and Mindfulness on neuroendocrine dysfunction and its appropriate target patients groups. Previous studies of CBT have found to have a positive effect in increasing cortisol output in fatigue patients. As ACT has been found to have a positive effect of the symptoms observed in chronic fatigue in this study, there is reason to believe that further adjustment of ACT could contribute to a positive effect on several levels of this disease, ranging from changes at a neuroendocrine level to life quality.

This study aimed to find out whether ACT had an effect on salivary cortisol in patients with subjective chronic fatigue by showing significant changes after a 3.5 week long work-focused rehabilitation. No significant difference was found in cortisol output after treatment in the fatigue group. Further findings indicate a positive effect of ACT on reducing symptoms of chronic fatigue patients. This study highlights the importance of understanding the role of neuroendocrine pathology in patients with chronic fatigue for achieving maximum effect of therapy.

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Appendix

Multidisciplinary intervention return to work

Work related ACT intervention

Tools needed for implementing the work related ACT intervention:

- Work/values compass
  This instrument is used to assist the patient in identifying and raising awareness of life areas, which have been associated with increased acceptance of chronic conditions. It is also intended to aid patients in gaining a global perspective of their life, thereby viewing their symptoms in a global context. This will emphasize the suffering caused by their symptoms.

- Cognitive model
  An illustrative model of the interaction between cognitions, behaviour, emotions, symptoms and the social environment.

- Circle of symptoms
  A model of how chronic symptoms can develop and are maintained.

- Model of the structure and process of conflicts
  Adapted from Van der Vliert (1998)

- Mindfulness exercises
  A series of exercises that allows the patient to experience and practice mindfulness. This is intended to give the patient an alternative way of thinking that inspires acceptance instead of attempting to control thoughts and symptoms. It also directs attention to the present through breathing, and inspires an open curious attitude towards life and its experiences.

- Model of communication
  A model that illustrates stages and fazes in communication.

- ACT metaphors
  A series of examples and exercises that is used to show the patients how control is not a useful strategy and how thoughts and reality sometimes fuse together. It also includes possible scenarios for the client's future.

- Genogram
  An overview of the client's relatives and how the patient values their present relationship.

- Overview over goals and actions

A schematic overview of the patients actions toward superior and sub goals.

- Prochaska & DiClementes model of change (2001)
  And illustration and description of the transtheoretical model of change based on the work of Prochaska and DiClemente (2001). Describes five stages of change and how we flow from one stage to another over time.

- Symptom diary
  An overview of symptoms on a day-to-day basis as reported by the patient.

Total duration and frequency of the intervention:

- The ACT work intervention consists of eight group sessions and five individual consultations over a period of 3,5 weeks. Each group session lasts 90 minutes. The individual sessions last 45 minutes. The individual consultations were voluntary and based on individual needs, while the group sessions were mandatory.

The group sessions outlined:

Session 1: Socialisation to the ACT model and motivating the patient for change

In order for patients to get motivated to change their lifestyle and the way they think, we must give them a thorough introduction and explain the biological and psychological basis for our method. It is essential that the patient understand the bio psychosocial model, the evidence and logic behind the ACT principles. The patients have to find the concept plausible and manageable in order to be positive regarding the upcoming change. Change does not come easy, and often it can be quite difficult to stay motivated. Especially when patients are asked to change their interpretation of symptoms that in many instances have been an important part of their life. Understanding and participation from the patients is crucial for their motivation.

- The session consists of the following goals:
  1. Introduce the work/values compass, the bio psychosocial model, “the stress cup” and mindfulness.
  2. Introduce the circle of symptoms, how patients sometimes shop for health care services searching for the treatment that will “cure” them.
  3. Introduce the change model. (Adapted from Prochaska & DiClemente, 1991).
  4. Categorise and describe the different roles the patients have in their life.
  5. Describe different problem-solving strategies that the patients have used to solve their symptoms up to arriving at HHF.

Tools:

Model of change (Prochaska & DiClemente, 2001)

Work/values compass

Circle of symptoms

The cognitive model

Session 2: Barriers and the issue of control

In order for the patients to change their coping strategies, it is necessary for them to understand how they have coped with their symptoms up till now. During the process of describing their coping strategies, we also wish to identify what the patients view as obstacles for their return to work. Once they have defined a number of obstacles the therapist and patient consider how their current coping strategies have affected these obstacles. It is important to separate short- and long-term effects considering that avoidance often have beneficial short-term effects. In the long-term, avoidance will draw the patient further away from work. This insight into how their coping mechanisms have in fact worsened their situation is intended to put the patients in a state of creative hopelessness. This state can be defined as a moment of insight. When you cannot limit or control your symptoms, what then? When gaining this insight patients will seek to change their coping strategies. A viable alternative, which is presented by the therapist, is the ACT principles.

- The session consists of the following goals:
    1. Gain an increasing awareness of the barriers that are keeping them from working.
    2. Achieving insight towards becoming a more active part of their life through experiencing creative hopelessness.
    3. Increasing the patients existing resources.

Tools:

Mindfulness exercises

Work/values compass

Session 3: The consequence of control and the difference between pain and suffering

This session continues the work towards understanding the consequences of attempting to control your symptoms. The therapist focuses on interpretation of symptoms. If patients consider something to be dangerous and overwhelming, the natural response is to avoid it. However, there is room for interpretation in every situation, also regarding symptoms. Appraisal of symptoms is in cognitive psychology considered essential for either a sense of coping or of failure.

- The session consists of the following goals:
  1. Gaining insight on how attempts to control symptoms are not a useful strategy.
  2. Understanding the difference between pain and suffering.
  3. Understanding how we use mental scripts and avoidance as coping.
  4. Experiencing how a breach of values can lead to more suffering.

Tools:

Mindfulness exercises

Symptom diary

Work/values compass

Session 4: Family and important supporters

This session includes family and people identified by the patient as important in their change process. It is held at HHF and the focus is to increase awareness and anchoring the change process the patient is experiencing with important people in that patient's life.

- The session consists of the following goals:
  1. Presenting the work ACT intervention.
  2. Describe how the family and other important people can help the patient back to work.
  3. Present a model of communication and how different ways of communicating affect us.
  4. Describe the role of patient and the role of caretaker.

Tools:

Model of communication

Work/values compass

Session 5: You are not your thoughts.

A salient part of ACT is the concept of cognitive defusion. How people consider their thoughts to be fused with reality instead of just viewing them as thoughts. Cognitive distance and mindfulness is used to help patients gain the perspective of thoughts being abstract and separated from the self. The concept of cognitive defusion also includes operant and respondent conditioning of language. Relational responding and derived relational responding is thought to undergo change in the process of defusion. We revisit and adapt the patients current non-beneficial associations between language and thoughts.

- The session consists of the following goals:
  1. Learning to separate thoughts and reality.
  2. Gain distance to your thoughts.
  3. Learn to observe thoughts as something separated from the self.
  4. Define rules patients have about symptoms and causality.

Tools:

Mindfulness exercises

Work/values compass

Circle of symptoms

The cognitive model

Session 6: Communication and conflict

Humans are born with ability and desire to communicate. This is the basis for all human interaction. The work related ACT treatment views communication as a skill that can be developed in each patient and is a necessary tool for managing a dynamic work situation. This session is focused on analysis of the individual communication styles and strategies. The patients are taught how to communicate in a "mindful" fashion and how to train your attention in communication settings. Self-assertion is also an important part of the patients communication training.

The session consists of the following goals:

1. Familiarize the patients with the communications model
2. Observe the global communication and our own contribution

3. Learn to recognize dysfunctional communication strategies like bullying and conflicts.
4. Coping with dysfunctional communication strategies. What can we do?

Tools:

ACT metaphors

Communication model

Mindfulness exercises

Model of the structure and process of conflicts

Session 7: Language

Cognitive defusion is revisited and practiced through this session. It can be viewed as a continuation and elaboration of the concept and consequences of cognitive fusion and defusion.

- The session consists of the following goals:
  1. Understand how our language affects our behaviour.
  2. Gain insight in to what characterises our use of language.
  3. Se how simple changes of perspective influences our perception of symptoms and tasks.

Tools:

ACT exercises

Mindfulness exercises

Work/values compass

Circle of symptoms

The cognitive model

Session 8: Recap and staying committed to value-guided behaviour

The patients are encouraged to gather their experiences, methods, techniques and explanations and let this be a foundation for further change. “The values backpack” is a central tool in this

process. It is also a question of prioritizing exercises and experiences that they consider relevant for their values based actions.

- The session consists of the following goals:
  1. Recap the coping strategies and the process the patient have been through.
  2. Motivate and commit the patient to leading a value-guided life.

The individual sessions outlined:

Session 1 & 2: Building a working alliance and identifying the patient's goals and values

The first session is committed to building a good relationship/working alliance between the patient and the therapist. They should get to know each other and the therapist should survey the patient's history (especially medical history) and how their life has been influenced by their symptoms. The second session should allow the therapist to get to know the patients values. Together they should develop the work/values compass. The therapist uses this session to underline and explain how the concept of values is viewed in ACT. They should also begin to specify and concretise ideal and actual values. In this process gaps between the two should be analysed.

Tools:

Genogram

Work/values compass

Session 3, 4 & 5: Cooperation, planning and identifying goals in regards to values

The main concern in these sessions is to help the patient to commit to his/hers chosen values. This is achieved by providing structure and concretise goals that the patient will strive for in his/hers return to work. These sessions have a high degree of adaptation to the individual and their preferred values.