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# Neurocognitive and endocrine dysfunction in women with exhaustion syndrome

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# KORTISOLOPOLIS

”den moderna identitetskrisen kan endast lösas om vi förlorar medvetandet”

*Hannah Arendt*

först ramlade fräknarna av
sedan bröstvårtsnäbbarna

håret
la sig som ängsull

naglar sved sig ur

munnen torkade ihop som en
sårskorpa och

föll

här är så tyst att
jag kan höra
kärnorna gnissla
i apelsinen

Hela vägen hit har asfalterats jag har en skog i huvet

Detta land har ur sin inneboende brist på jämlikhet och insisterande likhetssträvan uppvisat allvarliga strukturella skador. Mättad tillväxt slår huvudet i taket.

innevånare vars tanke och känsla inte längre orkar
trängas i de i förväg givna strukturernas vindlingar i hjärnan utan bryter nya vägar.
Här blir natten dag och platsen förlorar sitt rum.

krasar under mina fötter ännu varken vatten eller is

dessa stigar vaggar nya gångarter väcker sömn helt lätt

delar upp en persons jag i olika delar varav en del underordnar sig en tydlig struktur och en annan aldrig kan sätta sin fot i det rummet igen

Det personliga är politiskt

det är för personligt betyder det är för politiskt

Jag har slut hud

Det finns inte en kvinna som inte känt sig väggen
Inte en känsla som leds dit

mödar sig att gå igenom
mota denna väggs slutna absoluta
Jag känner därför kan jag vara fri

Detta är inte min övertygelse detta är min pliktkänsla

Tappa tråden vad betyder det? Är det alltid dåligt att tappa något? Som att förlora ansiktet?

GE MIG EN BOKSTAVSORDNING ATT KLÄ DET OGRIPBARA I

Förslag på ett par nya ord:

hansvar

hanpassa

som i:

hon har hansvar att hanpassa sig

du som säger paranoia jag som säger ja men tänk om

tänk om

samtiden leder in i väggen
nätverket stramar åt

utbränd återvinns som fossilt bränsle
smälter isar dödar jord

”ty det finns ingen navel, vare sig i mitten av jorden eller i mitten av havet”

*Emma Warg*

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# ABSTRACT

*"Just as you ought not attempt to cure eyes without a head or a head without a body, so you should not treat a body without a soul" - Aristotle*

Stress has emerged as one of the most important factors to consider in psychiatric diagnoses and has become a common reason for long-term sick leave (LTSL). Roughly 50% of LTSL due to psychiatric diseases are thought to be associated with work-related stress. The demarcation towards major depression is disputed, and no international consensus exists for how to diagnose and rehabilitate these individuals.

The Swedish National Board of Health has suggested the term "exhaustion syndrome" to integrate these individuals into stress-related disorders. Prominent features of this syndrome are fatigue, sleeping disorders, and cognitive dysfunction. The cognitive dysfunction may be due to an interaction between personality features, environmental factors, the biological effects of stress hormones, and dysfunction in key brain areas, notably the hippocampus and prefrontal cortex. A consistent feature of chronic stress is activation of the cortisol, or hypothalamic-pituitary-adrenal, axis, which may be linked to cognitive dysfunction. Increased glucocorticoid levels, mainly cortisol in humans, are known to impair memory performance. The aim of this thesis was to investigate whether patients with exhaustion syndrome exhibit specific alterations in an extensive set of biological, psychological and immunological variables.

Patients in Study 1 had significant cognitive impairment for specific tasks assumed to tap frontal lobe functioning. In Study 2 anxiety prone, worrying, pessimistic individuals with low executive drive and a persistent personality type were more likely to develop exhaustion syndrome. Decreased reactivity was found on the pituitary level after corticotropin releasing hormone (CRH) in exhaustion syndrome patients. The cortisol/adrenocorticotropic hormone response to CRH was slightly higher in patients compared to controls, indicating increased sensitivity at the adrenal cortex level. No differences were found in hippocampal volume. In Study 3, functional imaging revealed a different pattern of brain activation in working memory tests in patients with exhaustion syndrome compared to healthy individuals and patients with depression.

In summary, our data suggests an intimate link between personality and wellbeing, cognitive performance and neuroendocrine dysfunction, in exhaustion syndrome. We thus find similarities with major depression but also distinct differences between the exhaustion syndrome and major depression.

# SVENSK SAMMANFATTNING

Psykisk ohälsa är den sjukskrivningsorsak som ökat allra mest under de senaste årtiondena. Hälften av alla psykiatriskt relaterade långtidssjukskrivingar anses sammanhänga med arbetsrelaterad stress. I Sverige används diagnosen utmattningssyndrom för att beskriva dessa tillstånd av kronisk stress utan möjlighet till återhämtning, som resulterar i ohälsa. De vanligaste symptomen vid utmattningssyndrom är mycket stark trötthet, kognitiva problem och sömnstörning. I början av sjukdomsförloppet beskrivs ofta symptom som värk, buksmärtor, oro, ljud och ljuskänslighet, irritabilitet, minnes- och koncentrationssvårigheter. Sjukdomstiden är ofta utdragen för denna patientgrupp och det finns inga riktlinjer för hur patienter ska rehabiliteras. Det förefaller även som om dessa patienter visserligen förbättras i sin sjukdom men har kvar en överkänslighet mot stress som också gör att många återinsjuknar.

Det finns sedan länge en debatt om utmattningssyndrom skiljer sig från andra välkända psykiatriska sjukdomar, särskilt depression. Det har hävdats att utmattningssyndromet skiljer sig från egentliga depressioner avseende bl.a. faktorer som t.ex. hur patienterna ska rehabiliteras, att inte SSRI har den effekt på tillståndet som man ser vid depression och att den fysiologiska bakgrunden skiljer sig med en annan typ av störning i hypotalamus–hypofys–binjurebarkaxeln (HPA-axeln) som reglerar insöndringen av stresshormonet kortisol. Utmattningspatienter har också en annan typ av sömnstörning än den man vanligtvis ser vid depressioner. De symtom som patienternas ofta beskriver är upplevda minnes och koncentrations svårigheter samt sömnproblemen.

I vår första studie ville vi undersöka om det gick att med neuropsykologiska test bekräfta och beskriva de kognitiva problem som patienterna rapporterade. Resultaten visade att patienterna skiljde sig från friska försökspersoner i några avseenden men också att de på andra sätt fungerade bra. Framförallt uppvisade patientgruppen problem med uppmärksamhet och förmågan att arbeta snabbt och fokuserat. De hade också svårt klara komplexa uppgifter som kräver struktur, planering och gott bildminne. Här presterade patienterna sämre än en frisk kontrollgrupp men även sämre än det förväntade resultatet enligt testens normeringar. Ungefär hälften av patienterna uppfyllde kriterierna för psykiatrisk sjukdom, den vanligaste diagnosen var panikångest följt av depression.

I den andra studien ville vi undersöka om biologiska korrelat och sårbarhetsfaktorer, som man sedan tidigare vet har betydelse för och som påverkar kognitionen, kunde påvisas hos dessa patienter och om vissa faktorer var särskilt viktiga för att skilja ut dessa patienter från friska

individer. I denna studie kunde vi bekräfta de kognitiva störningar vi sett i vår första studie.

Stresshormonet kortisol har påtagliga effekter på hjärnans funktion i experimentella situationer och vid kraftigt förhöjda nivåer i blodet (Cushings syndrom). Hyperkortisolemi ses också (mindre uttalat) vid egentlig depression. Vid såväl Cushing som egentlig depression har man rapporterat volymminskningar i hippocampus, en struktur som har stor betydelse för minnesfunktioner. Det är också väl känt att kortisol påverkar minnesfunktioner. HPA-axeln hos patientgruppen uppvisade en nedsatt känslighet i hypofysen med lägre insöndring av adrenokortikotropt hormon (ACTH) efter stimulering med kortikotropin (CRH), samt en ökad känslighet i binjurebarken med ökad frisättning av kortisol i förhållande till mängden insöndrat ACTH. Vi kunde däremot inte se någon minskning i hippokampusvolym i patientgruppen. Andelen patienter som hade mätbara nivåer av den proinflammatoriska cytokinen interleukin 1β var också högre.

Vissa personlighetsdrag ökar sårbarheten för att insjukna i psykiatriska sjukdomar, därför ville vi studera om denna patientgrupp hade några sårbarhetsfaktorer som kunde förklara insjuknandet. Personlighets-data visade att patientgruppen utmärker sig genom att vara ängsliga och pessimistiska med låg självkänsla, vilket är vanligt vid många psykiatriska åkommor. Det som var speciellt för den här gruppen var att de utmärkte sig som ihärdiga, ambitiösa och pedantiska personer.

I den tredje studien lät vi patienterna göra två arbetsminnestester i en funktionell magnetkamera som mäter hjärnans aktivitets mönster. Vi mätte också kortisolnivåerna i saliv under ett dygn, för att studera dygnsrytmiken och för att se i vilken omfattning produktionen av kortisol minskade efter att försökspersonerna hade tagit en tablett innehållande syntetiskt kortison. Gruppen med utmattningssyndrom jämfördes sedan med en grupp patienter med egentlig depression som ännu inte påbörjat någon medicinsk behandling och en grupp med friska försökspersoner. Patienter med utmattningssyndrom hade ett annat aktivitetsmönster i hjärnan när de utförde den arbetsminnestest som är språklig och de aktiverade också delar av frontalloben mindre än de båda andra grupperna. Det fanns även en skillnad i dygnrytmiken av kortisol där patienterna hade en flackare insöndringskurva än de andra två grupperna.

Sammanfattningsvis tyder våra studier på att det finns ett samband mellan vår personlighet, den generella hälsan, kognitiv förmåga och neuroendokrin dysfunktion vid utmattnings syndrom. De kognitiva problem som avspeglar sig i testprestationer, avspeglas också i ett annorlunda aktivitets mönster i hjärnan för patienterna med utmattningsdepression. Vi har också funnit stöd för att det finns likheter med egentlig depression men också välavgränsade skillnader mellan utmattningssyndrom och egentlig depression.

# ABBREVIATIONS

| | |
|---|---|
| ACC | Anterior cingulate cortex |
| ACTH | Adrenocorticotropic hormone |
| BMI | Body mass index |
| C | Cooperativeness |
| CBO | Chronic burnout |
| CD | Claeson-Dahl inventory of learning and memory |
| CFS | Chronic fatigue syndrome |
| CRH | Corticotropin releasing hormone |
| CVMT | Continuous visual memory test |
| DALY | Disability-adjusted life year |
| DEX | Dexamethasone |
| DSM-IV | Statistical Manual of Mental Disorders: Fourth edition |
| fMRI | Functional magnetic resonance imaging |
| GAS | General adaption syndrome |
| HA | Harm avoidance |
| HAS | Hamilton anxiety scale |
| HPA-axis | Hypothalamic-pituitary-adrenal axis |
| ICD-10 | The International Statistical Classification of Diseases and Related Health Problems: 10th revision |
| IL-1β | Interleukin 1 beta |
| IQ | Intelligence quotient |
| IVA | The intermediate visual and auditory continuous performance test |
| LTSL | Long-term sick leave |
| MADRS | Montgomery Åsberg depression rate scale |
| MDD | Major depressive disorder |
| MONICA | Monitoring of trends and determinants in cardiovascular diseases |
| MRI | Magnetic resonance imaging |
| NS | Novelty seeking |
| P | Persistence |
| PLS | Partial least squares |
| PSQ | Perceived stress questionnaire |
| PTSD | Post-traumatic stress disorder |
| RD | Reward dependence |
| ROCFT | Rey Osterrieth complex figure test |
| SD | Self-directedness |
| SSRI | Selective serotonin reuptake inhibitor |
| ST | Self-transcendence |
| TCI | Temperament and character inventory |
| WHO | World Health Organization |
| WHO-QoL | WHO-Quality of life |
| WAIS-R | Wechsler's adult intelligence scale-revised |
| PLS-DA | Partial least squares discriminant analysis |
| TSH | Thyroid stimulating hormone |
| T3 | Triiodothyronine |
| T4 | Thyroxine |

# ORIGINAL PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Sandström A, Rhodin Nyström I-L, Lundberg M, Olsson T, Nyberg L. Impaired Cognitive Performance in Patients with Chronic Burnout Syndrome. Biological Psychology 2005; 69 (271-279)

II Sandström A, Peterson J, Sandström E, Lundberg M, Rhodin Nystrom IL, Nyberg L, Olsson T. Stress-related Cognitive Deficits in Relation to Personality Type and Hypothalamic-pituitary-adrenal (HPA) Axis Dysfunction in Women. Scandinavian Journal of Psychology 2010; (In Press).

III Sandström A*, Säll R*, Peterson J, Salami A, Larsson A, Olsson T, Nyberg L. Brain Activation Patterns in Major Depressive Disorder and Job Stress-Related Long-Term Sick Leave. (Submitted). * Joint first authorship

Paper I and II are reprinted and figures are shown with the permission of the publishers.

Paper I Elsevier

Paper II Wiley- Blackwell

# INTRODUCTION

Today, stress is one of the most significant health problems in modern society. This indicates an urgent need for investigations into the pathways linking stress and disease, the consequences of stress, and factors that may predispose an individual to developing a stress disease.

In this thesis, we investigated markers of vulnerability in individuals with exhaustion syndrome, such as personality, psycho-social stress, and general well-being, in relation to putative outcome factors, such as cognitive dysfunction, the hypothalamic-pituitary-adrenal axis (HPA-axis) and immunological variables, and structural and functional brain parameters. Importantly, this group of patients often have a history of high premorbid functioning prior to sick leave, rarely fulfilling the criteria for personality disorder and often having stable family situations [1-4]. From this perspective, comparing exhaustion syndrome with overlapping diseases, including major depression and post-traumatic stress disease (PTSD), is important.

The notion that traumatic damage to the brain has a substantial impact on emotions and behavior is widely accepted in all fields of medicine today. Despite a scarcity of evidence, the notion that stressful experiences and emotional states can influence the onset and progression of disease has existed for centuries and led many researchers to believe that feelings and experiences might change how the brain works, and even damage the brain [5, 6]. In World Wars I and II, systematic observations of young soldiers and Holocaust survivors that developed what we today call post-traumatic stress disorder (PTSD) and alexithymia pointed research to the deleterious effects of severe psychological trauma on the brain. One observation was that severe behavioral changes occur in persons who, prior to psychological trauma, were very well adjusted. Due to a lack of methods for observing the brain and cognitive processes, little progress has been made in attempts to understand why many of these persons never recovered and suffered from health problems throughout their lives.

Walter Cannon (1871-1945), one of the early pioneers in stress research, used the term homeostasis to refer to the efforts of the physiological systems to restore initial conditions after challenging situations or threats [7, 8]. Cannon focused on the response of the sympathetic-adrenal medullary system to emergency situations. An increase in epinephrine mobilize the body's energy resources, which increases blood pressure and heart rate, increases cardiac output (chronotropic and inotropic effect) and plasma glucose, changes blood coagulation, and decreases digestion. Cannon referred to these changes as the "fight and flight response" to emphasize the adaptive nature of these alterations, and viewed these

processes as events taking place locally in the body, independent of central nervous system control.

Hans Selye (1907-1982) is also considered to be one of the early pioneers of modern stress theory. His research efforts were mostly aimed at revealing neuroendocrine mechanisms that play a role in what he called "diseases of adaptation" [9]. Selye observed that patients suffering from different diseases often exhibit identical signs and symptoms; they just "looked sick". This observation led to the first step in his recognition of "stress", later describing general adaptation syndrome (GAS), as a response of the body to higher demands or "strain". The syndrome details how stress induces hormonal autonomic responses that, over time, can lead to ulcers, high blood pressure, arteriosclerosis, arthritis, kidney disease, and allergic reactions. The concept of stress stems from a misinterpretation of what Selye later stated should have been referred to as "strain". As a theoretical concept the word "stress" was problematic in many ways, "Stress, in addition to being itself, was also the cause of itself, and the result of itself." In Selye's understanding of stress, it referred to the general strain on the body caused by disease, injury, or psychological pressure. He also pointed to an "alarm state", "resistance state", and "exhaustion state". These stages are associated with particular biological markers, such as changes in hormone patterns and the production of more "stress hormones," and the gradual depletion of the body's energy resources. In the alarm state, the individual recognizes a challenge or threat and develops a "fight or flight" response. The stress hormones adrenaline and cortisol are both produced during this stage. In the resistance state, the body attempts to adapt to a persisting challenge. The adaptation or coping requires physiological or psychological resources, which are not infinite and may eventually get depleted. If the exhaustion state occurs, the stressful challenge has persisted too long. The immune system will be impaired, and long term damage and illness may result.

Notably, Selye acknowledged the HPA-axis and its impact on biological and psychological processes. Through these pioneering discoveries, the first connection between brain responses and bodily functions was established.

Over the years, contributions from social and biomedical sciences have shown that psychosocial factors and individual differences in coping style, emotional state, cognition, and appraisal have major impacts on the stress process [10, 11]. The brain was increasingly seen as the clear central mediator of physiological adjustments and behavioral responses to behavioral challenges [12]. One of the obvious reasons for this view is the fact that the brain determines what is threatening via sensory input and regulates the behavioral and physiological responses of the autonomic nervous system based on this information [13, 14]. The old concept of homeostasis did not address the ongoing accommodation to stressful life events and environmental challenges mediated by the brain. The concept

of allostasis was introduced by McEwen and colleagues and is the new conceptual framework for the study of stress-related disease [15].

The HPA-axis and immune, metabolic, and hormonal systems is involved in the process of protecting the organism from and adapting the organism to challenges. This process, referred to as allostasis, is an essential component of maintaining homeostasis [16]. This ongoing physiological accommodation to stressful conditions has a price, and the cost of adaptation has been termed allostatic load. Thus, allostatic load is the wear-and-tear on the body that results from chronic dysregulation. One example of allostasis is improved memory and immune function with moderate increases in cortisol, which helps overcome challenging situations. Persistently high concentrations of cortisol may have adverse effects, including inhibiting the formation of new neurons (neurogenesis) in the hippocampal region of the brain, possibly leading to cognitive deficits and dysregulation of the HPA-axis, which is an example of allostatic load [17, 18].

# Definitions and classifications of stress

In industrialized countries, psychiatric disease is the most reported cause of long-term sick leave (LTSL). According to the World Health Organization (WHO), depression is the leading cause of disability (*disability-adjusted life year,* DALY) in the world and the leading contributor to the global burden of disease for those aged 15-44 years for both sexes combined (WHO homepage: http://www.searo.who.int/en/Section1174/Section1199/Section1567/Section1826_8101.htm)

Since the early 1980s, the incidence of LTSL (more than 90 days) has increased dramatically in Sweden, especially among young people [2]. Long-term sick leave due to psychiatric illness, such as depression and fatigue, doubled during this period. The incidence of disability pension due to psychiatric problems increased 68% during the same period. More than 50% of these patients reported stressful work situations as the main cause of disease [1, 2].

The concept of burnout is adapted from occupational psychology and was initially a description of the frustration and emotional detachment seen in social and health workers [19, 20]. Originally, the term was not meant as a classification of disease, but rather a description of the process of exhaustion or adaption to an overwhelming work situation. Christina Maslach described burnout as a work-related syndrome that occurs among professionals working in health care, social care, and education [21]. The core symptoms of burnout were defined as emotional exhaustion, depersonalization, and reduced personal accomplishment. In a clinical setting, symptoms were expressed as cynical and negative attitudes about clients and feelings of detachment and shame about one´s own professional achievements.

Pines and Aronsson adapted the concept of burnout as a state of exhaustion and emotional drain but stressed the importance of tedium as a main feature for developing burnout [22, 23]. Burnout was also emphasized to be a consequence of long periods of emotionally demanding situations rather than merely a work-related phenomenon. Different research traditions have emphasized different symptoms of exhaustion and tried to operationalize the concept of burnout.

The demand-control model was originally proposed by Karasek [24]. The model describes two dimensions of the psychosocial work environment: job demands and decision latitude (control over work), and skill discretion (diversity of work and prospect for use of expertise). According to this model, jobs can be classified into high strain jobs and low strain jobs, which can be further combined with high or low levels of control—when the worker lacks the resources to deal with demands. High-strain jobs combined with low levels of control are considered to be the most risky type of job. Conversely, jobs with high strain can be intensely challenging, but if the workers have sufficient control over their activities and the freedom to use available skills this type of job is not associated with the development of disease. Low-strain jobs, with few demands and high levels of control, are predicted to have lower than average levels of strain. The model was later completed with the concept of support, stating that the level of psychosocial support has a major impact on the ability to cope with challenging situations, influencing general well-being [25].

Research efforts in the field of job-related stress is somewhat hampered by the lack of consensus about diagnostic criteria. Internationally, “depression” is the main category to use in the field of stress-related disorders, despite the fact that several scientific papers indicate that depression and job-related stress do not share patterns of physiological and psychological change [26-28]. As proposed by Åsberg and co-workers, burnout should not, in this view, be considered a necessary or abundant condition for developing a stress-related disease, rather it is a process or coping strategy to endure challenging situations at work that may, but do not have to, lead to disease or exhaustion syndrome.

Notably, the DSM-IV is based on “core” symptoms that are required to fulfill diagnostic criteria and on the notion that different psychiatric disorders are truly discrete disorders [29]. Biological findings often overlap in stress-related diseases, such as depression, burnout syndrome, chronic fatigue, maladaptive stress disorder, vital exhaustion, anxiety disorders, and PTSD, and fulfilling the criteria for one disorder may likely fulfill criteria for other stress-related or adjustment disorders [30, 31].

The Swedish National Board of Health and Welfare recently recommended a specific ICD-10 code (i.e. exhaustion syndrome, F43.8) to classify the closely related terms vital exhaustion, mental fatigue, and clinical burnout (Table 1). The diagnosis of exhaustion syndrome

exclusively comprises Swedish circumstances and was adjusted to international categorizations when writing our papers. In Paper I, we used the term “burnout”. In Paper II, we used the term “stress-related exhaustion”. In Paper III, we used the phrase “work stress-related long-term sick leave”. In the introduction of this thesis, “exhaustion syndrome” was used. The core symptoms of “exhaustion syndrome” are vital exhaustion and reduced endurance as a result of identifiable stress factors for at least 6 months [1]. Stressors can be identified both inside and outside of work-related situations

**Table 1.** Diagnostic criteria for exhaustion syndrome from the National Board of Health and Welfare in Sweden. All capital letters must be fulfilled for the diagnosis.

| | | |
|---|---|---|
| A | | Physical and psychological exhaustion for at least two weeks. The symptoms should be developed as a consequence of one or several stressors during at least six months. |
| B | | Evident lack of mental energy in the form of reduced initiative, reduced endurance, or an extended time for recovery after mental stress. |
| C | | At least four of the following symptoms almost every day during a two week period: |
| | 1 | Difficulties with concentration or memory |
| | 2 | Reduced ability to handle demands or to work with time pressure |
| | 3 | Emotionally unstable |
| | 4 | Disturbed sleep |
| | 5 | Physical weariness |
| | 6 | Physical symptoms as pain, chest pain, palpitations, digestive complaints, dizziness or sound hypersensitivity |
| D | | Symptoms should cause clinical suffering or reduced capacity at work, in social life or in other important respects. |
| E | | The condition is not caused by substances or somatic disease. |
| F | | If criteria are fulfilled for depressive episode, dysthymia or anxiety disorder, the exhaustion syndrome will be reported as secondary diagnosis. |

# Cognition

Long-term stress may have profound negative effects on the brain via multiple mechanisms. One of the core complaints in patients suffering from exhaustion syndrome is problems with memory or concentration [32-34]. One possible way to examine the “health” of the brain is a neuropsychological investigation of cognitive functioning. The neuropsychological domains investigated in this thesis are summarized in the following section. Essential domains in a hypothesized structure of human memory are shown in figure 1.

## Attention

Attention refers to both the ability to selectively pay attention and to voluntarily decide not, or inhibit the urge, to pay attention, in other words

to process relevant stimuli and ignore irrelevant stimuli [35-37]. Attention also refers to the ability to shift attention, to maintain alertness, and to update new information [38, 39]. Attentional processes are vital in control processes, such as executive function, working memory, and cognitive control [40]. One of these domains, and an important factor for everyday activities, is sustained attention, which reflects the ability to sustain mindful, conscious processing of stimuli and the ability to ignore the repetitive qualities of a stimuli that would otherwise lead to habituation and distraction from other stimuli [41, 42]. This domain means that one has the capacity to maintain attention to an activity over a longer period of time [41]. The concept of sustained attention is closely related to vigilance, arousal, alertness, and the ability to keep focus, which are all known to be affected by sleep deprivation and stress [43]. Mild stress is known to improve attentional processes, but severe and persistent stress is known to impair the ability to have sustained attention and keep focus [17, 44, 45]. Sustained attention is also important in cognitive control processes because maintaining activity against distractions until a goal is achieved is important.

Many patients with exhaustion syndrome complain about their inability to maintain alertness and keep plans, and that they easily get distracted. This problem is often demonstrated in everyday activities, such as making dinner and doing many things at the same time. The challenging endeavor of making a nice dinner out of a cookbook and keeping an eye on a struggling toddler making her way up the kitchen table at the same time, is suddenly impossible to achieve. If this challenge is supposed to be considered a decline in cognitive abilities, it could reflect problems with frontal cortex networks. At the same time, patients are often referring to their inability to stay awake and maintain alertness, which could reflect problems with networks engaging dorsal frontal and subcortical areas. These areas are known to be involved in activities that need a high level of alertness and vigilance [38].

## Memory

Theories of memory are many and complex. Memory is the end-product of learning, and one way to categorize memory is by defining the different stages of the learning process [46]: **encoding,** referring to the process of storing incoming information; **acquisition** registers inputs in sensory buffers and sensory analysis stages; **consolidation** creates a stronger representation over time; **storage** creates and maintains a permanent record; and **retrieval** refers to the process of utilizing or recovering stored information [47]. The abilities to recognize and recall memory are suggested to be dual processes [48, 49]. Studies of brain lesion patients have supported this view, showing that patients with hippocampal deficits can have severe deficits in recall but still be able to recognize items.

Memories are also defined by retention time and their content [50]; thus, we have identified **short-term memory** and **long-term memory**, and those memories can also be **declarative** or **non-declarative**, referring to the ability to have conscious (declarative) access or not (e.g., playing the piano vs. priming) [50]. Declarative memories can be divided into **episodic memory**, things we can recall about our own personal autobiographical history, such as being drunk for the first time, the first day at school, or your first love, and **semantic memory**. In contrast to episodic memory, semantic memory is about world knowledge, such as who shot John Lennon or how to differentiate hyenas from lions [51, 52]. The memory of what it felt like when John Lennon died and what you said to your husband when the hyenas were nibbling on your tent in Africa is more episodic in nature. The **encoding** of memory is associated with the activation of frontal regions and temporal areas, including the hippocampus. The encoding of verbal material is strongly associated with activation of the left hemisphere, and non-verbal memory is associated with a bilateral activation if the encoded material includes concrete objects, probably because verbal strategies are used to remember the items. The engagement of the hippocampus is most likely necessary for successful long-term memory encoding [46, 53]. Patients with damage to the medial temporal/hippocampal regions have been shown to have episodic memory deficits, and there is a strong correlation between the magnitude of damage and the degree of amnesia [54].

The **retrieval** of semantic and episodic memory is hemisphere-specific in nature; episodic memory retrieval activates the right prefrontal cortex and semantic retrieval involves the left prefrontal cortex. This specificity is also present when it comes to verbal vs. non-verbal memories [53, 55]. The processes of remembering (recollective matching) and knowing (familiarity discrimination) are suggested to be dissociated in terms of brain correlates [56]. Recollection involves the ability to freely recall the item and consciously retrieve contextual details associated with it (e.g., remembering that “mother” was presented as the second last item in the list), whereas familiarity involves confidently knowing that the item was on the list even though no specific information about its prior occurrence can be recalled, or to be able to discriminate between two words present on the list. Patients with damage to the hippocampus sometimes have severe deficits in recollection memory tests but perform well on tests in which they only have to make judgments about whether they recognize items. In clinical settings, these abilities are tested by presenting the subject with a free recall task and a recognition task (old vs. new discrimination) for both verbal and non-verbal tests.

**Working memory** represents a temporarily limited capacity store for retaining information over the short-term and performing mental operations with this information [57-59]. Baddeley and colleagues proposed two subordinate systems, the phonological loop and the visuospatial sketchpad, and the central executive function that presides over the interactions between these two systems. Brain lesion studies and

functional magnetic resonance imaging (fMRI) studies have, to some degree, supported the distinct nature and anatomical locations of these subsystems. Lesions in the left hemisphere are known to impair verbal memory, and right hemisphere lesions produce more severe deficits in visuospatial memory. Neuroimaging studies have also supported this view by showing neural activation in the left part of the prefrontal cortex during the maintenance of verbal information. The neural correlates of visual information have been associated with frontal and parietal areas in the right hemisphere. Other studies point out that all higher order functions are mediated by distributed large-scale networks, which suggests a dynamic interaction between the left and right temporal regions modulated by specific task demands [60].

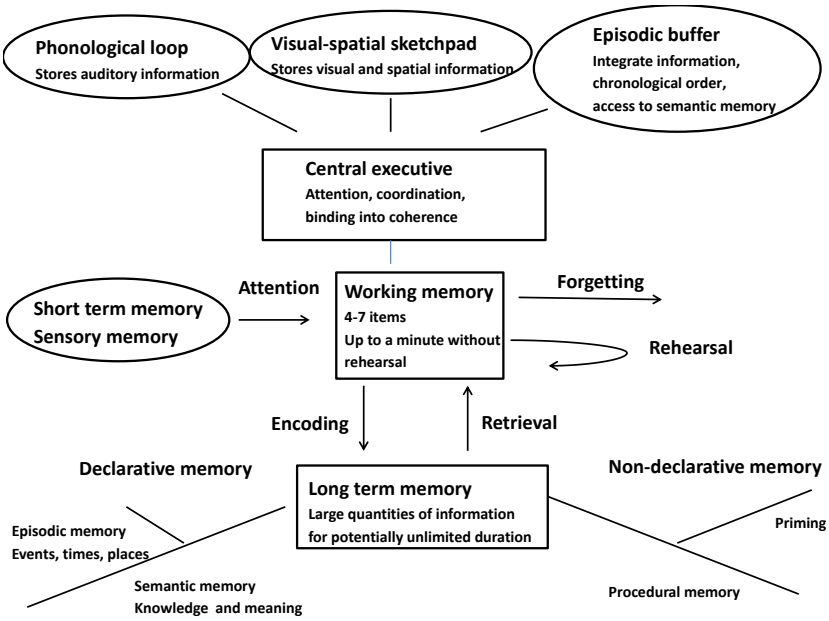


**Figure1.** Memory adapted after Baddeley and Tulving. Time and content are hypothesized to be the two main distinctions that define different forms of memory [51, 61].

## Visuospatial function

Visuospatial ability comprises the analysis of spatial information and understanding spatial relations. Two main streams of visual processing occurs in the brain [39]. A higher occipital-dorsal network is responsible for perceiving spatial relations between objects in a top-down manner, and a lower ventral stream recruits an occipital-temporal network subserving object identification in a bottom-up manner [62].

Damage to the dorsal route may impair the ability to make judgments about spatial relations and the patient's ability to use visual information to guide their actions, such as grabbing a hammer or reaching for the doorknob. Lesions in the ventral route are common in agnosia (inability to identify objects).

## Executive function

Executive function refers to higher order functions that require planning, flexibility, and the ability to inhibit inappropriate behavior and update new information, such as goal-oriented behavior [39, 63]. Executive function is highly dependent on attentional processes and is mainly about controlling information processing. Frontal lobe lesions are known to sometimes affect executive function [64-66].

To what extent executive functions can be considered unitary in the sense that they are reflections of the same underlying mechanism or ability is not known. Often postulated executive functions, such as shifting between mental sets or tasks (shifting), updating and monitoring working memory content (updating), and inhibition of proponent responses (inhibition), could represent the latent factors responsible for the performance of executive tasks.

Everyday tasks, such as making dinner, are highly dependent on good executive functioning. Before making the dinner one must plan what to eat, check what is already in the refrigerator, remember what to buy to be able to make that special dish, read information and remember what was just read if using a recipe, and follow an order (e.g., chopping the onion before frying it and boiling the water in time to add the spaghetti). While cooking one must stay with the initial plan, even if talking to a 3-year-old at the same time, and one must be able to be flexible enough to maybe pick up the phone in the middle of the task. The progress of the work must also be constantly evaluated and changes made if it is not going well (e.g., begging one's husband for help if the 3-year-old suddenly decides to strangle the cat). Activities such as these are often a problem for patients with exhaustion syndrome.

# Previous findings regarding cognitive dysfunction in stress related disease

## Exhaustion syndrome and related diagnoses

As noted earlier, patients with exhaustion syndrome often complain about problems with memory, concentration, and executive function. A few studies have made attempts to verify these deficits. Support for patients' subjective feelings of cognitive impairment is given in some earlier studies that identified specific cognitive dysfunction linked to exhaustion syndrome [26, 32, 67]. The problems with attention, visuospatial learning, and memory that patients often complain about are consistent with studies of stress-induced deficits in visuospatial capacity and working memory [18, 26, 68, 69]. The pattern shown in some of these studies, intact performance on tests with familiar verbal materials combined with slowed speed and impaired performance on tests with novel non-verbal stimuli, suggests frontal cortex/medial temporal cortex-network dysfunction. These findings are well in line with recent data from rodents and humans, suggesting that chronic stress may impair attention control in conjunction with disrupted plasticity in prefrontal cortex networks [70].

## Major Depression

Notably, cognitive impairment is also a common feature of major depressive disorder (MDD) [71-73], and the degree of cognitive impairment has been associated with the number of prior depressive episodes and increased HPA-axis activity [74, 75].

Significant impairment in working memory and declarative memory has been reported in MDD patients [76-78], with episodic memory dysfunction being the most robust finding [79]. Interestingly, depression may reflect problems in information processing within neural networks rather than chemical imbalances [80]. Thus, problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and antidepressant drugs may improve information processes by inducing plastic changes in neuronal networks, gradually leading to improvements in neuronal information processing and mood recovery. These changes may be the reason why psychological and pharmacological therapies, electroconvulsive shock treatment, and placebo effects might all lead to improved information processing and mood recovery through mechanisms that initiate similar processes of neuroplasticity and may also explain the delayed appearance of clinical improvement with antidepressant drugs. These slow and gradual effects may reflect a slow maturation of neuronal connections [80]

## PTSD

In the field of post-traumatic stress, several studies have suggested that severe psychological trauma can lead to problems with attention, executive functioning, visuospatial ability, learning, and memory [81, 82]. Most findings point to the possibility of fronto-temporal dysfunction. Functional imaging studies have shown decreased hippocampal activation with memory tasks [83], which is in line with the difficulties in episodic memory, and visuospatial ability has been repeatedly shown in PTSD victims. Because most of the individuals exposed to traumatic events do not develop PTSD, it has been suggested that individuals that do develop PTSD share pre-existing markers of vulnerability to PTSD, such as low IQ and smaller hippocampal volume [84, 85].

# Personality

The research area of personality and personality disorder usually tries to identify what kind of patterns of adjustment and healthy behavior that help individuals adapt and effectively respond to ongoing demands. Abnormal personality traits are seen as acquired or innate biological processes and/or genetic elements that interact with the environment towards maladaptive function within the social context in which the person must function [86].

Many attempts have been made to identify the main categories and features of personality. The Neo-Five Factor Personality Inventory (NEO-FFI), Minnesota Multiphasic Personality Inventory (MMPI), and Cloninger's Temperament Character Inventory (TCI) are three commonly used inventories of personality. The so-called five-factor model [87] has been widely adopted as a consensual framework. The five factors are most commonly labeled as extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience. Several psychological traits are closely linked to depression and anxiety, such as the "big five" personality factors neuroticism and extraversion [88].

The MMPI scales were originally created based on groups with known psychopathologies. The test was proposed to be an atheoretical model capturing important aspects of behaviors that constitute well-known psychopathologies. The personality traits defined and measured by MMPI are hypochondriasis, depression, hysteria, psychopathic deviation, masculinity–femininity, paranoia, psychoasthenia, schizophrenia, hypomania, and social introversion. Because the concept of the MMPI is based on defined psychopathologies, it is difficult to argue that it is not hypothesis driven and circular reasoning is hard to avoid.

From a biological view, responses to stress presumably stem from temperament-based personality features, such as approach, avoidance, and attentional regulation systems [89, 90], and the core properties of investigation are the understanding of the basic properties of self-regulation and how those properties are manifested in human behavior.

In this thesis, the psychobiological model of personality developed by Cloninger was used. This dimensional model includes four temperament factors that are considered to remain stable throughout life, and three character factors that are thought to change in response to social learning and life experiences. The four main dimensions of temperament are: novelty seeking, describing the tendency towards excitement in response to novel or rewarding stimuli; harm avoidance, which is assumed to represent the tendency to respond intensely to signals of adverse stimuli; persistence, described as a temperament that can explain the maintenance of behavior; and reward dependence, reflecting the tendency to respond intensely to signals of reward and to maintain behavior previously associated with reward. Individuals with a high persistence score tend to be industrious, hard-working, perfectionists, persistent, and stable despite frustration and fatigue, Temperamental dimensions are hypothesized to be relatively stable traits, highly heritable, and linked to variations in the serotonergic system.

The three main dimensions of character are self-directedness, cooperativeness, and self-transcendence, measuring resourcefulness and maturity traits concerning individual and social adaptation; thus, they are considered vulnerability factors for the risk of personality disorder and depression. Character dimensions are considered to be changeable states, developing in adults and depending on factors such as psychological well-being.

Hypothetically, certain personality features could play a role in being predisposed to developing exhaustion syndrome. However, the same features could be a consequence of the stress. The role of personality traits in stress-related disease are complicated by the mutual interactions between stress-related symptoms, comorbid DSM axis-I disorders such as depression and anxiety, and personality disorders. State-dependency refers to the instability of personality measurements over time, in contrast to trait-dependency, which implies stable personality factors. Importantly, decreased psychological health is known to “prime” individuals to be influenced by “mood bias” and to report bad life experiences and affirm negative feelings, thereby influencing results in self-directedness and depression measures [91].

# Previous findings about Personality in stress related disease

## Exhaustion syndrome and related diagnoses

Persistence interacts with vital exhaustion and gender. A Finnish study showed that exhausted women with high persistence scores express the highest level of physiological stress reactivity [92]. The study investigated cardiac reactivity in relation to two tests that invoke stress, the arithmetic task and the public speech task. Notably, exhausted women with high persistence scores had a heightened cardiac response to stress, and exhausted women were physically most stressed during a public speech.

Persistence is characterized by reference to others; persistent people want to be more driven and do things better than other people, which may partly explain why the public speech test invoked so much stress in this group. The authors of the study pointed out that persistence is not thought to be an innately typical temperamental trait of women. The trait is also not innately related to cardiac reactivity or likely to lead to exhaustion, but if a woman has an innate tendency for persistence and perfectionism, she might be more likely than men to become exhausted, which, in turn, could heighten her cardiac stress reactivity [92].

Appels [93] investigated a special high-risk group in a rehabilitation program after myocardial infarction and found a relation between exhaustion, myocardial infarction and extreme perfectionism. Appels interpreted this context as referring to different environmental gender expectations. In both of the above papers, the authors concluded that some people might have an innate tendency to physiologically overreact to daily challenges, which is likely to lead to exhaustion.

High persistence levels were also found in a group of patients with environmental illness [94]. The rapid changes that are so characteristic of our modern society can be a challenge for individuals with high persistence in regards to adjusting and adaptation, which may result in various symptoms, especially stress-related symptoms. High-persistence individuals probably have difficulty accepting their own limits and, therefore, may tend to blame external factors, such as environmental illness, as the cause of their symptoms (attribution).

In conclusion, harm avoidance, self-directedness, and persistence seem to be vulnerability factors, or at least associated factors, for depressive disorders and other stress-related diseases. Other studies have shown that heightened negativity is also associated with a greater likelihood of developing an illness [95].

## Major Depression

Temperament may play an important role in coping with stress. Patients with a history of depressive disorders have very high harm avoidance scores, even in remission [96, 97]. Patients who fail to respond to antidepressant treatments generally have higher harm avoidance scores before treatment than those who respond [98]. The personality dimensions of harm avoidance and self-directedness have been associated with depression and anxiety in numerous studies [99]. High harm avoidance scores and low scores in self-directedness have been interpreted to be linked to a reduced ability to cope with stress and a genetic vulnerability to develop depression. Studies of the relationship of temperament dimensions with biological markers of depression have found reward dependence and harm avoidance scores to be significant predictors of morning hypercortisolemia in depressed individuals [100]. Correlations between platelet serotonergic markers (5-HT2a receptors) and harm avoidance scores in depressed patients have also been reported [101].

## PTSD

Variations in personality structure are associated with vulnerability to developing PTSD [102-104], as well as the severity of symptoms in patients with PTSD [105], [106]. Higher neuroticism and harm avoidance scores measured either before or after a traumatic event have also predicted the onset of PTSD diagnosis.

# HPA-axis

Many studies show that stressors induce biological changes over time, at both the hormonal and neurochemical levels [107, 108]. The HPA–axis, autonomic nervous system, emotional networks, immune system, and other neuroendocrine systems constitute the stress system. The stress system is activated during strain or allostasis, influencing central and peripheral functions that are important for adaptation and survival [109-111]. Two main classes of stress hormones are differentiated, glucocorticoids (mainly corticosterone in animals and cortisol in humans) and catecholamines (mainly norepinephrine and epinephrine).

The HPA-axis is a hormonal axis with origins in the secretion of corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP), which are both produced by the paraventricular nuclei of the hypothalamus into the hypophyseal portal system [112]. CRH activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary. When ACTH is secreted by the pituitary gland, it reaches the adrenal glands via the bloodstream, thereby stimulating the secretion of cortisol (figure 2). Cortisol mainly exerts its effects by binding to the low affinity glucocorticoid receptor (GR), and the high affinity mineralocorticoid

receptor (MR). In the brain, the MR is predominantly localized in the hippocampus, amygdala, and prefrontal cortex, which are brain structures known to be involved in learning and memory [12, 113]. The GR is widespread throughout the brain but expressed at high density in the hippocampus, prefrontal cortex, paraventricular nuclei of the hypothalamus, and amygdala. The expression of these receptors is highly dependent on neurotransmitters, including serotonin, and norepinephrine. The binding of glucocorticoids to nerve cells that express MR have been associated with enhanced plasticity of the hippocampus, improved long-term potentiation (LTP) of memory, and improved cognitive function. On the other hand, GR activation has been associated with decreased LTP and impaired cognitive function [114].

By binding to corticosteroid receptors in the brain, glucocorticoids also inhibit further secretion of CRH from the hypothalamus and ACTH from the pituitary (negative feedback). The activated HPA-axis regulates body functions, such as glucose and lipid metabolism and immunity, which promotes survival in life-threatening or demanding situations. The HPA-axis also has important effects on the brain. Several studies have shown the role of glucocorticoids in the regulation of neuronal survival and neurogenesis, influencing the size of the hippocampus [115]. Notably, the hippocampus is an important structure related to the consolidation of new memories and emotional appraisal processes [116]. High levels of glucocorticoids are thought to cause a state of reduced metabolic activity in certain cells in the hippocampus, impairing the ability to withstand excitotoxic processes in glia and other cells, which can contribute to cellular damage in the brain [117].

The effect on cognition, the immune system, and allostatic load after activation of GR produce the classic inverted U-shaped response to increasing exposure to stressors [118]. An absence of normal glucocorticoid production results in impaired immunity and impaired cognitive performance [119], but moderate levels of cortisol enhance immune and cognitive functions [120], probably by enhancing synaptic plasticity in hippocampal areas. At the far end of the U-shaped curve, the actions of high levels of cortisol inhibit the activity of the peripheral immune system and impair memory functions under overwhelming stress [121]. The connection between the HPA-axis and cognitive function thus has massive support from experimental studies and clinical research [122].

In patients suffering from Cushing's syndrome with profound hypercortisolemia [123], increased irritability, insomnia, depression, and cognitive disturbances are commonly seen. Patients with Cushing's syndrome also show hippocampal volume loss that is at least partially reversible with treatment. However, long-term decreases in cognitive impairment are not uncommon [124].

In a longitudinal study, Lupien et al. identified a subgroup of individuals that exhibit elevated and increasing cortisol levels [113]. Interestingly, these individuals tended to develop impaired cognition and lose hippocampal volume over the years. Healthy postmenopausal women who reported higher levels of life stress over a longer period of time prior to imaging, also had decreased mean gray matter volume in the hippocampus and orbitofrontal cortex [125].

The function of the immune system and HPA-axis is closely interrelated. Some pro-inflammatory cytokines and other immune cells in the periphery and from the brain profoundly affect the HPA-axis and may directly or indirectly (via activation of the HPA-axis) contribute to cognitive dysfunction [126, 127]. Several major pro-inflammatory cytokines, such as interleukins IL-1β, IL-2, IL-6, and TNF-α, are elevated in depression and high pro-inflammatory cytokine concentrations are hypothesized to contribute to hippocampal neurodegeneration [114]. Therapy with interferon is also known to affect cognition and mood [128].

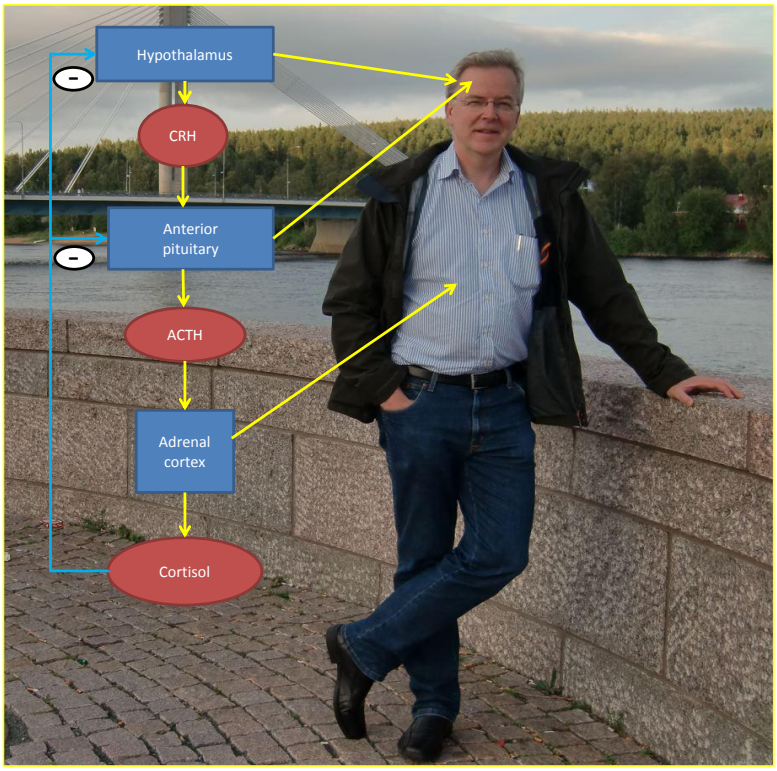


**Figure 2.** The hypothalamic-pituitary-adrenal axis (HPA-axis). Following a stressor, the hypothalamus releases CRH, which activates the pituitary gland, leading to the secretion of ACTH. Increased ACTH levels are detected by the adrenal cortex, which then secretes glucocorticoids. Secreted cortisol exerts a negative feedback on the pituitary and hypothalamus.

# Previous findings about HPA-axis dysfunction in stress related disease

## Exhaustion syndrome and related diagnoses

Stress-related disorders, including PTSD, fibromyalgia, and chronic fatigue syndrome, have been suggested to be linked to lower levels of circulating cortisol and increased feedback sensitivity [129-131], but these findings have not been consistent [132].

The cortisol awakening response (CAR) can be defined as the change in cortisol concentration that occurs during the first hour after waking from sleep [133, 134]. Findings from patients with burnout have shown conflicting results, with increased [135], decreased [133], or normal [136] awakening response. One study from Sweden showed that lower diurnal cortisol variability in burnout patients was related to slower cognitive performance [67], which is consistent with a flattening of the diurnal curve in stressed populations [137]. Another Swedish study showed that patients with job-induced depression show marked attenuation of the HPA-axis response to DEX/CRH stimulation [26].

## Major Depression

Depression is characterized by increased HPA–axis activity in approximately 50% of patients [138]. Antidepressants directly regulate HPA-axis function, including up-regulation of MR and GR in the brain, and its normalization has been suggested to be a necessary predecessor of the clinical response to antidepressant drugs [139].

Despite the fact that patients with PTSD and MDD share many symptoms, and half of patients with PTSD also fulfill the criteria for MDD, there is a striking difference in HPA-axis patterns. Patients with MDD often display heightened basal cortisol, non-suppression by dexamethasone (DEX), and normal or slightly blunted cortisol increases in response to stress [138]. This typical pattern of HPA-axis functioning is seen in 40-60% of patients diagnosed with MDD. The question of whether this HPA-axis dysfunction is a state or trait phenomenon in MDD has been debated. In a study by Holsboer et al., first-degree family members of patients with unipolar depression displayed a similar, though quantitatively more modest, pattern of dysregulation than that observed during a major depressive episode [140].

## PTSD

Decreased HPA-axis activity and steroid feedback super-sensitivity, which often lasts for decades after the initial trauma, has been repeatedly found in PTSD [129]. Prospective, longitudinal designs support the possibility that cortisol levels may constitute a vulnerability factor associated with the risk of PTSD in some cases. Numerous studies have shown that low cortisol is associated with early trauma, a finding consistent with the observation of an inverse relationship between childhood emotional abuse and cortisol levels in the adult children of Holocaust survivors, survivors of natural disasters and women exposed to childhood sexual abuse [129, 141], etc. In addition, lower morning cortisol levels and higher afternoon cortisol levels have been observed in individuals who were near the September 11, 2001 disaster [142].

# AIMS OF THE THESIS

## General aims

The general aim of this thesis was to investigate how patients with exhaustion syndrome and healthy individuals differ in an extensive set of cognitive, endocrine, immune, and personality variables. We also wanted to investigate stress-related structural and functional changes in the brain.

## Specific aims

I To study cognitive function in patients with exhaustion syndrome.

II To study the functional brain activity patterns in patients with exhaustion syndrome, and patients with major depression.

III To study personality features in patients with exhaustion syndrome.

IV To study HPA-axis function, selected immune parameters, and brain morphology in patients with exhaustion syndrome.

# METHODS

This section is intended to briefly describe the methods that were central to these studies. Detailed descriptions of the methods are found in the different papers. A schematic overview of the included assessments is shown in Table 3.

# Patients and controls

A schematic overview of subject characteristics is shown in table 2.

**Table 2**. Subject characteristics across study samples. All individuals were women

| | Age | Education | Depression Diagnosis | Anxiety Diagnosis | Axis I Diagnosis |
|---|---|---|---|---|---|
| **Paper I** | | | | | |
| Patients | 43 (25-60) | 14 (7-20) | 19 (28.4 %) | 23 (34.3%) | 27 (40.3%) |
| Controls | 39 (27-39) | 15 (12.5-18) | 0 | 0 | 0 |
| **Paper II** | | | | | |
| Patients | 39.3 (26-53) | 14 (11-18) | 11 | 12 | 12 (60%) |
| Controls | 38.6 (27-50) | 15 (12.5-18) | 0 | 0 | |
| **Paper III** | | | | | |
| Patients | 37.3 (32-45) | | | | |
| Controls | 29.2 (27-30) | | | | |
| MDD | 25.2 (21-31) | | 10 (100%) | | 10 (100%) |

# Paper I

Seventy-five consecutive female patients referred to the Quranten Institute of Stress and Trauma with a preliminary diagnosis of chronic burnout (CBO) were considered for inclusion in the study. Sixty-eight patients (89%) agreed to participate. One patient was subsequently excluded due to previous head trauma. Fifteen healthy individuals were recruited from the Northern Sweden part of the WHO MONICA (Monitoring of trends and determinants in cardiovascular diseases) study by matching individuals according to age and education [143].

## Paper II

Twenty consecutive female patients referred to the Quranten Institute of Stress and Trauma with a preliminary diagnosis of CBO were included in the study. Sixteen healthy individuals were recruited from the Northern Sweden part of the WHO MONICA (Monitoring of trends and determinants in cardiovascular diseases) study by matching individuals according to age, body mass index (BMI), and education[143].

Inclusion and exclusion criteria for Papers I and II: All individuals had a sick leave of at least 3 months due to symptoms suggested to be due to CBO: exhaustion, sleeping problems, and depersonalization [21]. In addition, the individuals had had symptoms of exhaustion for a long period of time prior to the sick leave. The individuals all had identifiable stressors in their work situations. All individuals reported problems with concentration and/or memory and complained about emotional instability. Possible associated medical disorders were extensively investigated primarily by primary care physicians before referral and all individuals were examined by an endocrinologist to control for endocrine disorders. Individuals suffering from associated medical disorders, including endocrine disorders, and who had a history of severe head trauma were excluded, as well as individuals treated with anxiolytic or psychotropic drugs and those with a BMI greater than 30. Postmenopausal women were excluded.

## Paper III

Ten female patients with work stress related LTSL, ten female patients with unipolar major depression and ten healthy female individuals were included in the study. The depressed patients were recruited from the department of psychiatry at Umeå University hospital. The stress-patients were recruited from the Stress clinic at the same hospital and were a part of a larger study aiming at exploring work related long term stress.

Exclusion criteria were presence of left-handedness or ambidextrousness, co-morbid psychiatric disorders, known abuse of alcohol or drugs, endocrinological diseases and neurological disorders. Individuals with a BMI >30 kg/m$^2$ and individuals without regular menstrual cycle were also excluded. All participants were native Swedish speakers. For the stress group, additional exclusion criteria were: Other diseases that could result in fatigue and/or stress related symptoms; other diseases that could be a reason for future sick leave; other diseases or treatments that could interfere with active participation; post-traumatic stress disorders; unemployment for more than two years prior to participation; speech and language difficulties and need for individual therapy.

The depressed patients and the controls were all medication-naïve. In the LTSL group, 4 patients were taking SSRI anti-depressants. None of them were taking tricyclic anti-depressant medication.

**Table 3.** A schematic overvie of the assessments used in the studies. (for abbreviations see page 11)

| | Study I | Study II | Study III |
|---|---|---|---|
| Participants | 67 Patients<br>16 Controls | 20 Patients<br>16 Controls | 10 Patients<br>10 Controls<br>10 MDD |
| Assessment scales | | Burn-out and tedium<br>PSQ<br>Prime-MD<br>DSM-III (psychosocial stress)<br>WHO-QoL | Burn-out and tedium<br>PSQ<br>MADRS<br>HAS |
| Neuropsychological assessment | WAIS-R (11 tests)<br>IVA<br>CD<br>ROCFT | WAIS-R (11 tests)<br>IVA<br>CD<br>ROCFT | 2-back<br>CVMT |
| Personality inventory | | TCI | |
| Brain imaging method | | Structural MRI | fMRI |

# Stress

Different set of inventories were used to investigate self-perceived health, psychosocial, environmental, and affective status factors known to have an impact on stress-related disease and health. In all papers, burnout was measured using the Burnout tedium measure [23], a 21-item self-reported questionnaire measuring physical, emotional, and mental exhaustion at work. Items are scored on a 7-point scale ranging from never (1) to always (7). The perceived stress questionnaire (PSQ) is a 30-item self-rating instrument designed to assess perceived stress during the previous month. Items are scored on a 4-point scale ranging from almost never (1) to usually (4) [144].

In Paper 2, we used the WHO quality of life (QoL), a self-reported questionnaire that assesses QoL during the previous 2 weeks in four domains: physical health, psychological health, social relationship, and environment. The 26 items are scored on a 5-point scale ranging from not at all (1) to very much (5). Higher scores indicate better QoL.

The PRIME-MD was used for psychiatric screening. This system consists of two components: a one-page patient questionnaire (PQ) and a 12-page clinical evaluation guide (CEG) comprised of a structured interview containing modules for mood, anxiety, eating disorders, alcohol abuse, social phobia, and obsessive-compulsive disorder. The PRIME-MD system has been constructed to conform to DSM-IV criteria [29, 145].

The Severity of Psychosocial Stressors Scale (DSM-III-R) was used for coding the overall severity of psychosocial stressors that may have

contributed to the development, recurrence, or exacerbation of a mental disorder. Events are coded from none to catastrophic in six levels [29].

In Paper 3, the severity of depression was measured with the Montgomery-Åsberg Depression Rating Scale (MADRS) [146, 147]. To be included in the depression group participants had to have a minimum score of 20, which reflects moderate to severe depression. Anxiety levels were measured using the Hamilton anxiety scale (HAS).

# Cognition

An extensive set of neuropsychological tests were used to cover important cognitive domains. In Papers 1 and 2, Wechsler's Adult Intelligence Scale – Revised (WAIS-R) was used to estimate general cognitive abilities [148, 149]. The Rey Osterrieth Complex Figure (ROCF) test was used to measure visuospatial constructional ability and visuospatial memory [150]. The Claeson Dahl inventory of learning and memory - revised (CD) was used to measure efficacy in the individual's ability to immediately recall auditory verbal materials and the ability to recollect the words attached to the learning situation [151, 152]. The Intermediate Visual and Auditory Continuous Performance Test (IVA) was used to measure impulsivity, response inhibition, and general consistency in response times, and it was used to measure the individual's ability to stay on task, identify problems related to sustaining attention and effort over time, and total variability in the speed of mental processing. The IVA is sensitive to an unusual prevalence of slow reaction times, measuring the reaction times of all correct responses, and it is sensitive to problems related to slow mental processing [153, 154]. The IVA consists of two major components: (1) the Full Scale Response Control Quotient (FullScRCQ), which is based on equal weights of the Auditory Response Control Quotient (AUDRCQ) and the Visual Response Control Quotient (VISRCQ); and (2) the Full Scale Attention Quotient (FullScAQ), which is based on equal weights of the Auditory Attention Quotient (AUDAQ) and the Visual Attention Quotient (VISAQ). The AUDRCQ and VISRCQ are based on equal weights (one-third each) of their respective *Prudence, Consistency,* and *Stamina* scales. *Prudence* is a measure of impulsivity and response inhibition. *Consistency* measures the general consistency of response times and is used to measure the ability to stay on task. *Stamina* is used to identify problems related to sustained attention and effort over time. The AUDAQ and VISAQ are based on equal weights (one-third each) of their respective *Vigilance, Focus,* and *Speed* scales. *Vigilance* is a measure of inattention. *Focus* reflects the total variability of the mental processing speed and is sensitive to an unusual prevalence of slow reaction times. *Speed* measures the reaction time of all correct responses and is sensitive to problems related to slow mental processing

In Paper 3, we used two cognitive tests adapted to imaging protocols. The n-back test of working memory and a visual recognition test of episodic

long-term memory. The *n*-back task is a commonly used working memory task in fMRI studies; individuals are presented with a series of stimuli and required to respond if the current stimulus matches the stimulus displayed *n* positions before the current. In our version, single words were displayed and the individuals told to indicate whether the displayed word was the same as the one displayed two words earlier (2-back). We also used a visual recognition task that consisted of a set of black and white abstract and non-verbal pictures drawn from the Continuous Visual Memory Test (CVMT) [155]. The pictures were displayed one at a time and the individuals told to respond "yes" or "no" if they recognized the picture from

## MRI

The hippocampus was investigated with T1-weighted magnetic resonance imaged in 1-mm coronal slices using a 0.5 T superconducting magnet (Philips, Netherlands) as previously described [156]. The following measurements were performed on both the right and left sides of the brain [157]:

1. The CA1 region. This line describes the thickness of the hippocampus.

2. The thickness of the CA2/3 regions.

3. Hippocampal area. The total cross-sectional area (in $mm^2$) of the hippocampus was measured with a grid placed on the hippocampus. For details see Paper II.

## fMRI

Functional MRI captures changes in neural activity over time and during different cognitive tasks. Increased brain activation in a specific region of the brain leads to a higher demand for oxygen in that region. By measuring changes in the ratio of oxygenated and deoxygenated hemoglobin, the local changes in neuronal activation can be estimated. Because oxyhemoglobin and deoxyhemoglobin have different magnetic properties, a signal change is produced and recorded during imaging. This blood-oxygen-level-dependant (BOLD) signal provides an estimate of changes in local neuronal activation.

In this thesis, the individuals performed two cognitive tasks during the fMRI investigation: the 2-back task and a visual recognition task. A blocked design was used, which also included a low-demand baseline condition that was intended to cause similar sensory-motor activation during the experimental tasks. For both tasks, responses were given by pressing one of two buttons using the right or left index finger. In the baseline condition, the letters "xxxxx" were displayed either to the left or right side on the computer screen and the individuals told to press the

button on the corresponding side. All stimuli (2-back words, pictures, or letters) were displayed for 2.5 s, followed by a 0.5 s fixation cross, and all blocks consisted of 16 stimuli. The blocked-task paradigm altered between the baseline condition, the 2-back condition, and the visual memory condition, which was repeated in five sessions in sequential order. Stimuli were presented in the same order to all individuals during all sessions. Behavioral performance was recorded for response reaction times and accuracy. Prior to fMRI scanning, individuals were instructed and underwent a trial version of the task to ensure they understood the instructions. Data was collected using a 1.5 T Philips Intera scanner (Philips Medical Systems, Netherlands). Functional T2*-weighted images were collected with a single-shot gradient echo EPI sequence used for BOLD imaging. The sequence had the following parameters: echo time, 50 ms; repetition time, 3000 ms; flip angle, 90 degrees; field of view, 22 × 22 cm; 64 × 64 matrix; and 3.9 mm slice thickness. Every 3.0 s, 33 slices were acquired. To eliminate signals arising from progressive saturation, five dummy scans were performed prior to image acquisition. In the scanner, cushions and headphones were used to reduce head movement, dampen scanner noise, and for communication with the subject. The stimuli were presented on a semi-transparent screen that the individuals viewed through a tilted mirror attached to the head coil.

Presentation and reaction times were handled by a PC running E-Prime 1.0 (Psychology Software Tools, PA, USA). Responses were collected with fiber-optic response boxes, one in each hand (Lumitouch reply system, Lightwave Medical Industries, Canada). After the functional imaging, high resolution T1- and T2-weighted structural images were acquired. The images were then pre-processed and analyzed using SPM2 (Wellcome Department of Cognitive Neurology, UK) implemented in Matlab 7.1 (Mathworks Inc., MA, US). Prior to analysis, the images were corrected for slice timing and realigned to the first image volume in the series. The images were then normalized to a standard anatomic space defined by the MNI atlas (SPM2), and were finally spatially smoothed using an 8.0-mm full-width at half-maximum isotropic Gaussian filter kernel.

## Personality

In Paper 2, Cloningers TCI was used to investigate personality features. The TCI contains 238 items with true/false answers. The TCI assesses four temperament features and three character dimensions. The four temperament features are: *novelty seeking*, impulsive vs. rigid; *harm avoidance*, anxious vs. risk-taking; *reward dependence*, approval seeking vs. aloof; and *persistence*, overachieving vs. underachieving. The three character dimensions are: *self-directedness*, executive functions such as tolerance, tendency toward forgiveness, and helpfulness; *cooperativeness*, legislative functions such as being tolerant and helpful;

and *self-transcendence*, judicial functions such as being intuitive, judicious, and aware.

# HPA-axis

In Paper II, cortisol sampling was performed within 10 days of cessation of menstrual bleeding, and 24-hour urine sampling was used to estimate the glucocorticoid production rate. Saliva was sampled at 07:00, 11:00, 16:00, 19:00, and 22:00 for diurnal cortisol levels. A "low-low" dose (0.25 mg) overnight dexamethasone suppression test was to test the negative feedback sensitivity of the HPA-axis. ACTH stimulation (0.25 mg Synacthen® intravenously) was used to estimate adrenal cortex reactivity. CRH (1 μg/kg body weight) stimulation was used to test pituitary (ACTH) and adrenal cortex (cortisol) reactivity.

On day 1, individuals started the 24-hour urine collection. On day 2 a saliva cortisol curve was collected. On day 4 the Synacthen-test was performed. On day 6 the CRH test was performed.

In Paper III, a 24-hour saliva cortisol curve was measured, followed by an overnight 0.25 mg dexamethasone suppression test.

## Other biological measures

In all of the studies, patients were screened by routine blood analysis (e.g., liver and kidney function tests, electrolyte levels, and thyroid hormone levels) to exclude diseases that may interfere with further testing. In Paper II, plasma cytokine levels, specifically interleukins (IL-1β, IL-6), IL-1 receptor antagonist, and TNF-α, were also analyzed.

# Statistics

## Paper I

Group differences were tested with the Mann-Whitney U-test. Due to a large number of variables in one test (IVA), multivariate analysis of variance (MANOVA) was used. Weighted test scores were transformed into T-scores to allow comparisons with normative data.

## Paper II

Multivariate analyses were conducted using partial least-squares discriminant analysis (PLS-DA; SIMCA software, version 11.5). Mann-Whitney U-tests were used to test for group differences, except for proinflammatory cytokines where $\chi^2$ tests were used.

## Paper III

Partial least-squares (PLS) were used to analyze group differences in time-varying distributed activation patterns during imaging. Statistical parametric maps (SPM) were used to analyze fMRI data. PLS-DA was used to investigate patterns of data describing group differences. Non-parametric statistics (Kruskal Wallis) with bonferroni correction were used to test for group differences. Repeated measures analysis (ANOVA) for the 07:00 and 11:00 assessments of saliva cortisol was used to assess putative group by time interactions.

# RESULTS

## Paper I

Patients with exhaustion syndrome had significant alterations in cognitive performance relative to controls and the normative values for each test. Specific cognitive impairments in non-verbal episodic memory (figure 3) and visual and auditory attention measures (figure 4) were present in the exhaustion group. No differences were found in verbal memory and general intelligence compared to controls and normative values when measured by WAIS-R.

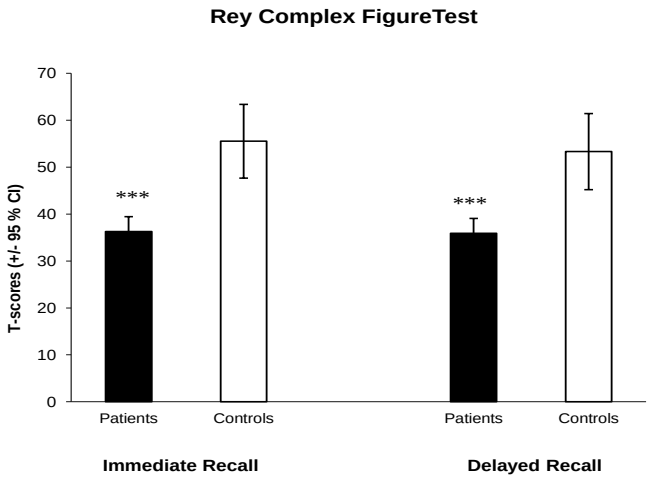


**Figure 3** Results of the Rey Osterrieth complex figure test measuring non-verbal episodic memory and visuospatial functioning, immediate and delayed recall. *** p<0.001. Expected mean value = 50. Patients performed below the expected mean for both tests. Data are means± 95% confidence interval (CI).

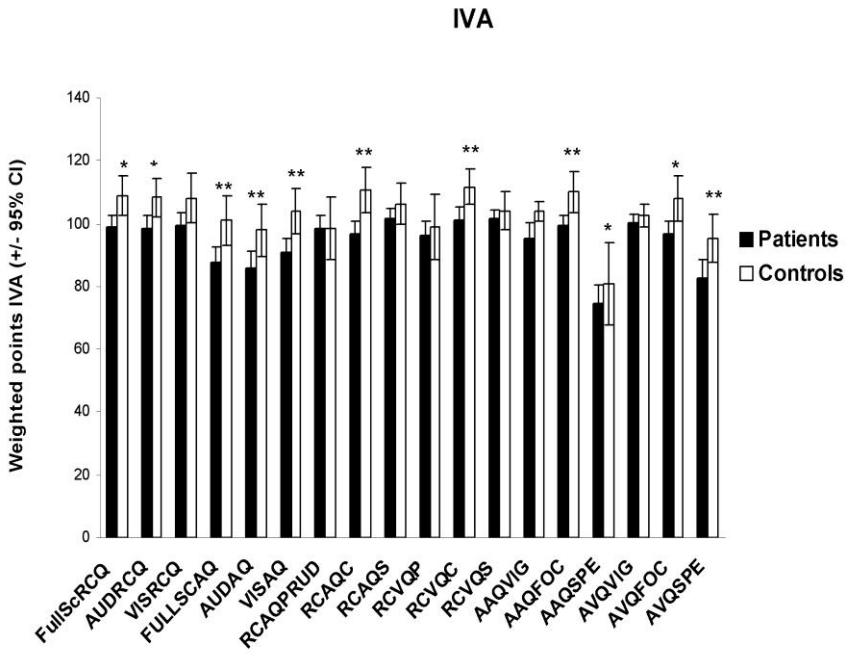


**Figure 4.** Results of the Intermediate Visual and Auditory Continuous Performance Test (IVA) measuring attentional processes. Expected mean value = 100. * p<0.05, ** p<0.01.Data are means ± 95% confidence interval.

# Paper II

We found a clear separation between the study groups in the discriminant analysis (figure 5) based on 35 variables. Minimal overlap indicated a powerful model in the multivariate analysis. The model identified four clusters of variables that discriminated patients from controls (figure 6). In summary, cluster number 1 revealed higher scores in harm avoidance and persistence and lower scores in self-directedness in the patient group. Patients also had lower QoL and general well-being. Patients experienced more psychological stress than controls. The cognitive cluster (no. 2) showed the same kind of cognitive deficits found in Paper I, with impaired visuospatial memory and decreased performance in attention measures. In cluster 3, HPA-axis variables revealed significantly decreased reactivity on the pituitary level in patients, with lower ACTH levels at 5-90 min, univariate analysis also showed significant differences at 30-90 minutes after CRH injection and a lower ACTH area under the curve response to CRH. The cortisol/ACTH response to CRH was slightly higher in patients compared to controls, with the 30 min response being a significant predictor of group also in univariate analysis. Patients also had a tendency toward a higher cortisol response to Synacthen®, albeit not

significant. In cluster 4, a set of anthropometry, thyroid hormones and IL-1β, was positively correlated with being a patient, with significantly lower circulating levels of TSH compared to controls, whereas free T4 levels were slightly higher in patients. A significantly higher proportion of patients had detectable levels of IL-1β. No differences were found in hippocampal volume. A list of the VIP-values for all included variables (i.e., VIP> 1.2) and results from non-parametric statistics (Mann-Whitney) are shown in Table 4.

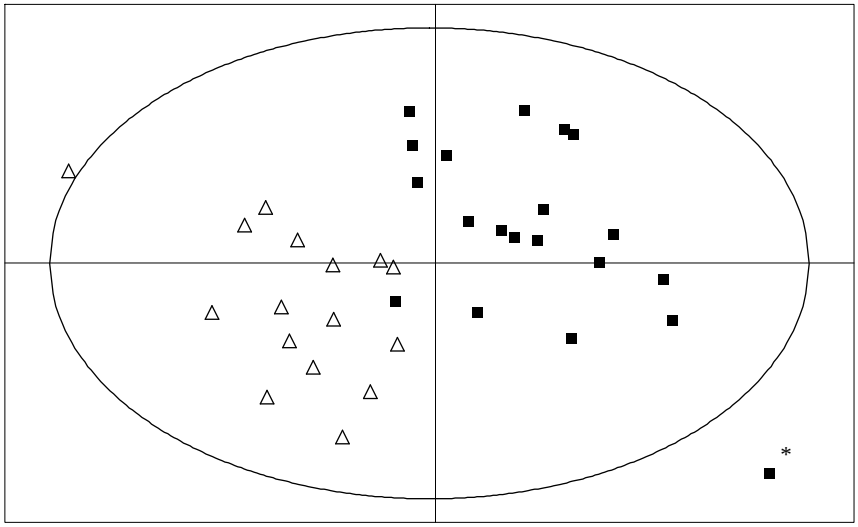


**Figure 5.** Results from the discriminant analysis (PLS-DA) detecting variables that separate patients from controls. The score plot indicates a clear separation between the two groups. Minimal overlap indicates a powerful model. One outlier was detected (■ *: this patient fulfilled criteria for major depression). Patients and controls were significantly separated along component 1 (left/right). Explained variance ($R^2$)=0.78 with predictive value (goodness of prediction) Q=0.59. ■=Patients, Δ=Controls.

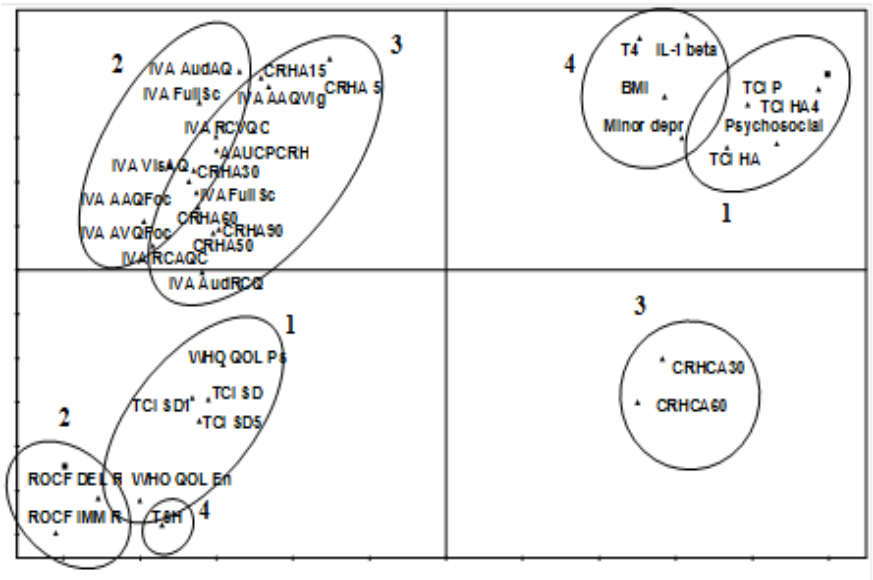


**Figure 6.** Variables contributing to the separation of patients and controls. Only variables with a VIP-value >1.2 were included (34 variables). Variables clustered together are strongly associated. Variables located on the right side of Origo were positively correlated with patients and negatively correlated with controls, and vice versa for variables located on the left side of Origo.

**Cluster 1.** Variables positively correlated with being a control subject: personality factors and behavioral variables (World health organization psychological well-being and quality of environment (WHOQOL Ps, WHOQOLEn) and temperament and character inventory (TCI) SD, TCI-1, and TCI SD5), self-directedness, responsefulness, and congruent character. Variables positively correlated with being a patient: TCI HA+, TCI HA4, and TCI P (harm avoidance, asthenia, persistence). Minor depression.

**Cluster 2.** Cognitive variables: Rey Osterrieth Complex figure, immediate and delayed recall (ROCF IMM R, ROCF DEL R), Intermediate Visual and Auditory Continuous Performance Test (IVA), auditory attention quotient (Aud AC), full scale attention quotient (Fullsc), response control visual quotient consistency (RCVQC), visual attention quotient (Vis AQ), attention auditory quotient focus (AAQFOC), full scale response control quotient, attention visual quotient focus (AVQ FOC), response control attention quotient consistency (RCAQC), auditory response control quotient (AUD RCQ).

**Cluster 3.** HPA-axis variables positively correlated with control individuals: ACTH response to CRH 5, 15, 30, 60, and 90 minutes after CRH injection (CRHA 5, CRHA 15, CRHA 30, CRHA 60, CRHA 90); ACTH area under the curve after CRH (AAUCPCRH). Variables positively correlated with being a patient: cortisol divided with ACTH 30 and 60 min after CRH (CRHCA30, CRHCA60).

**Cluster 4**. Biological variables: T4, IL-1β, body mass index (BMI).

**Table 4.** Summary of variables explaining model (VIP>1.2) in Simca PLS-DA in Figure 6 (for abbreviations se page 11).

| VIP-Variables | VIP-value | Mann-Whitney |
|---|---|---|
| ROCF Imm | 2.199 | <0.001 |
| TCI - HA4 | 1.994 | <0.001 |
| ROCF Del | 1.966 | 0.002 |
| Psychosocial stressors | 1.771 | 0.001 |
| TSH | 1.770 | 0.010 |
| WHO QoL Environment | 1.690 | 0.036 |
| TCI - P | 1.665 | 0.003 |
| IVA - AVQFoc | 1.636 | 0.001 |
| IVA - RCVQC | 1.628 | 0.749 |
| IVA - RCAQC | 1.567 | 0.003 |
| CRHA 30 | 1.530 | 0.016 |
| IVA- VisAQ | 1.529 | 0.003 |
| TCI - HA | 1.492 | 0.003 |
| AAUCPCRH | 1.471 | 0.039 |
| CRHA 60 | 1.470 | 0.031 |
| IVA - FullScAQ | 1.469 | 0.004 |
| IVA - AAQFoc | 1.438 | 0.006 |
| IL -1 beta | 1.413 | 0.015 |
| CRH - 5 | 1.409 | 0.511 |
| CRHA 15 | 1.392 | 0.180 |
| IVA - FullScRCQ | 1.370 | 0.011 |
| TCI - SD1 | 1.356 | 0.070 |
| TCI - SD5 | 1.351 | 0.019 |
| CRHA 50 | 1.339 | 0.038 |
| IVA- AudAQ | 1.337 | 0.019 |
| Minor depression | 1.319 | 0.022 |
| IVA - RCVQC | 1.307 | 0.016 |
| IVA - AudRCQ | 1.296 | 0.029 |
| CRHA 90 | 1.294 | 0.046 |
| CRHCA 60 | 1.277 | 0.161 |
| TCI - SD | 1.268 | 0.026 |
| CRHCA 30 | 1.254 | 0.043 |
| IVA – AAQ vig | 1.232 | 0.266 |
| WHO QoL Psychological | 1.206 | <0.001 |

# Paper III

The main finding in Paper III was that exhaustion syndrome patients under-recruit areas within the prefrontal cortex during demanding working memory performance. Differences were found in the right dorsolateral prefrontal cortex (dlPFC) and left ventrolateral prefrontal regions (vlPFC) (figure 7). These findings are in agreement with our previous neurocognitive tests, suggesting frontal cortex dysfunction. PLS-DA revealed a significant separation of the three groups we examined (figure 8) based on the variables shown in figure 9. A tendency of the diurnal curve for cortisol to flatten in the exhaustion group was suggested by the multivariate model (figure 9). Repeated measures ANOVA indicated a significant group by time interaction between controls vs. work stress LTSL patients at 07:00 and 11:00 saliva cortisol.

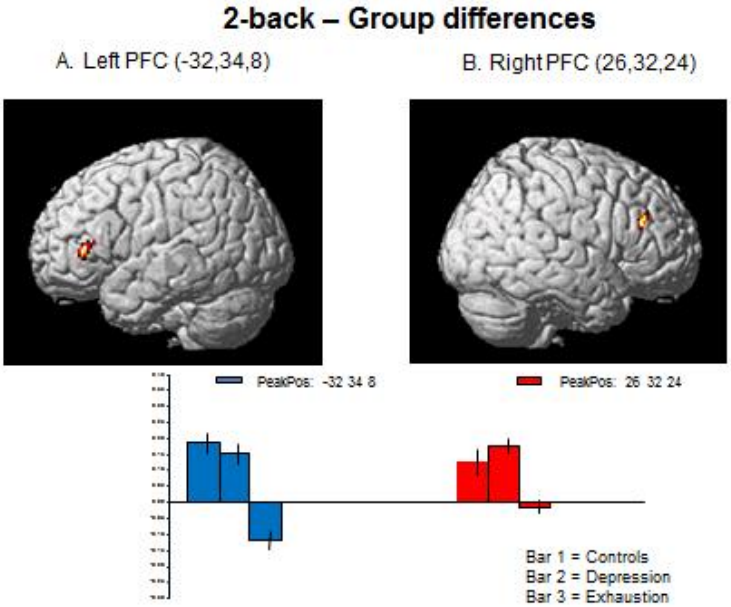


**Figure 7.** A, Brain regions with significant brain activation differences during n-back compared to baseline. Less activation was found in left ventrolateral frontal regions (local maxima x,y,z= -32, 34, 8) in the exhaustion syndrome group compared to depressed individuals and controls. The blue bars show the mean brain activity levels in 2-back controls, depression, and work-related stress, respectively. B, Brain regions with significant activation differences during n-back compared to baseline, with less activation in the right dorsolateral prefrontal cortex (local maxima x,y,z= 26, 32, 24) in the exhaustion syndrome group compared to depressed individuals and controls. The red bars show the mean brain activity levels in 2-back for controls, depression, and work-related stress, respectively. Error bars are standard error of means (SEM).

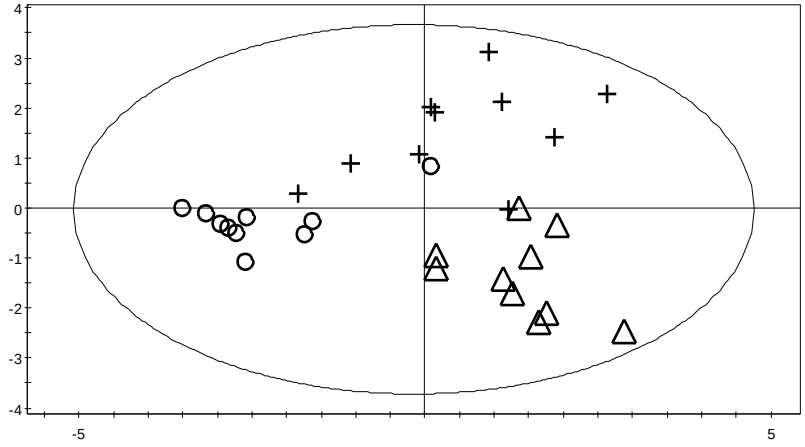


**Figure 8.** A model using a projection into two dimensions provided a significant separation. Explained variance ($R^2$)= 0.65 with predictive value (goodness of prediction) Q= 0.68 (R2Y intercept<0.2, Q2Y intercept<-0.04 by permutation test) based on behavioral and cortisol data. The horizontal axis represents the first partial least squares component, and the vertical axis represents the second component.
+ = Exhaustion, Δ = Depression, O = Control.

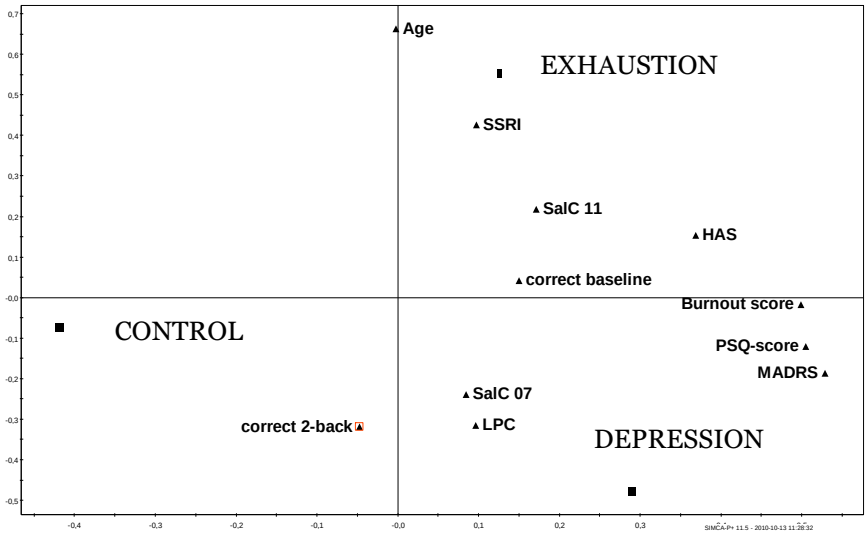


**Figure 9.** Variables that contributed to the separation of controls and patients with depression (MDD) or exhaustion syndrome. Only variables with a VIP-value > 0.8 were included (11 variables). Variables clustered together are strongly associated. Variables located on the right side of origo were positively correlated to patients and negatively correlated to controls, and vice versa for variables located on the left side of origo. In the second vertical axis stress patients are separated from depressed patients. Included variables in their order of importance are: age, Montgomery Åsberg depression rating scale (MADRS), Perceived Stress Questionnaire (PSQ) score, burn-out score, selective serotonin reuptake inhibitor (SSRI), leukocyte particle concentration (LPC), Hamilton Anxiety Scale (HAS), saliva cortisol measured at 11:00 (SalC 11) and 07:00 (SalC07), percent correct response in 2-back memory test (Correct2), and correct response at baseline (Correct baseline)

# DISCUSSION

## Cognition

The work in this thesis started with a clinical observation of a group of patients that were referred to as burnout patients in the 1990s. Many of these patients underwent investigations of working capacity requested by the Swedish Social Insurance Company. In these investigations, cognitive function was evaluated. That this group of patients shared a pattern of similar deficits soon became evident. In the clinical interview, many patients reported their cognitive problems to be the main reason why they could not manage work, and patient-reported cognitive limitations at work were related to work output. Many patients described easily developing coping strategies for many situations connected to overload in their everyday life except for the cognitive problems that occurred in complicated situations that required divided attention. That this group of patients did not recover from illness in a way that was expected relative to their former performance level and relatively young age also became clear with time. Treatment with SSRIs helped surprisingly few of these patients. Over the years, and with increasing long-term sick leave (LTSL), a need to describe and investigate this group of patients became apparent. As my profession is that of a psychologist and my special field is neuropsychology, I became interested in the complaints regarding memory and concentration problems that almost all of these patients expressed. The field of stress-related disease is, of course, of special interest to psychologists as this field is the main arena for the complex nature of brain-body interactions, or as an old philosopher would express it, the old dichotomy of matter vs. spirit.

In this thesis, we showed that women on LTSL due to exhaustion syndrome have specific cognitive deficits [33, 34, 158]. The patient group performed well on neuropsychological tests designed to measure general intelligence, and as a group they performed above the expected mean according to normative values in verbal tests. This good result is probably due, partly, to using old learning strategies, and is also indicative of good pre-morbid cognitive function. Good results in the main part of the neuropsychological test battery also exclude concern about malingering.

In Paper 1, we showed that cognitive deficits occur mainly in the domains of attention and non-verbal episodic memory. The ROCFT-test used to measure non-verbal episodic memory is highly dependent on good executive functions [159, 160]. Non-verbal memory deficits may reflect hippocampal dysfunction [156, 161], but if the problem is more executive in nature and demands good working memory function, it might reflect frontal cortex dysfunction [162]. One of the clinical observations in this patient group was that they did not exhibit good strategies to solve the ROCFT-test, which may point more in the direction of frontal cortex

dysfunction. This finding is in line with the IVA results showing that patients performed below the expected mean according to normative values and compared to controls.

Cognitively demanding tasks are known to activate the prefrontal cortex, and recent studies have found increased activation in the dlPFC as a common response to increased cognitive load in working memory tasks [163, 164]. The question of whether this activation reflects cognitive control processes or general arousal demands is still unclear [57]. Cognitive control processes depend on prefrontal activation, but these regions must interact with diverse regions in the brain, and the actual function of a specific region may depend on the network that sub-serves these functions [58]. The pattern of cognitive deficits with intact performances on tests with verbal materials, along with slowed speed and impaired performance on tests with novel non-verbal stimuli, suggest frontal cortex/medial temporal cortex network dysfunction and was replicated in Paper 2. This finding is also consistent with other studies of stress-induced deficits in visuospatial capacity and working memory [165, 166].

Episodic memory function is generally impaired after damage to the hippocampus [167]. The involvement of hippocampal structures in new information encoding and consolidating memory is well established, but what role the hippocampus plays in memory storage is not clear [168]. Patients with selective damage to the hippocampus often perform well on recognition memory tests and semantic memory but may have severe deficits in recollection. Patients with frontal lobe lesions do not show classical memory impairment like in amnesia, but they may exhibit impairment in recall tests of memory [47]. This impairment is suggested to be a function of the lack of adaptive strategies and organization that is typical of frontal lobe lesions. The problems with memory recall in ROCFT that were present in most patients are probably due to lack of planning and adaptive strategies necessary for receiving good test results in this particular test; 11/20 patients in Paper 2 had a T-score < 30 on ROCFT (expected mean 50), and 7/20 patients had <7 in block design (expected mean 10). The ROCFT was administered first in the second test session. Therefore, the results cannot be attributed to exhaustion.

In Paper III, our hypothesis was that patients with exhaustion syndrome, patients with major depression, and healthy controls have different functional brain activity patterns during working memory tests. We also hypothesized that individuals would differ in diurnal salivary cortisol rhythmicity. We used two different multivariate statistical methods, as well as univariate methods, in these analyses. The PLS reflects the time-varying distributed patterns of the brain (as a function of a task) without any assumption about how conditions collate to form a pattern and shape of the hemodynamic response function, which underpins the results from univariate statistical parametric maps (SPMs). Thus, the findings of lower frontal activity and slower performance in n-back are supported by the

PLS multivariate modeling of behavioral data and fMRI signal changes, as well as univariate data from fMRI BOLD signals. PLS-DA also revealed that cortisol measures and results from the 2-back working memory task contributed to the difference between the three groups (figures 8 and 9).

# Brain Imaging

On the basis of the specific cognitive deficits in our two previous studies, we expected to find differences in frontal cortex activity between exhausted patients, patients with MDD, and healthy controls in Paper III, an fMRI study measuring brain activation during one verbal and one non-verbal working memory test. The main finding in this study was that patients with exhaustion syndrome have lower levels of frontal activation in demanding verbal working memory tests compared to patients with depression and healthy individuals. Differences in activation were observed in the dlPFC and vlPFC, but overall we found pronounced similarities in brain activation patterns across all three groups. A common frontoparietal network was activated during both the verbal and non-verbal memory tasks. No significant differences were found in cognitive test performance during fMRI scanning, but a tendency for slower reaction times was observed in all tests for exhaustion syndrome patients. This difference was most pronounced in the n-back.

A putative link between long-term stress and alterations in cognition and brain activation may be increased glucocorticocid exposure (see also below). Previous imaging studies have thus shown that pharmacological doses of cortisol reduces glucose uptake in the hippocampus [169], which could explain, in part, the hippocampal-mediated memory impairments seen in MDD. Glucocorticoids have also been shown to lead to reduced activation in the posterior right medial temporal lobe with a maximal decrease in the parahippocampal gyrus, a region associated with successful verbal memory retrieval of declarative memories [170]. In a fMRI study by Oei et al. [171], cortisol treatment reduced hippocampal activation bilaterally during memory retrieval. In addition, decreased activation was found in the prefrontal cortex. This retrieval deficit during stressful conditions has been hypothesized to allow the brain to encode or consolidate more important information as evidence suggests that retrieval interferes with encoding [172]. In PTSD patients, the opposite pattern of lower basal cortisol levels with a blunted diurnal rhythm is repeatedly found [129]. In a study of individuals with acute PTSD, significantly less gray matter density was observed in the right pregenual ACC, and shape differences that probably cause the relative differences in total volume measures were found. This finding was interpreted as possible volume differences in surrounding structures (i.e. cingulum, corpus callosum, or medial frontal lobes). Results from imaging studies on stress have provided divergent results, most likely due to differences in the experimental designs. Taken together, an involvement of the prefrontal and limbic regions in psychological stress processing at least

partly related to glucocorticoid exposure, has been suggested [173]. In this, a reduced cerebral blood flow in the orbitofrontal regions in response to stress seems to be the most consistent finding. The other most robust finding is deactivation of the hippocampus in stress-induced situations [174].

## Personality measures and behavioral variables

The cluster of personality variables separating patients from controls in Paper 2 had high scores on harm avoidance and low scores on self-directedness. This profile is a well-known feature of many psychiatric conditions and merely reflects an anxious, rather than risk-taking, person with poor executive drive. The high scores on persistence reflect an overachieving, perfectionist, and to a certain degree rigid, personality and may point to a specific personality profile in exhaustion syndrome; at the end of this continuum we find patients with obsessive compulsive disorder. Very high demands on one's own performance, to be orderly and persistently try to manage your job, are of course of value in job settings. If these demands mean that you ignore your own well-being and are incapable of changing strategies for how to handle demands at work, it might be mal-adaptive. The self-esteem of highly persistent individuals can be argued to be, to a great extent, based on performance-based self-image.

In this view, persistence is a vulnerability factor for stress-related symptoms, and high persistence individuals are prone to attribute their individual problems to factors outside themselves, such as environmental factors [94]. This pattern of high scores in harm avoidance and persistence with low scores in self-directedness has also been shown in chronic fatigue syndrome [175].

Earlier data showed that harm avoidance and self-directedness are predictors of vulnerability to depressive symptoms and anxiety. Thus, harm avoidance may be a marker of emotional vulnerability to depression, whereas self-directedness reflects executive functions that are necessary for avoiding depression. In this cluster, the WHO-QoL revealed that patients are less satisfied with their environment than controls.

Patients have experienced to a higher degree traumatic life events, indicating that factors other than job stress constitute a burden to these patients. Several studies in the field of post-traumatic stress have shown that severe psychological trauma can lead to problems with attention, executive functioning, learning, and memory [81, 176, 177]. Scores on behavioral variables indicate that psychosocial stress might be one of the variables that contribute to illness in this group.

Affective disorder was present in 40-60% of patients. However only 7.5% fulfilled the criteria for MDD and 10% for minor depression. This figure is much less than what has been reported in other studies [26, 27]. A possible reason for this might be that our patients were diagnosed by primary care physicians, whereas patients in other studies are often diagnosed by psychiatrists. The most reported affective disorder was panic anxiety (19%). Notably, most patients reported that anxiety problems developed and worsened over time secondary to exhaustion.

We decided to enroll only women in our studies, mainly due to the fact that women are over-represented in exhaustion diseases, as well as depression and other affective disorders. Because the number of individuals was limited, we were able to ensure a more homogenous sample.

## HPA-axis

One of the objectives of this thesis was to analyze HPA-axis variables in patients with exhaustion syndrome and MDD. Hypercortisolemia, increased cortisol production rates associated with increased cortisol responsiveness at the level of the adrenal cortex, is a prominent feature in MDD. However, exhaustion syndrome patients seem to have a distinct HPA-axis dysfunction with some similarities to MDD, including an augmented response at the adrenal level with an increased cortisol/ACTH response after CRH. In contrast, a decreased pituitary (ACTH) response was also found in exhaustion patients. This finding is in agreement with previous reports indicating HPA-axis hypoactivity in atypical depression and “burnout” patients [133, 178]. Notably, the patients included in this study had no earlier history of psychiatric illness, and only one patient fulfilled criteria for MDD. Rydmark et al. found an attenuated dex – CRH response in patients on LTSL due to job-stress. Notably they used DEX suppression before the CRH injection (i.e., the DEX-CRH response) [26]. This test may probe the stress-induced hypothalamic mediation of vasopressin co-expression in CRH neurons, acting to augment CRH effects [179]. Thus, studying DEX-CRH responsiveness in subgroups of patients with long-term stress/chronic burnout with and without concomitant major depression would be of interest.

We found no significant alterations in saliva cortisol diurnal rhythm and feedback sensitivity of the HPA-axis among patients with exhaustion syndrome. Decreased levels of circulating cortisol and increased feedback sensitivity have been suggested in other neuropsychiatric disorders, including PTSD, fibromyalgia, and chronic fatigue syndrome, but the findings have been inconsistent. In burnout/exhaustion syndrome patients, an increased [135], decreased [133], or normal awakening salivary cortisol [136] has been found. Methodological issues need to be solved before conclusions can be made about these results as the test procedures differ between studies. Of note lower diurnal cortisol

variability in burnout patients was related to slower cognitive performance in a recent study [67]. Together with our study, this finding might suggest that this patient group has a distinctive HPA-axis pattern that differs from that seen in MDD. Overall, the healthy and depressed patients showed more similarities, albeit the poorest health in all measures of well-being was seen in the depressed group; the fact that they seem more cognitively unaffected might be due to the fact that this was their first episode of depression. Many episodes of major depression and their severity are correlated with structural and functional changes in the brain. These changes are believed to be associated with the hypersecretion of glucocorticoids.

In Paper III, the multivariate model suggested a flattened diurnal curve regarding saliva cortisol, and this finding was supported by repeated measures ANOVA showing a significant group by time interaction in the morning (i.e., for patients with exhaustion syndrome versus conrols).

In paper II no changes in hippocampal volumes were found, despite separate analyses of the hippocampal subregions. This result does not preclude that functional changes in forebrain-limbic circuits may influence symptomatology in these patients. Physical and psychosocial stress paradigms, as well as animal models of depression, have well established that stress produces functional alterations in the hippocampus, linked to a decrease in hippocampal cell proliferation and neurogenesis [176]. Recurrent depressive episodes are associated with a reduced hippocampal volume, and hippocampal neurogenesis has been implicated in the pathophysiology of depression [180] [181]. Reductions in hippocampal volume may also develop as a possible protective reaction to increased excitotoxic signals. This reaction may be confined to subregions of the hippocampal formation, notably the CA1 region [182].

# General aspects of the papers

One of the core problems in writing this thesis has been the choice of diagnostic category. The National Board of Health and Welfare in Sweden has added “exhaustion syndrome” as a supplementary diagnosis to the Swedish version of ICD-10. This change is very helpful when communicating in a Swedish context but is of little help when communicating internationally as major depression has been the main diagnostic category to describe exhaustion syndromes. In our first study, the term “burnout” was used, in Paper II we used “stress-related exhaustion”, and we used “work stress-related long-term sick leave” in Paper III. One of the criticisms against the concept of exhaustion syndrome is that this is not a homogeneous group; the logical error here is to assume that major depression is not a heterogeneous group.

However, one of the greater challenges is to put the increasing number of psychiatrically ill persons into a political perspective and try to find answers as to why women are over-represented in these groups. A wealth

of research clearly shows that socio-economic status (SES) is related to children's cognitive growth and academic achievement. Functional neuroimaging evidence suggests that SES regulates the relationship between phonological awareness and reading-related brain activity [183, 184]. Prefrontal cortex activity critical for attention is decreased in children with low SES, as well as decreased executive functioning, working memory, cognitive flexibility, and semantic fluency [185]. Taken together, these findings indicate that the social environment shapes neural structures and processes [186]. In adults, perceived social standing is suggested to be a critical predictor of health outcome. In the works of Gianaros and colleagues, reductions in the gray matter in the perigenual area of the anterior cingulate cortex were found in individuals reporting lower levels of perceived social standing in a healthy community sample [187]. Social support is also a well-known factor to consider in stress research because it has implications for health and well-being, and even mortality [188]. Collaboration between the fields of biological psychology and social science would probably give rise to new and exciting research questions.

Low social support has been reported in numerous studies of exhaustion [189, 190], but this was not confirmed in any of our studies. Instead, exhaustion syndrome patients reported satisfaction with their psychosocial support. On the other hand, depressed patients in Paper III reported low social support.

# Limitations and future directions

In all three papers we had a limited number of individuals. In Paper III, each group consisted of 10 individuals each, and missing data was also a problem in this study. These limitations hamper the statistical evaluation of data. Multivariate statistical methods based on projection methods (principal component analysis) used in this thesis are the most appropriate choice when handling matrices with more variables than individuals. We wanted to find out whether a phenotypical pattern can be attributed to exhaustion syndrome, including personality traits, HPA-axis variables, hippocampal volume, immunological variables, earlier traumatic life experiences, and lifestyle factors. When examining the number of variables included in Paper II (157 variables) and relatively few individuals, the statistical method chosen is of key importance. The problem with examining two variables at the same time is a high risk of statistical type 2 errors, i.e. you might miss a difference that is actually there, in contrast with many variables and the risk for type 1 errors, i.e. you might detect random effects that are not valid. We used projection to latent structures by means of partial least squares (PLS Simca 11.5). In order to examine the most important variables in the model that discriminate patients from controls, projection to latent structures discriminant analysis (PLS-DA) was used. Two dummy Y-variables were created (patients and controls) and the variables “burnout” and PSQ excluded to avoid circularity. The PLS-DA revealed four clusters of variables that separate patients from controls. In summary, this analysis suggested an intimate link between cognitive performance, personality, well-being, and neuroendocrine dysfunction in the phenotypic expression of stress-related cognitive dysfunction. This thesis provides a good structural overview of data correlation patterns but cannot override the questions of power problems that must be asked with small study groups.

We only enrolled women in our studies, but the cognitive problems shown in this thesis are also present in men with exhaustion syndrome and would be interesting to examine.

Most of the participants had quite a high educational level compared to the mean value for the Swedish population (14 vs. 11.9 years) [191]. This difference might influence the validity of our studies because people with a high level of education normally perform above normative values in verbal memory tests [192].

Unfortunately, a significant age difference was found between the groups in Paper III, which hampers the interpretation of these data. Because we wanted to examine unmedicated samples, the depression group that experienced their first episode of major depression was significantly younger than the exhaustion group. This difference does not explain why the exhausted patients failed to recruit frontal regions normally activated during working memory tasks, but this finding may reflect a cognitive

deficit that evolves over time and, thus, might not have affected the relatively younger depressed patients who were recently diagnosed. The question of age-related cognitive decline was not addressed in this thesis. From earlier studies, considerable overlap is obvious between the areas showing stress-related decreases in gray matter volume in humans and animals [125] and the areas that show gray matter volume differences in aging [193]. Of course age-related atrophy might correlate with life-time exposure to stress and traumatic events.

Examining the sleep patterns in patients with exhaustion syndrome is evidently a very important field of investigation as sleep disturbances are a main complaint in many psychiatric diseases and a very important clinical problem. Whether the described pattern of cognitive dysfunction correlated with poor sleep would have been interesting to investigate. Most patients in the study reported sleeping problems, and the most reported problems were difficulty falling asleep, frequent awakenings, and early waking. Some patients reported excessive sleeping of 10-13 sleep hours per night. Many patients reported sleeping disorders as the first observed health problem in the development of disease. Increasing evidence suggests that disturbed sleep patterns disturb behavior, cognition, and affective function. Abnormalities in sleep–wake rhythms, appetite, and social rhythms have been observed in almost all psychiatric conditions and a variety of other central nervous system and psychosomatic disorders [194, 195]. Despite strong evidence, a gap in our understanding of the neural mechanisms of this interaction obscures whether sleep disorders are the underlying causes or merely symptoms of behavioral problems. Improved sleep is well known to enhance the efficacy of pharmacotherapies for psychiatric conditions and memory in traumatic brain injury [196]. Despite growing evidence, the neurobiological basis of the connection between sleep and health is largely unknown. In addition to alertness and arousal, the circadian timing system regulates learning and memory, and sleep strengthens memory traces and promotes mental restructuring [197].

In research of psychological health, self-reported symptoms are the core features in the operationalization of diagnostic categories. One of the problems though is that Selye observed that many conditions, from severe infectious diseases to ruthless sorrow, “makes people look sick and feel sick“, which expresses the problem with knowing what we truly observe. The complex nature of mind/body interactions and all factors involved give rise to multiple downstream actions that are not accountable here. For example, glucocorticoids have multiple effects on the central nervous system and bodily functions, and stress is an important mediator of glucocorticoid release. On the other hand, many other hormones/ neurotransmittors, such as epinephrine, norepinephrine, and dopamine, affect cognition and behavior. Further studies of these factors would therefore be of major interest.

Executive dysfunction is probably a core cognitive problem in this patient group, and fMRI investigations are taking us closer to the source of central nervous output. Unfortunately, we lack a variety of tests of executive function that are applicable to the fMRI paradigm.

The lack of consensus about how to treat these patients has given rise to numerous rehabilitation programs offering mindfulness training, cognitive behavioral therapy, and garden therapy, among others. Randomized control trials of interventions to examine environmental influences on physiological indicators of stress load are needed. We still do not know much about the tipping point where accommodation to stress turns into disease. Given that the brain is the central mediator of allostasis, we need to explore how core emotional systems react and adapt to stressful conditions as these brain areas have been shown to be the most likely to display long-term structural and functional differences following environmental challenge. The question of whether neural plasticity is affected by therapeutic interventions needs also to be answered.

# CONCLUSIONS

Patients with exhaustion syndrome have specific cognitive impairments with decreased attention and non-verbal episodic memory compared to healthy controls and normative values according to neuropsychological testing. These patients also exhibit a different activation pattern and lower level of frontal activation on fMRI during a verbal working memory test compared to patients with major depression and healthy controls; less activation was observed in the right dorsolateral prefrontal cortex and left ventrolateral frontal regions. Hippocampal volumes did not differ between groups.

The personality of exhaustion syndrome patients consists of high scores in harm avoidance and persistence and low scores in self-directedness relative to healthy controls, which suggests an anxious, sad, and over-achieving personality. High scores in harm avoidance and low scores in self-directedness are found in many psychiatric conditions, including depression and anxiety disorders, but persistence may be a personality trait that contributes to the development of exhaustion syndrome. We found that 40-60% of patients with exhaustion syndrome fulfill the criteria for psychiatric disease according to DSM-IV.

The pituitary (ACTH) response to CRH was decreased in exhaustion syndrome patients compared to healthy controls. The cortisol/ACTH response to CRH was increased in exhaustion patients compared to healthy controls. Exhaustion syndrome patients also had flattened diurnal cortisol rhythmicity. In addition, a higher proportion of patients had detectable circulating levels of the pro-inflammatory cytokine IL-1β compared to controls.

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