Rehabilitation for improved cognition in stress-related exhaustion
Cognitive, neural and clinical perspectives

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For Valter, Edvin and Marcus
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Abstract

Stress-related exhaustion disorder (ED) has been associated with concomitant cognitive impairment, perceived by patients to have large impact on everyday life. However, little is known about how to address cognition in stress rehabilitation and how this could influence stress recovery over time. The aim of this thesis was to evaluate the efficacy of additional cognitive and aerobic training for patients with ED who participated in a multimodal stress rehabilitation program. A further aim was to explore the neural correlates of ED. The main focus of this thesis was on cognitive training, the effects of which were studied from a cognitive, neural, and clinical perspective (Study I-III). The final part of this thesis (Study III) broadened the perspective and investigated the long-term effects of cognitive and aerobic training on cognitive and clinical outcomes.

Study I and II evaluated the effects of process-based cognitive training immediately following the intervention. The results from Study I showed that generalization of training effects following cognitive training was selective and restricted to tasks similar to those trained. The cognitive training group showed a greater reduction in burnout symptoms, and partial support was given for fewer subjective cognitive complaints compared to stress rehabilitation alone. Study II used functional neuroimaging to explore the neural effects of cognitive training, showing training-related activation increases at high working memory load; however, conclusions were restricted due to the small sample.

Study II additionally explored the neural correlates of ED by investigating within-group associations between burnout level and functional neural response during working memory updating. The results revealed that patients with higher levels of burnout showed greater recruitment of working memory-related regions during task execution, potentially reflecting a compensatory mechanism serving to uphold task performance.

Study III evaluated the clinical utility of addressing cognitive impairments in stress rehabilitation. Here, the effects of cognitive and aerobic training on several ED-related variables were investigated 1 year after the intervention. Cognitive training was associated with a small and lasting improvement in cognitive performance. Aerobic training yielded improvements in episodic memory immediately following the intervention, but no significant difference was found between the aerobic training group and the control group at 1-year follow-up. For psychological health and work ability, no additional benefits were seen for the added interventions relative to stress rehabilitation alone. However, a long-term improvement in burnout symptoms favouring cognitive training was observed when restricting the analysis to only include patients who had completed the
intervention. This highlights the importance of supporting patients in adhering to added treatments.

In sum, the papers in this thesis provide initial evidence of neurocognitive plasticity in patients with ED and tentatively suggest that cognitive improvements following cognitive training may translate into alleviated clinical symptoms. These results support the argument that interventions targeting cognitive impairments holds a place in the effective rehabilitation of ED.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>6-QEMP</td>
<td>6-item Questionnaire of Everyday Memory Problems</td>
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<tr>
<td>BOLD</td>
<td>Blood-oxygen-level-dependant</td>
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<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<td>ED</td>
<td>Exhaustion disorder</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression scale</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases</td>
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<tr>
<td>MMR</td>
<td>Multimodal stress rehabilitation</td>
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<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
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<tr>
<td>PPC</td>
<td>Posterior parietal cortex</td>
</tr>
<tr>
<td>PRMQ</td>
<td>Prospective and Retrospective Memory Questionnaire</td>
</tr>
<tr>
<td>RECO</td>
<td>Rehabilitation for Improved Cognition</td>
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List of papers


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Huvudfokus för avhandlingen var att belysa effekterna av kognitiv träning. Målsättningen var att undersöka om kognitiv träning kan leda till förbättrad kognitiv funktion för patientgruppen och om en sådan eventuell förbättring kan kopplas till förändringar i hjärnans aktivitetsmönster, förbättrad psykisk hälsa och ökad arbetsförmåga. I den sista studien i avhandlingen undersöktes långtidseffekter av datorbaserad kognitiv träning och fysisk konditionsträning.

I den första delstudien undersöktes effekterna av kognitiv träning omedelbart efter avslutad intervention. Resultaten visade att patienter som genomgick kognitiv träning förbättrades på icke-tränade uppgifter som liknade de uppgifter som ingick i träningsprogrammet. De skattade även en lägre grad av utmattning jämfört med kontrollgruppen och upplevde själva att minnesförmågan hade förbättrats.

I den andra delstudien fick patienter med utmattningssyndrom genomföra en arbetsminnesuppgift, samtidigt som de genomgick funktionell magnetkameraundersökning för att mäta hjärnans aktivitetsmönster. Resultaten visade att patienter med hög grad av utmattning klarade uppgiften lika bra som patienter med lägre grad av utmattning. Patienter med hög grad av utmattning aktiverade dock delar av hjärnan som är viktiga för arbetsminnet i högre utsträckning under uppgiftsutförandet. Detta kan tyda på att patienter med svårare utmattning måste anstränga sig mer mentalt för att klara uppgiften. Patienter som genomgått kognitiv träning uppvisade ökad aktivitet i arbetsminnesrelaterade områden i hjärnan under den deluppgift som ställde högst krav på arbetsminnet. Dock var deltagaranalysen i denna analys litet, vilket innebar att några säkra slutsatser inte kunde dras.

Introduction

As society changes, new challenges arise. In today’s labour market, exposure to work-related stress has been recognized as one of the primary occupational health risk factors, associated with impaired mental health (Stansfeld & Candy, 2006) and substantial societal costs (Hassard, Teoh, Visockaite, Dewe, & Cox, 2018). Psychological ill-health has become one of the main causes for long-term sickness absence (Henderson, Glozier, & Holland Elliott, 2005), and the development of effective primary, secondary, and tertiary prevention of stress-related illness is of key importance on an individual and a societal level.

Stress is used to describe the emotional and physiological responses that arise when current demands are perceived as exceeding the available coping resources (Lazarus, 2006). The stress reaction is essentially adaptive, leading to physiological changes that aim to prepare the individual to handle the challenge at hand; however, too much stress can compromise health and resiliency through the chronic strain of stress-induced physiological alterations on bodily systems (McEwen, 1998). Stress also has widespread effects on the structure and function of the brain (Lupien, McEwen, Gunnar, & Heim, 2009), and concomitant cognitive impairments following long-term stress exposure are being highlighted (Deligkaris, Panagopoulou, Montgomery, & Masoura, 2014).

With an increasingly complex society, higher demands are being placed on cognitive functions across almost all aspects of life. At work, the ability to solve problems, plan and structure work tasks, process information, and adapt to changing work conditions has become essential for many employees. In life in general, people are required to make a vast amount of daily choices, stay focused and goal-directed, inhibit and select from an endless stream of information, and solve increasingly complex problems. For individuals suffering from stress-related illness, cognitive impairments may lead to a vicious circle, in which impaired cognitive function reduces the ability to handle current demands, requiring more effort to conduct everyday tasks, in turn leading to increased stress symptoms. Additionally, cognitive deficits may negatively influence the ability to assimilate psychological treatment. Therefore, cognitive impairments need to be taken into consideration for the effective rehabilitation of individuals suffering from stress-related illness.

The focus of this thesis is on evaluating the efficacy of interventions targeting cognitive impairments within the context of stress rehabilitation for patients with stress-related exhaustion disorder (ED). It centres around the question of whether it is possible to counteract the negative influence of long-term stress on the brain and cognition through targeted interventions. The main focus is on
cognitive training, the effects of which are investigated from a cognitive, neural and clinical perspective (Study I-III). The final part of this thesis (Study III) widens the perspective and addresses the long-term effects of cognitive and aerobic training on cognition and ED recovery.

This thesis is organized into four parts. First, I will provide an overview of the clinical and neurocognitive characteristics of stress-related ED and the interventional approaches for addressing cognitive impairments that are the focus of the thesis. Second, I will describe the design and methodology of the Rehabilitation for Improved Cognition (RECO) project, which generated the data for the included studies. Third, I will provide a summary of the empirical studies, and fourth, I will discuss and synthesize the findings.

**Stress-related exhaustion disorder**

Despite the rapid increase in stress-related ill health, the research field is still hampered by a lack of international consensus on how to define and classify clinical cases of individuals who have fallen ill due to stress exposure. One of the most well-known constructs of work-related stress is burnout (Maslach, Schaufeli, & Leiter, 2001); however, this is not a clinical diagnosis, and various theoretical conceptualizations of the concept exist. A recent review of the literature on clinically significant burnout revealed that a broad range of diagnoses had been employed to describe the symptoms presented by patients, including work-related neurasthenia, undifferentiated somatoform disorder, reactions to severe stress and adjustment disorder, and major depression (Grossi, Perski, Osika, & Savic, 2015). In this context, careful consideration of the various conceptualizations used to define the patient group is warranted, especially when attempting to integrate research findings in the field.

In Sweden, ED has been adopted into healthcare practices as a clinical diagnosis for patients who have fallen ill due to long-term stress exposure (National Board of Health and Welfare, 2003). This section will focus on describing ED and its relationship to the burnout concept, outline the clinical characteristics related to the diagnosis, and discuss the available evidence regarding treatment and prognosis. Henceforth, the term ED will be used when referring to patients who have been diagnosed using the Swedish diagnostic criteria. However, when considering the broader body of international research on clinical burnout and stress-related illness, in which patients may have been classified using other definitions or diagnostic criteria, the more generic term stress-related exhaustion will be used.
Burnout and exhaustion disorder

Perhaps the most influential conceptualization of burnout is the one proposed by Maslach et al. (2001), who defined it as a condition characterized by emotional exhaustion, depersonalization, and reduced professional accomplishment. In their definition, burnout was seen as a condition arising from chronic job stress that mainly affected highly engaged workers in helping professions. Emotional exhaustion reflects the core dimension of burnout and refers to the depletion of physical and emotional resources that occurs as a response to chronic job stress. As a way of coping with emotional stress, workers may develop a detached and cynical attitude towards aspects of the job, in particular towards the recipients of care, which is reflected in the second dimension: depersonalization. The final dimension, reduced personal accomplishment, refers to self-appraisals of impaired productivity. Another widely adopted definition characterized burnout as the chronic depletion of an individual’s energetic resources, centred around the dimensions emotional exhaustion, physical fatigue and cognitive weariness (Melamed, Kushnir, & Shirom, 1992; Melamed, Shirom, Toker, Berliner, & Shapira, 2006). Even though these definitions of burnout differ somewhat, they also share similarities, particularly in the emphasis on exhaustion being a central component of the construct.

Although widely used, the concept of burnout was originally intended to describe the relationship between an individual and his or her job, rather than a classification of illness. Diagnostic criteria for burnout are currently not included in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013), and in the International Classification of Diseases (ICD-10; World Health Organization, 1992), burnout can be found under the category “Problems related to life-management difficulty” and is thus not considered a mental disorder. In 2003, the Swedish National Board of Health and Welfare outlined diagnostic criteria for ED to facilitate clinical diagnosis and rehabilitation for patients suffering from stress-related illness. The diagnosis has since been included in the Swedish version of the ICD-10 under the heading “Reaction to severe stress, and adjustment disorders” (F43.8A, Table 1). ED can thus be seen as a formal diagnosis for operationalizing clinical burnout, with particular emphasis on exhaustion. As might be expected, patients with ED also exhibit high burnout levels (e.g., Glise, Ahlborg, & Jonsdottir, 2012).
Clinical characteristics

ED is characterized by symptoms of physical and mental exhaustion due to psychosocial stressors, present for a minimum duration of 6 months before diagnosis. Although burnout research has traditionally focused on work-related stress exposure, psychosocial stressors preceding ED may also arise in private life, such as relational conflicts or caring for a family member, or in the combined burden from work- and nonwork-related factors (Hasselberg, Jonsdottir, Ellbin, & Skagert, 2014). Core symptoms include a clear lack of mental energy, manifested as reduced initiative, decreased endurance, or increased need of time for recovery after mental stress. Patients also frequently report cognitive impairments, and problems with memory and concentration have been included as part of the diagnostic criteria. Additional symptoms include emotional instability, physical fatigue, and reduced ability to handle demands or work under time pressure. Clinically, ED is characterized by a lack of balance between activity
and restitution, and it has been suggested that insufficient sleep and recovery may be an important mechanism mediating the association between stress exposure and ED development (Grossi et al., 2015). Comorbid symptoms of depression and anxiety are prevalent; however, these symptoms seem to subside more rapidly than symptoms of burnout following rehabilitation (Glise et al., 2012).

Given that ED is a diagnosis exclusively related to Swedish circumstances, its prevalence has not been well established to date. Stress-related illness is one of the most common reasons for sick leave in Sweden today (Swedish Social Insurance Agency, 2017), and population-based studies have classified between 8% (Persson, Österberg, Viborg, Jonsson, & Tenenbaum, 2017) and 16% (Glise, Hadzibajramovic, Jonsdottir, & Ahlborg, 2010) of participants as possible ED cases, using self-report forms directly corresponding to the diagnostic criteria. Although long-term follow-ups are scarce, one previous study showed that following stress rehabilitation, one third of ED patients still reported high burnout levels 18 months after initiating treatment (Glise et al., 2012), suggesting that the duration of illness can be long-lasting, despite extensive rehabilitation.

### Cognitive aspects of stress-related exhaustion

Patients with ED frequently report cognitive impairments as one of their main symptoms. When the diagnosis was first introduced in 2003, problems with memory and concentration were part of the diagnostic criteria; however, at that time this was mainly based on clinical observations and the prevalence and nature of cognitive impairments in stress-related exhaustion had not been empirically validated. During the past decade, several studies have investigated cognitive functioning in patients with stress-related exhaustion, showing that the condition is de facto associated with selective cognitive impairment (see Deligkaris et al., 2014, for a review). Furthermore, patients frequently report high levels of subjective cognitive complaints (Eskildsen, Andersen, Pedersen, Vandborg, & Andersen, 2015; Krabbe, Ellbin, Nilsson, Jonsdottir, & Samuelsson, 2017; Oosterholt, Maes, Van der Linden, Verbraak, & Kompier, 2014; van der Linden, Keijser, Eling, & Schaijk, 2005; Österberg, Karlson, & Hansen, 2009), suggesting that stress-related cognitive impairments are perceived by patients to have a substantial impact on everyday functioning.

As will be outlined in more detail below, cognitive impairments emerge mainly in the areas of executive function, working memory, attention and processing speed, and episodic memory. Whether cognitive impairments constitute a vulnerability factor or a consequence of stress-related exhaustion has not yet been empirically investigated. However, the fact that patients are generally highly educated (e.g., Glise et al., 2012) and perform equal to healthy controls in tests estimating premorbid cognitive abilities, such as verbal intelligence (Eskildsen et al., 2015;
Jonsdottir et al., 2017; Krabbe et al., 2017; Rydmark et al., 2006; Österberg et al., 2009) may suggest that the latter is a more valid assumption. The following section will outline the available evidence relating to cognitive impairments in stress-related exhaustion, drawn from cross-sectional and longitudinal studies.

**Cross-sectional studies**

**Executive function**

Executive function can be defined as several distinct, yet overlapping, top-down cognitive control processes necessary for goal-directed behaviour. They include prioritizing and sequencing behaviour, creating and maintaining an idea of what information is most relevant for the task at hand, inhibiting distracting information, switching between mental sets, and utilizing relevant information to support decision making. Executive functions are particularly important in novel, non-routine situations and when demands for concentration are high (Banich, 2009; Diamond, 2013). A closely related construct is cognitive control, which is often used interchangeably with executive function in the literature (J. D. Cohen, 2017). One of the most influential models of executive functions was proposed by Miyake et al. (2000), who conceptualized executive functions as three separate, yet moderately correlated, cognitive processes: *updating* of working memory representations, *shifting* between tasks or mental sets, and *inhibition* of dominant responses (see also Friedman & Miyake, 2017; Miyake & Friedman, 2012). These basic processes in turn contribute to performance on more complex executive tasks.

Impaired executive functioning has been observed in patients with stress-related exhaustion (Jonsdottir et al., 2013; van Dam, Keijsers, Eling, & Becker, 2011), specifically with respect to inhibition (Ellbin, Engen, Jonsdottir, & Nordlund, 2018; van der Linden et al., 2005), shifting (Öhman, Nordin, Bergdahl, Slunga Birgander, & Stigsdotter Neely, 2007), and updating (Krabbe et al., 2017; Oosterholt, Van der Linden, Maes, Verbraak, & Kompier, 2012). Furthermore, impairments have been reported for verbal tests with high executive demands (Ellbin et al., 2018; Krabbe et al., 2017; Öhman et al., 2007). However, intact performance has also been observed in executive tasks, with respect to shifting (Oosterholt et al., 2014; Oosterholt et al., 2012), updating (Oosterholt et al., 2014), and inhibition (Jonsdottir et al., 2013; Oosterholt et al., 2014; Oosterholt et al., 2012).

**Working memory**

Working memory refers to the ability to temporarily hold information in mind while mentally working with it. Several models of working memory exists, perhaps the most influential one proposed by Baddeley and Hitch (1974).
According to their model, working memory is composed of three storage systems: the phonological loop and the visuospatial sketchpad, which are involved in the temporary storage of verbal and visuospatial material, and the episodic buffer, which is concerned with integrating information held in working memory with long-term memory representations. It also comprises one control system: the central executive, which is responsible for directing and controlling attention during the task at hand. The central executive taps into several processes that fall under the executive function domain and some researchers have included working memory as a core executive function (cf. Diamond, 2013). Recent models have conceptualized working memory as being composed of several interacting components, involving the interplay between attentional and executive processes in conjunction with perceptual and long-term memory representations (i.e., the content of working memory; Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015).

Impairments in short-term and working memory have been observed in patients with stress-related exhaustion (Jonsdottir et al., 2013; Rydmark et al., 2006), although normal performance has also been reported (Oosterholt et al., 2014; Öhman et al., 2007). One study found intact performance on a standard working memory index but evidence of impairment on a more executively demanding working memory task with high attentional demands (Eskildsen et al., 2015).

Attention and processing speed
Attention refers to the ability to maintain focus and concentration on a task. It is a multifactorial construct comprising several sub-processes, such as alerting (e.g., sustained attention and vigilance), orienting (e.g., directing and shifting attention), and maintaining executive/top-down controlled attention (Petersen & Posner, 2012). It shares some conceptual overlap with executive function, as the ability to inhibit distracting information and shift between mental sets are important components of attentional control (Chun, Golomb, & Turk-Browne, 2011; Petersen & Posner, 2012). Another related concept is processing speed, which is usually assessed through cognitive tests requiring the ability to react to and work rapidly on tasks with high attentional demands.

For patients with stress-related exhaustion, several studies have found impairments in tasks requiring sustained attention (Krabbe et al., 2017; Sandström et al., 2011; Sandström, Rhodin, Lundberg, Olsson, & Nyberg, 2005; van der Linden et al., 2005). In tests assessing processing speed, studies have shown somewhat conflicting results, with evidence of intact (Jonsdottir et al., 2013; Sandström et al., 2005) and impaired (Ellbin et al., 2018; Eskildsen et al., 2015; Österberg et al., 2009) performance. Some studies have suggested intact performance for basic processing speed and reaction time tasks, along with
impairments in more complex speed and attentional tasks (Krabbe et al., 2017; Rydmark et al., 2006; van der Linden et al., 2005; Öhman et al., 2007).

Learning and memory
Memory encompasses several abilities that share a common label, implicating that further subdivision of the concept is generally necessary to fully grasp an individual's memory capacity. A basic distinction can be found between short-term/working memory (outlined above) and long-term memory. The latter can be further subdivided into declarative memory and procedural memory. Declarative memory includes the ability to encode, store, and retrieve information of factual knowledge (semantic memory) and events that are anchored in space and time (episodic memory). Episodic memory is reliant on the hippocampus (Tulving & Markowitsch, 1998), and this memory function has received particular interest in the stress-cognition literature due to the impact of stress hormones on hippocampal structure and function (Lupien & Lepage, 2001).

For patients with stress-related exhaustion, normal (Ellbin et al., 2018; Eskildsen et al., 2015; Rydmark et al., 2006; Österberg et al., 2009) and mixed findings (Jonsdottir et al., 2013; Sandström et al., 2011; Sandström et al., 2005) have been reported for episodic memory performance. One study suggested impairments in learning and memory when encoding had high requirements of strategic organization and attentional control (Öhman et al., 2007). Additionally, two studies found pronounced deficits in prospective memory (Eskildsen et al., 2015; Öhman et al., 2007), which is the ability to remember an intended future action.

Taken together, the literature on cognitive impairments in stress-related exhaustion yields a rather heterogeneous picture, with evidence of intact and impaired cognitive performance within the investigated domains. Some of these discrepancies can probably be attributed to methodological issues, such as differences in study populations, and to the use of different instruments to assess study outcomes. Additionally, the effect sizes of the difference in cognitive performance between patients with stress-related exhaustion and healthy controls have generally been shown to be of small-moderate magnitude (e.g. Ellbin et al., 2018; Eskildsen et al., 2015; Jonsdottir et al., 2013) and some of the previous studies in this area may have been inadequately powered due to small samples. Integration of findings in the field is further complicated by the fact that executive function, working memory and attention share some conceptual overlap, relating to the overall ability to exert cognitive control over thought and behaviour (J. D. Cohen, 2017), which is reflected by differences in how tasks are classified across studies, and the use of tasks that simultaneously tap into several of these cognitive processes. These discrepancies aside, it is clear from the available evidence that cognitive impairments in stress-related exhaustion
emerge mainly on tasks with high requirements of cognitive control, while performance on tasks involving familiar material and more automatic processing demands are usually intact.

**Longitudinal course**

A few studies have investigated the prospective time-course of stress-related cognitive impairments, using follow-up intervals ranging from 10 weeks to 3 years. During the follow-up period, patients participated in a variety of rehabilitative measures; most of them were based on cognitive behavioural therapy (CBT; Jonsdottir et al., 2017; Oosterholt, Maes, Van der Linden, Verbraak, & Kompier, 2016; Oosterholt et al., 2012; van Dam, Keijsers, Eling, & Becker, 2012), one consisted of a workplace intervention (Österberg, Skogsliden, & Karlson, 2014) and one was described as treatment-as-usual focusing on guidance concerning return-to-work (Eskildsen, Andersen, Pedersen, & Andersen, 2016).

Oosterholt et al. (2012) found that impairments in updating and processing speed were still evident immediately following 10 weeks of CBT, despite observed improvements in emotional exhaustion and subjective cognitive complaints. Using longer follow-up intervals, ranging between 1 and 3 years, remaining impairments in executive function (Oosterholt et al., 2016; van Dam et al., 2012), short-term and working memory (Eskildsen et al., 2016; Jonsdottir et al., 2017), attention and processing speed (Eskildsen et al., 2016; Österberg et al., 2014), episodic memory (Eskildsen et al., 2016; Jonsdottir et al., 2017) and prospective memory (Eskildsen et al., 2016) have been found. Furthermore, patients continue to report elevated levels of subjective cognitive complaints (Eskildsen et al., 2016; Oosterholt et al., 2016; Oosterholt et al., 2012; Österberg et al., 2014). However, cognitive improvement in relation to healthy controls has also been observed during the follow-up interval, specifically with respect to executive function (van Dam et al., 2012), prospective memory and processing speed (Eskildsen et al., 2016), and a reduction of self-reported cognitive failures (Eskildsen et al., 2016; Oosterholt et al., 2016; Oosterholt et al., 2012).

Taken together, cognitive impairments in stress-related exhaustion may be long-lasting and continue to impact patients’ everyday life several years post-rehabilitation. However, indications also exist that some improvement occurs across time, suggesting that the stress-related cognitive deficits are at least partly reversible. The degree to which stress-related cognitive impairments are amenable to interventions specifically directed at improving cognition remains unclear; therefore, the main focus of this thesis is to investigate whether interventions targeting cognitive impairments in the context of stress
rehabilitation can improve cognitive performance in patients with ED, and whether such effects could be sustained across time.

**Neural aspects of stress-related exhaustion**

It has been well established that prolonged stress exposure can have detrimental effects on brain structure and function. Regions that are particularly sensitive to stress-exposure include the hippocampus (Lupien & Lepage, 2001; McEwen, 1998), the prefrontal cortex (PFC; Arnsten, 2009; Arnsten, Raskind, Taylor, & Connor, 2015) and the amygdala (Roozendaal, McEwen, & Chattarji, 2009), regions involved in learning and memory, executive function and working memory, and threat processing respectively. Collectively, these regions are central for adaptation to stress and involved in evaluating the potential threat and emotional salience of a stressor, as well as in coordinating the physiological, behavioural, cognitive, and emotional responses necessary for effective coping (McEwen & Gianaros, 2011). However, they are also adversely affected by periods of prolonged stress or unsuccessful adaptation to stressors.

Animal models have shown that long-term stress exposure can lead to structural remodelling of the hippocampus through shortening of dendrites, loss of spine synapses, and suppressed neurogenesis (McEwen & Gianaros, 2011). In humans, smaller hippocampal volumes have been observed in stress-related disorders such as depression (Videbech & Ravnkilde, 2004) and post-traumatic stress disorder (O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015). However, it is not clear whether smaller hippocampal volumes reflect a consequence of stress exposure, such as through the neurotoxic effects of stress hormones on the hippocampus (Sapolsky, Krey, & McEwen, 1986), if it constitutes a vulnerability factor for developing stress-related disorders (Gilbertson et al., 2002; Lindgren, Bergdahl, & Nyberg, 2016), or if it involves a combination of both mechanisms (Lupien et al., 2009). Furthermore, not only the hippocampus, but also the PFC and the amygdala, show structural and functional changes following stress exposure. Exposure to sustained stress leads to neuro-plastic remodelling of the PFC, as demonstrated by animal models through reduction in dendritic length and branching and reduced spine density (Arnsten, 2009; Arnsten et al., 2015). In healthy adults, 1 month of exposure to psychosocial stress has been associated with disrupted functional connectivity within the frontoparietal network, paralleled by impairments in attentional set shifting (Liston, McEwen, & Casey, 2009). In contrast, long-term stress can cause hypertrophy in the amygdala through increased spine density and dendritic growth (Roozendaal et al., 2009). Collectively, the observed structural and functional brain changes associated with stress exposure shifts the brain from reflective, top down behavioural, emotional, and cognitive regulation to a more reflexive, affective, and habitual state (Arnsten et al., 2015). In the short run, these changes can be adaptive and aid in fine-tuning
the brain to rapidly handle the threat at hand. However, under conditions of chronic stress, this can lead to a vicious circle in which an initial stressor causes further stress through the negative influence on several brain structures necessary for effective coping and the successful termination of the stress reaction.

A few studies have investigated the neural correlates of stress-related exhaustion, providing some evidence of differences between patients and healthy controls in neural structure and function. Decreased striatal and increased amygdala volumes have been observed, along with reduced cortical thickness and grey matter volume in the PFC – including the medial and dorsolateral PFC – and the anterior cingulate cortex (Blix, Perski, Berglund, & Savic, 2013; Savic, 2015), although one previous study showed no difference in PFC volumes (Rydmark et al., 2006). Notably, no differences in hippocampal volumes have been reported (Blix et al., 2013; Rydmark et al., 2006; Sandström et al., 2011; Savic, 2015). Additionally, weaker functional connectivity has been observed between the amygdala and frontal regions, specifically the medial PFC, dorsolateral PFC, and motor cortex, as well as the anterior cingulate cortex (Golkar et al., 2014; Jovanovic, Perski, Berglund, & Savic, 2011). Behaviourally, impaired ability to down-regulate negative emotion has been associated with reduced cortical thickness in the PFC (Savic, Perski, & Osika, 2017) and functional disconnection between the amygdala and the anterior cingulate cortex (Golkar et al., 2014). One study showed evidence of lower functional neural activation in the PFC during working memory processing, compared to healthy controls and patients with depression (Sandström et al., 2012). To date, only one longitudinal study has been conducted, showing that between 1 and 2 years after treatment, baseline thinning of the PFC and reduction of striatal volumes had normalized, while enlargements in the amygdala and cortical thinning of the superior temporal gyrus remained (Savic et al., 2017).

In sum, the neural underpinnings of stress-related exhaustion are not well established and, to date, only a few neuroimaging studies have been conducted in this patient group, the majority of which have focused on brain structure and/or emotional regulation. Therefore, in Study II, functional neuroimaging and a cognitive task paradigm were employed to shed further light on the functional neural correlates of the cognitive impairments associated with ED.

**Rehabilitation of cognitive impairments**

Despite the fact that stress-related exhaustion has been associated with persistent cognitive impairments, perceived by patients to negatively influence everyday life, little is known about how to address cognition in stress rehabilitation. However, drawing on empirical studies on non-pharmacological interventions
that aim to improve cognition in other populations may provide some insight regarding which components might be useful in stress rehabilitation. Two interventional approaches that have received a widespread interest in the literature are cognitive training and aerobic exercise, and, as will be outlined in more detail below, these interventions show potential as means of improving cognitive function. These approaches might also be viable methods for targeting cognitive impairments for patients with stress-related exhaustion. The main focus of this thesis is on cognitive training, delivered in the broader context of a stress rehabilitation program. This section will therefore start by giving an overview of the cognitive training field by outlining different approaches, discuss the concepts of training gains and transfer and their neural correlates, and explore the application of cognitive training in mental illness. However, part of this thesis also addresses aerobic exercise training, and this section will close with a brief overview of the use of aerobic exercise as an interventional approach for improved cognition.

Cognitive training
Cognitive training can be defined as structured practice on standardized and cognitively challenging tasks, focused on one or several specific cognitive domains (Clare & Woods, 2004). It rests on the notion of plasticity, which is the brain’s capacity to respond to new experiences through structural reorganization and concurrent changes in behaviour (Lindenberger, Wenger, & Lövden, 2017; Lövden, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). The fundamental assumption is that by posing environmental demands that continuously challenge the available cognitive resources, the individual’s cognitive capacity might be extended.

Approaches to cognitive training
Cognitive training can be conducted in many different ways, but overall, two broad approaches have emerged: strategy training and process-based training. Strategy training involves teaching strategies to improve performance in specific tasks, such as training mnemonic strategies (Ball et al., 2002; Derwinger, Neely, Persson, Hill, & Backman, 2003) or problem-solving abilities (Ball et al., 2002). Process-based cognitive training on the other hand, aims at strengthening cognitive processes central for complex cognition, most commonly focused on training of executive function and working memory. The underlying assumption of process-based training is that by strengthening cognitive functions important for proficient information processing, other cognitive abilities that rely on these functions could benefit as well. Several different approaches have been empirically investigated, such as training single (Dahlin, Nyberg, Bäckman, & Neely, 2008; Karbach & Kray, 2009) or multiple (Sandberg, Rönnlund, Nyberg, & Stigsdotter Neely, 2014) executive functions, as well as tasks targeting aspects
of working memory (Brehmer, Westerberg, & Bäckman, 2012; Chein & Morrison, 2010; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). A final approach to cognitive training is using a multifactorial training regimen, targeting several different cognitive functions. Using this approach, it is possible to train a broader range of abilities and to use a combination of process-based and strategy training. One example of this is a study by Schmiedek, Lövden, and Lindenberger (2010), who used a multifactorial program to train episodic memory, working memory, and processing speed. A multifactorial approach may be particularly useful for clinical populations, such as ED, as it allows for the use of different training tasks that are chosen to target the specific impairments associated with the condition.

**Training gains and transfer**

It is generally acknowledged that by extended practice on a specific task, performance on that task will improve. Of key importance in cognitive training interventions, however, is whether such training-related gains extend beyond the specific training situation to other tasks, abilities or contexts. This is the notion of transfer. Transfer can broadly be separated into two categories: near transfer, which is the generalization of training effects to tasks targeting the same cognitive abilities as those trained, and far transfer, which is the generalization of training effects to untrained abilities.

A longstanding view of transfer stipulates that generalization of learning depends on the common elements shared between tasks, indicating that for transfer to occur from one task to another, they need to tap into similar cognitive processes (Woodworth & Thorndike, 1901). For strategy training, transfer effects seem limited to the very near and dependent on the specific trained strategy (e.g., Verhaeghen, Marcoen, & Goossens, 1992). The limited transfer effects following strategy training surged a growing interest in process-based training interventions with the hope that improved executive function and working memory could yield performance increases in a broader range of untrained tasks, due to the association between these abilities and higher order cognitive functions, such as fluid intelligence (Engle, Tuholski, Laughlin, & Conway, 1999; Oberauer, Schulze, Wilhelm, & Suss, 2005).

Improvements on trained and near transfer tasks following process-based cognitive training have been demonstrated by several authors (e.g. Brehmer et al., 2012; Chein & Morrison, 2010; Dahlin, Nyberg, et al., 2008; Karbach & Kray, 2009; Sandberg, Ronnlund, Nyberg, & Neely, 2014). Additionally, some studies have shown encouraging far transfer to areas such as sustained attention (Brehmer et al., 2012), reasoning ability (Jaeggi et al., 2008; Karbach & Kray, 2009), and reading comprehension (Chein & Morrison, 2010). However, the issue of transfer following process-based cognitive training is not without debate and authors of recent meta-analyses have questioned the possibilities of reaching
generalizations of training effects beyond the very near (Melby-Lervag, Redick, & Hulme, 2016; Soveri, Antfolk, Karlsson, Salo, & Laine, 2017). As has been pointed out (e.g. Noack, Lövden, & Schmiedek, 2014; Shipstead, Redick, & Engle, 2012), the field suffers from several methodological issues, limiting firm conclusions regarding training efficacy. This includes relying on single tasks when assessing transfer, making it difficult to disentangle performance changes related to the use of task-specific strategies from improvements in the targeted cognitive constructs. Additionally, many studies have used no-contact control groups, making non-specific factors such as motivation and expectancy effects possible confounders. Furthermore, studies are often based on small samples, resulting in a lack of power to detect significant effects. Finally, most cognitive training studies have restricted the evaluation of training effects to immediately post intervention, making the duration of potential transfer effects an understudied area. For healthy adults, the available evidence indicates that improvements on trained tasks are quite stable, at least up to 1.5 years after training, whereas the breadth and duration of transfer effects seem more limited (Dahlin, Nyberg, et al., 2008; Sandberg & Neely, 2016; Zinke et al., 2014), although there have been demonstrations of long-term stability for broader transfer effects with the use of more extensive training (Schmiedek, Lövden, & Lindenberger, 2014). The potential of giving rise to long-term benefits on cognitive function may be particularly relevant for patients with ED, as the associated cognitive impairments may endure several years post rehabilitation.

*Neural mechanisms underlying training gains and transfer*

Executive function and working memory rely primarily on the PFC, the posterior parietal cortex (PPC), and the striatum (Eriksson et al., 2015; Owen, McMillan, Laird, & Bullmore, 2005); thus, these are the primary regions of interest when investigating neural changes following process-based cognitive training (Constantinidis & Klingberg, 2016). Previous process-based cognitive training studies have reported increased (Olesen, Westerberg, & Klingberg, 2004) and decreased (Brehmer et al., 2011; Schneiders, Opitz, Krick, & Mecklinger, 2011; Schneiders et al., 2012) frontoparietal activation following training, as well as increased functional connectivity within the frontoparietal working memory network (Jolles, van Buchem, Crone, & Rombouts, 2013). Increased activation is generally interpreted as a greater recruitment of cortical units or a stronger neuronal response within a specific unit, whereas decreased activation is thought to reflect increased neural efficiency and less executive control requirement (Constantinidis & Klingberg, 2016; Dahlin, Bäckman, Neely, & Nyberg, 2009). A recent meta-analysis synthesizing the available literature found that process-based training of working memory modulated neural activation primarily within the working memory network, showing training-related changes across several regions of the PFC, including the dorsolateral PFC, the inferior frontal gyrus, and the frontal eye field, as well as the anterior cingulate cortex, the PPC, and the
striatum (Salmi, Nyberg, & Laine, 2018). Increased activation following training was observed primarily in prefrontal and striatal regions, whereas decreased activation was found in the parietal cortex. When compared to perceptual–motor learning, authors concluded that process-based working memory training and perceptual–motor learning engaged similar neural networks, suggesting that training-related neural effects are largely related to domain-general learning processes, but that working memory training was specifically related to modulation of dorso- and ventrolateral PFC activation.

With respect to the neural mechanisms underlying transfer effects, this has been more scarcely investigated, as most neuroimaging studies on cognitive training have focused on neural correlates of trained task improvements. However, results from the meta-analysis by Salmi et al. (2018) suggested that the frontostriatal network may play a key role in transfer effects, associating transfer with increased activation in the striatum and the inferior frontal gyrus, in conjunction with decreased dorsolateral PFC activation. More specifically, transfer within the working memory updating domain has been found to be mediated by the striatum (Dahlin, Neely, Larsson, Bäckman, & Nyberg, 2008; Salminen, Kuhn, Frensch, & Schubert, 2016), suggesting that transfer of learning occurs when trained and transfer tasks engage overlapping neural systems.

**Cognitive training in mental disorders**

For clinical populations, the issue of transfer ultimately relates to whether training effects are generalized into clinically meaningful patient outcomes, for instance, by translating into improved everyday functioning or alleviated clinical symptoms. As Keshavan, Vinogradov, Rumsey, Sherrill, and Wagner (2014), proposed, cognitive training for individuals with mental disorders involves identifying impairments in the neural system- and the related cognitive functions that are most relevant for a patient group's clinical and behavioural outcomes, and then targeting these processes through training. Because impairments in executive function and working memory occur in several mental disorders (see Snyder, Miyake, & Hankin, 2015 for a review) and because these cognitive abilities are important in several aspects of everyday life (e.g., Diamond, 2013), process-based cognitive training has received increasing interest as a potential means for improving functional outcomes in clinical groups. Additionally, deficits in executive function and working memory have been associated with clinical features of mood and anxiety disorders such as depressive rumination (Joormann, Yoon, & Zetsche, 2007) and worry (Eysenck, Derakshan, Santos, & Calvo, 2007); therefore, researchers have hypothesized that improved cognitive control may also translate into alleviated clinical symptoms of depression and anxiety. In a recent review, authors concluded that the clinical benefits of cognitive control training for depression are promising (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017) and the results of an initial meta-analysis
showed that computerized cognitive training had positive effects on aspects of cognition, as well as on depressive symptomatology and daily functioning in depression (Motter et al., 2016). However, as Koster et al. (2017) pointed out, the findings in the field are mixed with substantial heterogeneity between studies, many of which suffer from methodological limitations. Furthermore, the underlying mechanism through which cognitive control training influences clinical outcomes is not yet well established.

To date, no studies have investigated the efficacy of cognitive training in patients with stress-related exhaustion. Therefore, the three studies in this thesis sought to broadly explore this issue, by investigating the immediate (Study I) and long-term (Study III) effects of cognitive training on trained and transfer tasks, as well as their neural underpinnings (Study II). In line with Keshavan et al. (2014) recommendation, the cognitive training program was designed to target the specific impairments and related brain regions known to be adversely affected by long-term stress. Based on the literature reviewed above, Figure 1 displays the neural regions and cognitive functions of relevance for patients with ED, as well as the clinical functions that could putatively be linked to impairments in these neural and cognitive processes. Because stress-related exhaustion has been primarily associated with deficits in prefrontal-dependent cognitive control processes, strengthening of PFC regulation and its associated cognitive functions may serve the most important interventional target. An improved ability to exert top-down control of thought and behaviour could, in turn, provide a link whereby cognitive improvements following training may translate into alleviated clinical symptoms, e.g. by enhancing the ability to cope efficiently with stress and handle work demands. With this in mind, the multifactorial cognitive training program used in this thesis’s three studies emphasized process-based training of executive functions (see the bottom part of Figure 1). Additionally, due to the well-established link between stress and hippocampal-dependent memory processes, the program also included associative memory-binding training. The training program will hereby be referred to as “process-based cognitive training”.
Figure 1. A summary of the neural, cognitive and clinical functions of relevance for patients with ED and how selected functions could be targeted by process-based cognitive training. By strengthening PFC-dependent cognitive functions, the ability to exert top-down control of thought and behaviour could be improved, in turn providing a link whereby cognitive improvements following training may translate into alleviated clinical symptoms.

Aerobic training

The beneficial effects of physical activity on health outcomes are well-established (Warburton, Nicol, & Bredin, 2006). Increasingly, physical activity – particularly aerobic fitness training – has also been highlighted as a promising interventional approach for improving cognitive and brain functioning (Hillman, Erickson, & Kramer, 2008). The results of a meta-analysis of interventional studies for adult populations showed that aerobic exercise had a small-sized positive effect on cognitive performance across several cognitive domains (Smith et al., 2010). More specifically, executive functions and memory are the cognitive abilities most susceptible to physical exercise’s positive effects on cognition (Hötting & Röder, 2013), indicating that physical activity may be a particularly suitable mean of targeting stress-related cognitive deficits. To date, only one study has investigated how physical exercise affects cognitive functioning in stress-related exhaustion. Authors reported improvements in executive function, as well as in symptoms of burnout and depression, following a 12-week aerobic exercise intervention, stating that at follow-up, executive performance returned to the levels of healthy controls (Beck, Gerber, Brand, Puhse, & Holsboer-Trachsler, 2013). However, it should be noted that the control group was only tested once, making retest effects a potential confounder for the cognitive variables; in addition, the participants were recruited from the community and thus did not constitute a clinical population per se. To date, longitudinal follow-ups are scarce in physical activity interventions, and although there have been demonstrations of sustained cognitive improvements for older adults who are at risk of cognitive decline (Lautenschlager et al., 2008), no long-term studies have been conducted on
patients with stress-related exhaustion. As noted previously, the potential for sustained improvements in cognitive functioning is of particular relevance for this patient group; therefore, in Study III, we investigated the long-term effects of aerobic training on cognitive performance.

**Stress rehabilitation**

When the National Board of Health and Welfare introduced the ED diagnosis in 2003, its preliminary recommendations for treatment included psychological treatment (preferably in group), stress reduction, physical activity, vocational rehabilitation and potentially antidepressant treatment. More recently, two meta-analyses investigating the effects of interventions for stress-related exhaustion (Perski, Grossi, Perski, & Niemi, 2017) and employees with burnout (Ahola, Toppinen-Tanner, & Seppänen, 2017), showed no significant effects on symptoms of burnout, anxiety, or depression, as compared to treatment-as-usual or wait-list controls. Some indications for interventions including elements of vocational rehabilitation facilitating return to work were found (Perski et al., 2017). However, as authors point out, the field suffers from methodological issues such as a small number of trials, high heterogeneity across studies in terms of inclusion criteria and intervention content, and insufficient reporting of potential concurrent treatments in the control groups.

A schematic overview of the elements commonly included in multimodal stress rehabilitation (MMR) is presented in Figure 2. Common rehabilitative measures include group CBT, that focuses on stress management, recovery behaviours, and strategies for improved sleep; vocational rehabilitation, including workplace adjustments to promote a gradual return-to-work, as well as rehabilitation meetings with the patient, health care provider, employer, and the Swedish Social Insurance Agency; physical activity; and regular contact with a physician, who can oversee sick leave and provide antidepressant treatment if needed (Glise & Ahlborg, 2013; Glise et al., 2012; Stenlund et al., 2009).
As Figure 2 shows, rehabilitative measures that explicitly address cognitive impairments have not traditionally been part of stress rehabilitation. Thus, although cognitive deficits are a prominent feature of ED – potentially contributing to the condition by increasing stress and reducing coping efficiency – it remains unclear whether improved cognitive functioning translates into alleviated clinical symptoms. Physical activity is often part of stress rehabilitation, and some support has been given for increased exercise levels following MMR being associated with improved burnout symptoms (Lindegård, Jonsdottir, Borjesson, Lindwall, & Gerber, 2015). However, the relationships among aerobic exercise, cognitive functioning, and ED recovery remain unclear, and even less is known about the clinical usefulness of cognitive training. Therefore, in Study III of this thesis, we investigated the long-term effects of cognitive and aerobic training on variables related to ED recovery (psychological health and work ability) in addition to cognitive outcomes.
Aims

The overall aim of this thesis was to investigate the efficacy of interventions that target cognitive impairments in the context of stress rehabilitation for patients with ED. Specifically, the effects of cognitive training and aerobic training, added to a multimodal stress rehabilitation program, were investigated. Further aims were to explore the neural correlates of ED and whether cognitive training leads to changes in functional neural response in this patient group.

Study I and Study II evaluated the effects of cognitive training immediately post-intervention, by carefully examining the range of transfer to non-trained cognitive tasks (Study I) and training-related neural underpinnings (Study II). Study III broadened the perspective and investigated the potential clinical utility of addressing cognitive impairments in stress rehabilitation, by examining the long-term effects of cognitive training and aerobic training on several ED related variables, including cognitive function, psychological health and work ability, 1 year post-intervention.

A schematic overview of the three studies is provided in Table 2.
<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Longitudinal (two time points; pre and post intervention)</td>
<td>Combination of cross-sectional and longitudinal (two time points; pre and post intervention)</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Cognitive training group (n = 27) Control group (n = 32)</td>
<td>Cross-sectional sample All study groups (n = 55)</td>
</tr>
<tr>
<td>Per protocol analysis</td>
<td></td>
<td>Longitudinal sample Cognitive training group (n = 10) Control group (n = 11)</td>
</tr>
<tr>
<td><strong>Assessments</strong></td>
<td><strong>Cognitive function</strong></td>
<td><strong>Cognitive function</strong></td>
</tr>
<tr>
<td></td>
<td>Letter Memory Running Span n-back Colour-Word Interference Test Trail Making Test Digit Span Forward Digit Span Backward Letter-Number Sequencing Recall of Concrete Nouns Digit Symbol Raven’s Matrices</td>
<td><strong>Psychological health</strong> Shirom-Melamed Burnout Questionnaire</td>
</tr>
<tr>
<td></td>
<td><strong>Subjective cognitive complaints</strong> 6-Item Questionnaire of Everyday Memory Problems Prospective and Retrospective Memory Questionnaire</td>
<td><strong>Psychological health</strong> Shirom-Melamed Burnout Questionnaire</td>
</tr>
<tr>
<td></td>
<td><strong>Psychological health</strong> Shirom-Melamed Burnout Questionnaire</td>
<td><strong>Brain imaging</strong> Functional magnetic resonance imaging</td>
</tr>
</tbody>
</table>
Methods

The data used in this thesis were collected within the RECO project, a three-armed parallel randomized clinical trial investigating the effects of additional cognitive training and aerobic training for patients with ED participating in a multimodal stress rehabilitation program. This section provides a general overview of the trial and descriptions of the participants, procedures and outcomes of relevance for this thesis.

The RECO project

The RECO project was conducted at the Stress Rehabilitation Clinic at the Umeå University hospital in Sweden. Participants were recruited consecutively from April 2010 until June 2013. During this period, all patients who were referred to the Stress Rehabilitation Clinic were screened for eligibility, using the following inclusion criteria: (1) confirmed diagnosis of ED according to the criteria established by the Swedish National Board of Health and Welfare; (2) 18 to 60 years of age, (3) currently employed, (4) considered by physician and psychologist as suitable for multimodal group rehabilitation, (5) no known abuse of alcohol or drugs, (6) no need for other treatment or rehabilitation, and (7) no participation in other intervention studies.

All patients participated in the Stress Rehabilitation Clinic’s usual care, a 24-week MMR program based on CBT. This program consisted of 22 weekly 3-hr sessions with groups of at most eight patients. Each group session started with a relaxation exercise, followed by a specific psychoeducational theme, such as stress and recovery, sleep and affect. Additionally, each patient had two individual meetings with the group therapist to set and evaluate individual goals for behavioural change during rehabilitation, received an individual prescription for physical activity, and attended vocational rehabilitation meetings with the health care provider and employer.

After 12 weeks of MMR, patients were randomly allocated to one of three conditions, all involving continued MMR: (1) no additional training, (2) additional computerized cognitive training, and (3) additional aerobic exercise training. The additional trainings were conducted during the final 12 weeks of rehabilitation. Psychological variables, work ability and aerobic capacity were assessed before MMR (Baseline), before randomization (T1), after completing the intervention (T2), and 1-year post intervention (T3). Additionally, at T1, T2 and T3, participants completed a 2-hr neuropsychological test battery, assessing cognitive function. At T1 and T2, a subsample of patients also underwent
functional and structural magnetic resonance imaging. For a schematic overview over the trial, see Figure 3.

Figure 3. Flow chart of the RECO project.

Of the 161 patients who agreed to participate in the RECO project, 29 discontinued participation during the initial 12 weeks of MMR (i.e., before randomization). Thus, 132 patients with clinical ED diagnosis participated in the pre-intervention assessment (T1) and were randomly assigned to one of the three study conditions. Mean age was 43.36 (8.46); 84% of the participants were women, and 61% had a university education. Thirty-three percent scored higher than 10 on the Hospital Anxiety and Depression (HAD) depression subscale, and 61% scored higher than 10 on the HAD anxiety subscale at baseline (Zigmond & Snaith, 1983). Dropout rates differed significantly between the groups, with more patients dropping out from the two intervention groups than from the control group (control group: 24%; cognitive training group: 45%, aerobic training group: 55%, as measured at the 1-year follow-up). Extensive dropout analyses were conducted with respect to background variables (age, sex, educational level, and verbal ability) and psychological health (level of burnout, depression,
anxiety, and fatigue), and for the latter, complete data were available across all
time points for dropouts as well as final participants. Overall, very few differences
were found between patients who participated in the 1-year follow-up and those
who discontinued study participation (see the full article for details).

Interventions

Cognitive training
The computerized cognitive training program consisted of six tasks, which were
chosen to target the cognitive impairments associated with long-term stress. Two
tasks targeted the executive functions shifting and updating respectively. One
task targeted visuospatial short-term memory, and one task trained episodic
memory binding. The training program was adaptive, with three levels of
difficulty; when a participant reached 80% correct answers in one of the first two
levels, they moved up to a more difficult level. A description of the training tasks,
including the targeted cognitive domains and means of adaptive difficulty is
presented in Table 3.

The training program was web-based, which allowed the participants to train at
home on their personal computers. Each training session was approximately 15
to 20 min long and was performed 3 times per week for 12 weeks (36 total
sessions). During the first week, participants were instructed and performed the
training at the Stress Rehabilitation Clinic; thereafter, continued training at
home. A psychologist contacted each participant by telephone or e-mail to
provide motivational comments and to ensure that there were no technical issues;
this took place once per week initially and at sparser time intervals thereafter.

Aerobic training
The aerobic training consisted of indoor cycling (spinning), which was conducted
in instructor-led groups at an individually chosen training centre within the
participant’s municipality. Training was conducted 3 times per week during the
12-week intervention period, for 36 total sessions. Each session lasted 40 min.
The patients used chest belt heart monitors to monitor the intensity of the
training and were instructed to attain a moderate-vigorous intensity, equal to 70
to 85% of their maximum age-adjusted heart rates. A physiotherapist used the
pulse data to provide weekly written feedback to patients about their training
intensity, as well as motivational comments.
Table 3

*Tasks Included in the Cognitive Training Program*

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Task</th>
<th>Description</th>
<th>Difficulty adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>Updating</td>
<td><strong>Letter Memory Running Span</strong> Report the four last items from a list of</td>
<td>Increasing length of letter sequence (low: 4-7 items;</td>
</tr>
<tr>
<td>Updating</td>
<td></td>
<td>sequentially presented letters in correct order.</td>
<td>medium: 6-11 items; high: 5-15 items)</td>
</tr>
<tr>
<td>Executive function</td>
<td>Updating</td>
<td><strong>Keep Track Task</strong> Mentally classify words according to semantic categories</td>
<td>Increasing number of categories (low: three; medium:</td>
</tr>
<tr>
<td>Updating</td>
<td></td>
<td>(e.g., clothes, animals, or sports) and continuously update the last</td>
<td>four; high: five)</td>
</tr>
<tr>
<td>Updating</td>
<td>Shifting</td>
<td><strong>Alternating Runs With Digits</strong> Classify digits (1-9, excluding 5) as</td>
<td>Non-adaptive: presented using predictable task cuing (i.e.,</td>
</tr>
<tr>
<td>Shifting</td>
<td></td>
<td>odd/even or lower/higher than five depending on the position in a square,</td>
<td>in a clockwise manner)</td>
</tr>
<tr>
<td>Shifting</td>
<td></td>
<td>using background colour as an additional cue.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Alternating Runs With Letters</strong> Classify letters (A, B, D, E, X, Y, U, or Z) as</td>
<td>Non-adaptive: presented using unpredictable task cuing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>beginning/end of the alphabet or vowel/consonant depending on the cue</td>
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<td></td>
<td></td>
<td>accompanying each trial (a blue square or a red circle).</td>
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</tr>
<tr>
<td>Short-term memory</td>
<td></td>
<td><strong>Visuospatial Span Task</strong> Recall a sequence of squares in correct order</td>
<td>Increasing of span level after two correct trials out of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>based on items presented in a 4 x 4 grid with the squares changing colour</td>
<td>three</td>
</tr>
<tr>
<td></td>
<td></td>
<td>one at a time from green to red.</td>
<td></td>
</tr>
<tr>
<td>Episodic memory</td>
<td>Three-Word-Associates Task</td>
<td><strong>Task</strong> Memorize 12 triplets of location, object, and colour; recall the</td>
<td>Decreasing presentation time (low: 8 s / triplet;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>object and colour when the location is given as a cue.</td>
<td>medium: 5 s.; high: 3 s)</td>
</tr>
</tbody>
</table>
Measures

Cognitive performance
A brief description of the tasks used to assess training-related effects on cognitive function is provided in Table 4, including the cognitive domain targeted by each task. For the purpose of assessing training-related gains for the cognitive training group, the tasks were also categorized as either trained, near transfer or far transfer tasks. At T1, all participants also completed SRB:1, a multiple-choice synonym test that assesses verbal ability (Dureman, Kebbon, & Österberg, 1971).

Subjective cognitive complaints
To assess subjective cognitive complaints, the 6-Item Questionnaire of Everyday Memory Problems (6-QEMP) and the Prospective and Retrospective Memory Questionnaire (PRMQ) were used. The 6-QEMP consists of six items rated on a 5-point Likert scale from 1 (never) to 5 (very often) for three items and from 1 (much better) to 5 (much worse) for three items. A five-item version of this questionnaire has previously been used to assess subjective cognitive complaints in patients with stress-related exhaustion (Öhman et al., 2007; Österberg et al., 2014). The PRMQ consists of 16 items – eight items each that target prospective and retrospective memory failures – rated on a 5-point Likert scale from 1 (never) to 5 (very often; Crawford, Smith, Maylor, Della Sala, & Logie, 2003). For both questionnaires, higher scores are indicative of more subjective cognitive complaints.

Psychological health
Level of burnout was assessed using the Shirom-Melamed Burnout Questionnaire (Melamed et al., 1992); this 22-item questionnaire was rated on a 7-point Likert scale from 1 (almost never) to 7 (almost always). HAD was used to assess depression and anxiety (Zigmond & Snaith, 1983). The questionnaire consists of 14 items (seven each that target anxiety and depression), and is rated on a 4-point Likert scale from 0 to 3. To assess fatigue, the Checklist Individual Strength was used (Beurskens et al., 2000). This questionnaire consists of 20 items rated on a 7-point Likert scale from 1 (yes, that is true) to 7 (no, that is not true). Higher score indicated more symptoms for all measures.
<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Task</th>
<th>Description</th>
<th>Transfer domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>Letter Memory</td>
<td>Report the four last items from a list of serially presented letters in correct order.</td>
<td>Trained</td>
</tr>
<tr>
<td></td>
<td>Running Span</td>
<td>Report whether a presented digit (1-9) matches the digit presented one, two or three steps prior.</td>
<td>Near transfer</td>
</tr>
<tr>
<td></td>
<td>n-back</td>
<td>eria memory</td>
<td>Digit Span Forward</td>
</tr>
<tr>
<td></td>
<td>Digit Span Backward</td>
<td>Repeat a sequence of digits of increasing length in reverse order.</td>
<td>Near transfer</td>
</tr>
<tr>
<td>Short-term and working memory</td>
<td>Letter-Number Sequencing</td>
<td>Repeat a sequence of digits and letters of increasing length, with digits ordered from lowest to highest and letters ordered alphabetically.</td>
<td>Near transfer</td>
</tr>
<tr>
<td></td>
<td>Recall of Concrete Nouns</td>
<td>Free recall of 18 nouns across four presentations that are administered according to the selective reminding procedure (Buschke, 1973).</td>
<td>Near transfer</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>Digit Symbol</td>
<td>Transcribe as many symbols as possible according to a coding key during a 90 s trial.</td>
<td>Far transfer</td>
</tr>
<tr>
<td></td>
<td>Raven’s Advanced Progressive Matrices</td>
<td>Solve 3 x 3 pattern matrices in which one part of the pattern is missing.</td>
<td>Far transfer</td>
</tr>
</tbody>
</table>
**Work ability**

Work ability was assessed using the 10-item Work Ability Index (de Zwart, Frings-Dresen, & van Duivenbooden, 2002). The total scores ranged from 7 to 49, with higher values indicating better work ability. Additionally, we used sick-leave registry data from the Swedish Social Insurance Agency. Degree of sick-leave was indicated as a percentage of ordinary working time (0%, 25%, 50%, 75% or 100%).

**Aerobic capacity**

A submaximal test on a calibrated cycle ergometer was used to test aerobic capacity, with a pedalling frequency of 50 revolutions/min. The resistance was adjusted to reach a steady-state heart rate of at least 120 beats/min. Maximal oxygen uptake was estimated using Åstrands nomogram (Åstrand & Ryhming, 1954), adjusted for sex, age, body weight, workload and steady state heart rate (the mean heart rate across the last 3 min of the test).

**Brain imaging**

Functional magnetic resonance imaging (fMRI) is a neuroimaging technique for measuring haemodynamic changes associated with alterations in brain activity (see Huettel, Song, & McCarthy, 2009; Logothetis, 2008 for reviews). Because active neurons require energy in the form of oxygen and glucose, increased neural activation is supported by increased blood flow regionally, and this change in blood flow is measured by the blood-oxygen-level-dependent (BOLD) signal. Thus, the BOLD signal provides an indirect estimation of neural activity in a region of the brain over time. Of importance for the BOLD signal is the fact that the haemoglobin molecule’s magnetic properties differ depending on whether it is carrying oxygen; the MR signal of highly oxygenated blood is stronger than that of deoxygenated blood. The change in the BOLD signal following neural activity is known as the hemodynamic response, and it shows a short onset delay of 1 to 2 s. As a response to the increased metabolic demands of active neurons, cerebral blood flow to the active region increases, causing the BOLD response to increase until it reaches a maximum at 4 to 6 sec following the event; after that point, it slowly returns to baseline.

Study II’s methods for neuroimaging image acquisition, preprocessing and data analysis will be outlined in condensed form (see the full article for details). Briefly, the participants performed the $n$-back task during fMRI scanning. This is a measure of the executive function updating of working memory representations (hereby referred to as working memory updating), in other words, the ability to continuously monitor and update the content of working memory. Three task-load conditions were administered: 1-back, 2-back, and 3-back. For each condition, the participants judged whether the presented digit matched the one
that appeared one, two or three stimuli previously. Twenty-seven sequences (nine of each condition) were presented; each sequence consisted of 10 digits, each of which was presented for 1.5 s, with a cross presented for 0.5 s between each item. A blocked design was used to compare the neural activation during the more demanding task blocks (2-back and 3-back) with that of the less taxing condition (1-back). Thus, the 2-back and 3-back condition were used as indicators of neural activation during increasing working memory task load, and the 1-back condition (a low task load) served as a baseline.

The data were collected using a GE 3T scanner and analysed using a standard general linear model in SPM12. Prior to analysis, a number of pre-processing steps were completed, to ensure the quality of the data before statistical analyses and to remove artefacts and unwanted noise. More specifically, the images were aligned to correct for the time difference between the obtained slices within each volume (slice timing) and corrected for head movement (realigned and unwarped). Structural images were obtained and used to create a sample-specific group template (Ashburner, 2007) and the functional data were mapped onto the anatomical images and normalized to MNI space (coregistration and normalization). Finally, the data were spatially smoothed, i.e. blurring the data by spreading the intensity of each voxel across nearby voxels, to increase the signal-to-noise ratio (smoothing). The first-level analysis contrasted [2-back – 1-back] and [3-back – 1-back] for each participant and time-point. The individual contrasts were then included in the second-level random-effects analyses, which focused on burnout and related neural processing, as well as training-related changes in neural response.

Ethical considerations
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Umeå Regional Ethical Review Board (Dnr 2010-53-31). All participants received verbal and written information about the study, including a declaration that participation was voluntary and could be terminated at any time and without consequences. All participants provided written consent before inclusion. Personal information was treated confidentially, and each participant was assigned an individual code that can only be back-traced with the use of a coding key, that only authorized personnel can access. The data collected within the trial were used for research purposes only. Financial compensation of 600 SEK was provided to each study participant.
The empirical studies

Study I: Effects of a process-based cognitive training intervention for patients with stress-related exhaustion

Aims
The aim of Study I was to evaluate the effects of a process-based cognitive training intervention, offered as an addition to a multimodal stress rehabilitation program, on trained and non-trained cognitive tasks, subjective cognitive complaints and burnout levels.

Methods
Participants in this study were 59 patients with ED, 27 in the cognitive training group and 32 from the control group. The analysis was conducted by per protocol, with only those patients who completed the 12-week intervention period, as well as the T1- and T2-assessments, included. To evaluate training-related effects on overall cognitive function, we used a 2 (Group) x 2 (Time) mixed MANCOVA, including all nine transfer tasks, and controlled for age, sex, and verbal ability. This was followed by univariate 2 (Group) x 2 (Time) mixed ANCOVA’s for each cognitive test and for the measures of subjective cognitive complaints, using the same set of covariates. For the analysis of change in burnout following the intervention period, the same analytical approach was used but without covariates.

Findings and conclusions
The results from Study I revealed a large training-related improvement on the trained updating task, Letter Memory Running Span. The across-session change in overall cognitive performance, as measured by the nine transfer tasks, differed significantly between the groups. Follow-up analyses of each cognitive test revealed significant near transfer to updating (3-back) and episodic memory (Recall of Concrete Nouns). A significant interaction effect was also found for reasoning ability (Raven’s Matrices); however, this was largely due to decreased performance in the control group. Figure 4 shows the effect sizes (expressed in Cohen’s d) for all the cognitive tasks.
Figure 4. Effect sizes in Cohen’s $d$ for all cognitive tests, based on the pretest-to-posttest change for the training group and the control group respectively. Positive values represent improvements.

* $p < .05$. ** $p < .01$. *** $p < .001$.

The cognitive training group further showed a greater reduction on one measure of subjective memory complaints (the 6-QEMP, see Figure 5) and a greater improvement in burnout symptoms, compared to the control group.

Figure 5. Effect sizes in Cohen’s $d$ for the measures of subjective cognitive complaints, based on the pretest-to-posttest change for the training group and the control group respectively. Positive values represent improvements. 6-QEMP = 6-item Questionnaire of Everyday Memory Problems; PRMQ = Prospective and Retrospective Memory Questionnaire.

* $p < .05$. 
In summary, the results from Study I suggest that process-based cognitive training can lead to substantial improvements on trained tasks among patients with ED. Generalization of training effects was selective and confined to tasks similar to the trained tasks (i.e. updating and episodic memory). Partial support was given for a decrease in subjective cognitive complaints following cognitive training. Importantly, cognitive training also led to a greater reduction in burnout levels compared to MMR alone. Thus, despite the limited range of observed cognitive transfer, training effects seemed generalizable to aspects of patients’ everyday functioning.

**Study II: Neural activation in stress-related exhaustion: Cross-sectional observations and interventional effects**

**Aims**
The primary aim of Study II was to investigate the association between burnout and functional neural response during working memory updating in patients diagnosed with ED. A secondary aim was to extend the results from Study I by investigating the neural mechanisms of cognitive training in the context of stress rehabilitation.

**Methods**
The participants in Study II consisted of 55 patients who had complete fMRI and behavioural data at T1. Twenty-seven patients in the fMRI-sample completed the intervention and participated in the T2 assessment: 11 patients in the control group, 10 in the cognitive training group, and six in the aerobic training group.

**Behavioural data analysis**
Pearson correlation was used to investigate the association between burnout and cognitive test performance across all participants at T1. To investigate training-related changes in cognitive performance, 2 (Group) x 2 (Time) mixed ANOVAS’s were performed.

**Neuroimaging data analysis**
For the analysis of burnout and related neural processing during working memory updating, we investigated the association between burnout score at T1 (n = 55) and functional neural response during each of the 2-back and 3-back condition (with the 1-back condition as a baseline), at the whole-brain level. Next, we investigated whether a change in burnout following the rehabilitation period was associated with a change in functional neural response, based on data computed from the local maxima of the brain regions which showed a significant association with burnout at T1. This analysis was conducted across all 27 patients.
who had participated in the fMRI-scanning at T2, controlling for depressive symptoms and intervention group.

The analysis of training-related changes in functional neural response was conducted using an exploratory approach due to the small number of participants in each group (cognitive training: \( n = 10 \); control: \( n = 11 \)). First, brain regions showing a significant T1-to-T2 change in the cognitive training group were identified at a whole brain level; this was done separately for the 2-back and 3-back condition. Second, data computed from the local maxima in regions showing significant T1-to-T2 changes in the cognitive training group were analysed (relative to the control group), using 2 (Group) x 2 (Time) mixed ANOVA's. A training-related effect was defined as a region showing comparable levels of activation at T1, in conjunction with a more pronounced T1-to-T2 change in activation for the cognitive training group, relative to the control group.

**Findings and conclusions**

*Functional brain responses in relation to burnout severity*

At baseline, burnout score was positively associated with neural activation in several regions, including the rostral parts of the left superior frontal gyrus (BA 10; Figure 6a), the right and left PPC (BA 39 and BA 40, respectively; Figure 6b), and the striatum. These associations were most evident at moderate cognitive load (i.e., the 2-back condition). A positive association was found between change in burnout following stress rehabilitation and change in neural activation in the striatum in the 2-back condition (Fig 6c). No significant association between burnout level and cognitive test performance was found.
Figure 6. Selected regions showing a significant association with burnout score for 2-back relative 1-back depicted in red. Working memory network identified at baseline depicted in light grey. Burnout was positively correlated with neural activation in (a) the left superior frontal gyrus and (b) the right angular gyrus. Change in burnout following the rehabilitation period was positively associated with change in neural activation in (c) the left putamen.

**p < .01. ***p < .001.
These findings suggest that, for patients with ED, neural activation during working memory updating is modulated by burnout severity. The fact that burnout level was positively associated with neural activation, but unrelated to task performance, indicates that patients with high levels of burnout may need to recruit additional neural resources to uphold the same level of task performance as patients with lower burnout levels.

Changes in functional brain responses following cognitive training
Cognitive training yielded robust improvements on the trained updating task, (Letter Memory Running Span), outside of the scanner. Thus, the training-related effect that was demonstrated in Study I was confirmed also for the subsample of participants in Study II. However, in contrast to Study I, no near transfer to the n-back task (used as the in-scanner task in Study II), was found in this subsample of participants. Nevertheless, the analysis of the neuroimaging data revealed training-related increases in neural activation at high cognitive load (i.e., 3-back) across regions that are important for working memory updating, including the striatum (Figure 7), the thalamus and frontal regions.

Figure 7. A training-related increase in activation was found in the left putamen/pallidum in the 3-back condition.
Study III: Rehabilitation for improved cognition in stress-related exhaustion disorder: RECO – a randomized clinical trial

**Aims**
The aim of Study III was to investigate the long-term effects of cognitive training and aerobic training for patients with ED on (1) cognitive function; (2) psychological health, and (3) work ability. Thus, in Study III, we sought to explore whether addressing cognitive impairments in stress rehabilitation could have sustained effects on cognition as well as on ED recovery.

**Methods**
Study III’s participants consisted of 132 patients who participated in the T1 assessment and who were subsequently randomly assigned to one of the three study conditions. The analysis was conducted using the intention-to-treat principle, and included all available data across the three intervention groups and time-points. The statistical analysis was conducted using linear mixed-effects models (for a detailed description of the analytical approach, please refer to the original article). In contrast to Study I, in which training-related effects on cognitive test performance were investigated for each task separately, in Study III, we investigated cognitive functioning more broadly by creating composite measures for each targeted cognitive domain (see Table 4). Additionally, a domain-general composite was computed, to represent the mean of all transfer tasks (hereby referred to as the global cognitive score). Time and group membership was included in the model as binary coded variables, using the pre-intervention assessment and control group, respectively, as references. When evaluating long-term training-related effects, we were primarily interested in the Group x Time interaction from T1 to T3, which represents the difference in change from pre-intervention to 1-year follow-up for the cognitive training and aerobic training groups, relative to the control group. Standardized effect sizes (Cohen’s $d$) were calculated as the difference between intervention group and control group in terms of T1-to-T3 change, divided by the baseline standard deviation. For analysis of sick-leave data, we used a non-parametric design for repeated measures.

**Findings and conclusions**
The cognitive training group showed a long-term (1 year post intervention) training-related improvement on the global cognitive score (Figure 8a). The effect size suggested a small improvement (Cohen’s $d = 0.35$). This was paralleled by a large improvement on the trained updating task (Cohen’s $d = 0.87$; Figure 8c). Notably, the long-term training-related effect on the global cognitive score
occurred in the absence of any significant domain-specific cognitive changes. This suggests that the training-related improvement in cognitive functioning for the cognitive training group was not driven by a specific cognitive domain; rather, it reflected a small and general improvement across several cognitive tasks.

Figure 8. Changes across time for each group in (a) performance on the global cognitive score, based on the mean z-score of nine cognitive tests covering the domains of executive function, short-term and working memory, episodic memory, processing speed, and reasoning ability; (b) performance in episodic memory; (c) performance on the cognitive training criterion updating task; and (d) aerobic capacity. T1: pre intervention; T2: post intervention; T3: 1-year follow-up; VO_{2max}: maximal oxygen uptake.
For aerobic training, post intervention improvements were observed for aerobic capacity (as an indicator of training gains) and episodic memory (see Eskilsson, Järnholm, Gavelin, Neely, & Boraxbekk, 2017 for the primary report of the effects of aerobic training post intervention), however, no long-term effects were observed (Figure 8b and 8d). Authors of previous studies have associated improvements in episodic memory following physical exercise with improved cardiovascular fitness levels, both immediately after training (Hötting, Reich, et al., 2012) and at long-term follow-up (Hötting, Schauenburg, & Röder, 2012). Thus, long-term effects on episodic memory following aerobic exercise may depend on whether aerobic fitness levels are maintained or not. To further explore the relationship between aerobic capacity and episodic memory performance during the follow-up period, a post hoc analysis was conducted to investigate the relationship between change in aerobic capacity and episodic memory performance between T2 and T3 for the aerobic training group. Although a moderate positive relationship was observed between the variables, the analysis was restricted to 15 individuals and the effect did not reach statistical significance ($r = 0.49$, $p = .06$). Taken together, the results tentatively suggest that maintained exercise levels may be important to reach long-term effects on cognition following aerobic training.

For psychological health and work ability, general improvements were observed across time for all participants, with no differences between interventional groups. The distribution of sick-leave levels is displayed in Figure 9. In a post hoc analysis including only those patients who had completed the intervention period (i.e., per protocol), a greater decrease in burnout symptoms was observed for the cognitive training group relative to the control group at 1-year follow-up (Cohen’s $d = 0.51$).

**Figure 9.** The distribution of sick-leave levels for each group at the different time-points. T1: pre intervention; T2: post intervention; T3: 1-year follow-up.
In summary, the results from Study III suggest that cognitive training was successful in giving long-term effects on cognitive performance, as indicated by the global cognitive score, 1 year after the intervention. Aerobic training yielded improvements in episodic memory immediately following the intervention, but no long-term effect. For psychological health and work ability, no additional benefits were seen for cognitive or aerobic training, relative to MMR alone. However, extending the results from Study I, the results from Study III showed that cognitive training was effective in giving sustained improvements in burnout symptoms when restricting the analysis to those patients who completed the intervention.
Discussion

The overall aim of this thesis was to investigate the efficacy of interventions that target cognitive impairments in the context of stress rehabilitation. More specifically, the effects of cognitive training and aerobic training, offered as additions to a multimodal stress rehabilitation program for patients with clinical ED diagnosis, were evaluated with respect to cognitive performance as well as variables related to ED recovery. Further aims were to explore the neural correlates of ED and whether cognitive training leads to changes in functional neural response for this patient group. In the following section, I will start with synthesizing the main findings of the thesis, structured around the main outcomes of cognition, brain imaging, and psychological health and work ability. Thereafter, I will discuss the issue of adherence and the clinical implications of the findings and, finally, address the primary limitations of the thesis and make some suggestions for future research.

Cognition

Range of transfer following cognitive training

Training task gains were assessed using the criterion updating task (Letter Memory Running Span), and the results showed a large training-related gain immediately (Study I) and 1-year (Study III) after the intervention. These findings are in line with previous research on healthy adults (Brehmer et al., 2012; Dahlin, Nyberg, et al., 2008; Sandberg & Neely, 2016; Sandberg et al., 2014) and constitute an important starting point for this discussion, as they show that executive function task performance can be improved with training also for patients with ED and that these effects can be sustained over time.

In Study I, a detailed investigation of the range of transfer to nine different cognitive tasks, with varying degrees of overlap with the tasks included in the training program, was conducted. Overall, transfer effects were limited to the very near (i.e., updating and episodic memory) and the pattern of transfer in line with previous studies using similar training regimens (Dahlin, Nyberg, et al., 2008; Sandberg et al., 2014). The results from Study I thus concur with previous findings in the process-based cognitive training literature, showing that generalizations of training effects are generally narrow and related to tasks similar to those trained (e.g., Melby-Lervag et al., 2016; Soveri et al., 2017). This was further supported by the lack of domain specific transfer when effects were aggregated to the targeted cognitive domains (Study III). Contrasting these findings, however, a small improvement was observed following cognitive training across all transfer tasks, as reflected by the global cognitive score,
immediately after training and at long-term follow-up. The absence of domain-specific transfer suggests that the observed improvement on the global cognitive score was not driven by any specific cognitive domain, but instead reflects a small improvement across several different cognitive tasks. These results are intriguing, and I will now elaborate on some possible explanations for this.

**Cognitive training strengthens cognitive control processes?**
To better understand the training-related improvement on the global cognitive score, one may need to broaden the perspective from viewing the cognitive training program as targeting specific narrow cognitive abilities, and instead view it more broadly as cognitive control training (e.g., Koster et al., 2017). This view may be particularly relevant because it has been acknowledged that cognitive impairments in psychopathology are often seen across several different executive function and working memory tasks, pointing towards a general and potentially transdiagnostic deficit in cognitive control processes (Snyder et al., 2015). Within the unity/diversity framework, executive functions are conceptualized as three separate executive processes (updating, inhibition and shifting), as well as a common executive function ability, which spans across all three processes and relates to the overall ability to maintain task goals and use this information to provide top-down control of task-relevant responses (Friedman & Miyake, 2017; Miyake et al., 2000). These mental processes can be collectively seen as synonymous to the construct of cognitive control (J. D. Cohen, 2017). For psychopathological conditions, it has been suggested that deficits in executive functions may primarily be associated with the common factor (Snyder et al., 2015) and the impairments seen across several executive function and working memory tasks in stress-related exhaustion suggest that this might also be the case for this patient group. Therefore, training executive functions more broadly may be important. In our training program, all tasks targeted aspects of cognitive control, through the explicit training of executive function and short-term memory, as well as implicit requirements of sustained attention and high demands placed on working memory by several of the tasks. Importantly also, the transfer battery was primarily designed to assess cognitive functions sensitive to long-term stress, and six of the nine transfer tasks targeted executive function and short-term/working memory (Table 4). Taken together, our findings may suggest that by using a multifactorial cognitive training program with an emphasis on executive function and working memory, the ability to exert cognitive control during task performance is strengthened, which in turn is reflected by small gains across several tasks reliant on cognitive control processes.

**Cognitive training reduces mental fatigue?**
When evaluating transfer effects following cognitive training, it has been argued that the pattern of transfer needs to be theoretically plausible, with respect to
presence and absence of transfer, to support the assumption that any observed changes in cognitive performance are de facto related to improvements in the targeted cognitive abilities and not to any other confounding factors (Noack et al., 2014). The slim task- and domain-specific transfer effects observed in Study I and Study III of this thesis, in conjunction with the general improvement on the global cognitive score, imply that one cannot exclude the possibility of more generic mechanisms underlying the observed training-related cognitive improvement. These could be related to motivation or expectancy effects, an important issue which will be addressed in the section relating to methodological limitations. However, they could also be related to cognitive but nonspecific factors, such as a reduction in mental fatigue.

Mental fatigue is characterized by mental exhaustion and increased time needed for recovery following sustained cognitive task performance (Johansson, Berglund, & Ronnback, 2009), specifically characterized by difficulties in initiating and sustaining performance on tasks requiring self-motivation (Chaudhuri & Behan, 2000). The mechanisms of mental fatigue are not fully understood, but it has been proposed that the concept is interlinked with motivational processes and that investment of effort in a task is based on an evaluation of the energy demands (or costs) associated with task performance, weighted against the expected rewards of successful task completion (Boksem & Tops, 2008; Shenhav et al., 2017). When the costs exceed potential benefits, fatigue signals that conservation of energy resources and/or alternative behavioural strategies should be sought (Boksem & Tops, 2008). Overriding this signal may in turn lead to more chronic mental fatigue and impaired task performance (Boksem & Tops, 2008; Ishii, Tanaka, & Watanabe, 2014). Prior research has shown that patients with stress-related exhaustion experience high levels of effort being placed into cognitive tasks (Oosterholt et al., 2014; van Dam et al., 2011), as well as increased mental fatigue during and after neuropsychological testing (Krabbe et al., 2017), suggesting that mental fatigue may be a central characteristic of stress-related cognitive deficits. Furthermore, it has been proposed that cognitive performance during prolonged test sessions may be negatively influenced by fatigue (Jonsdottir et al., 2013). With this in mind, it is possible that the small improvement favouring cognitive training seen across several tasks during the 2-h test session may reflect improved cognitive sustainability. Importantly, improved cognitive control and reduced mental fatigue as possible mechanisms for improved cognitive performance following cognitive training are not mutually exclusive, because cognitive control inherently requires mental effort (Shenhav et al., 2017). Thus, improved cognitive control following cognitive training could lead to less mental effort being required to perform cognitively challenging tasks, in turn reducing the impact of mental fatigue on task performance.
In this context, it is interesting to consider that part of treatment in stress-related exhaustion often consists of gradual exposure to activities that may be associated with stress and fatigue reactions, while at the same time finding a balance between participating in these activities and restitution (Almén, 2017; Blonk, Brenninkmeijer, Lagerveld, & Houtman, 2006; Gerber, Jonsdottir, Arvidson, Lindwall, & Lindegard, 2015). Although somewhat speculative, one could apply the same line of reasoning to rehabilitation of cognitive impairments and view the cognitive training program as gradual exposure to cognitive tasks. In a qualitative study exploring patients’ experiences of the rehabilitative process within the RECO project, patients described the cognitive training as fatiguing and difficult, but also how it gradually became easier and that it was possible to use the tools learned in the MMR and take regular breaks to be able to conduct the tasks (Eskilsson et al., 2018). Thus, perhaps more focus should be placed on explicitly conducting cognitive training in conjunction with recuperating activities, to find balance between activity and restitution also in this context. However, this also raises the question of whether the positive effects observed in cognitive performance are specifically related to the cognitive training regimen used in our study (e.g., through improved cognitive control) or if other mentally challenging activities in conjunction with recuperating behaviours also could yield positive effects for this patient group.

**Effects of cognitive training on subjective cognitive complaints**

The results from Study I showed that cognitive training led to a moderate improvement in self-reported memory failures, as measured by the 6-QEMP, a measure which has previously shown to be sensitive to cognitive failures in stress-related exhaustion (Öhman et al., 2007; Österberg et al., 2014). In contrast, no significant effect was found for the PRMQ, either on the prospective or the retrospective subscale. We used a slightly modified version of the 6-QEMP, in which two of the items focused on present memory abilities in comparison with (1) before the stress-related illness and; (2) when the individual had the most problems with the stress-related illness. Thus, this questionnaire was potentially more specific than the PRMQ, in that perceived memory abilities were related to the course of illness. Elaborating a bit on the results of the PRMQ, it is interesting to note that, although non-significant, the effect size on the prospective subscale nevertheless suggested a small-to-moderate within-group improvement (Cohen’s $d = 0.46$) for the cognitive training group, whereas the effect size on the retrospective subscale was negligible (Cohen’s $d = 0.15$). Prospective memory may be of particular relevance for this patient group, because authors of previous studies have indicated that one of the most pronounced differences in cognitive performance between patients with stress-related exhaustion and healthy controls can be found on prospective memory tasks (Eskildsen et al., 2015; Öhman et al., 2007). The ability to remember an intended future action is related
to cognitive control processes (McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999) and the differential effect sizes seen for prospective and retrospective memory thus tentatively align with the interpretation that the training-related effect seen on the global cognitive score reflects improved cognitive control. Taken together, our results lend partial support for cognitive training leading to a reduction in subjective cognitive complaints.

**Long-term effects of aerobic training on cognitive function**

The results from Study III showed no significant long-term effects on cognitive performance following the aerobic training intervention. Thus, although an improvement in episodic memory was observed immediately after the intervention (Eskilsson et al., 2017), no difference was seen between the aerobic training group and the control group at 1-year follow-up. The malleability of memory functions following physical exercise has received much attention in the literature, due to converging evidence of exercise-induced neuroplasticity in the hippocampus (Erickson et al., 2011; Pereira et al., 2007). Even though much of the research in the field has focused on children and older adults (see Prakash, Voss, Erickson, & Kramer, 2015 for a review), middle-aged adults have also demonstrated improved episodic memory performance following physical exercise (Hötting, Reich, et al., 2012). The results from Eskilsson et al. (2017) thus extended the previous literature by suggesting that aerobic training can also facilitate episodic memory for patients with ED, and part of the aim of Study III in this thesis was to evaluate the long-term stability of these gains. To date, long-term follow-ups of aerobic exercise interventions have been lacking in the literature, however, following up on their initial study, Hötting, Schauenburg, et al. (2012) found that improvements in episodic memory following two different exercise interventions were sustained for those participants who had maintained their aerobic fitness levels at 1-year follow-up. In Study III, the aerobic capacity of the aerobic training group participants had returned to baseline levels at T3, and in conjunction with the moderate (albeit non-significant) positive relationship between change in aerobic capacity and episodic memory performance during the follow-up interval, our results tentatively suggest that sustained effects on episodic memory following aerobic training may be dependent on maintained aerobic fitness levels also for patients with ED. However, it should be noted that the non-significant long-term effect on episodic memory was partly due to an increase in performance for the control group during the follow-up interval (Figure 8b), making the results somewhat inconclusive, particularly because the longitudinal course of stress-related cognitive deficits in relation to ED recovery is not well established.
**Brain imaging**

**Associations between functional neural response and burnout severity**

The main finding of Study II was that level of burnout was positively associated with neural activation across several regions, including the rostral PFC, the PPC and the striatum, regions that are all involved in working memory processing (Eriksson et al., 2015; Owen et al., 2005). Furthermore, the striatal activation changed as a function of improved levels of burnout following stress rehabilitation. The striatum has been proposed to serve as a gating mechanism, regulating the updating of working memory representations in the PFC (O’Reilly, 2006) and the frontostriatal circuitry thus serves an important role in the allocation of cognitive control. As was described in the introduction, authors of previous neuroimaging studies have shown reduced cortical thickness and volume reductions in the PFC and the striatum in patients with stress-related exhaustion (Blix et al., 2013; Savic, 2015), and that structural changes in these regions had normalized at long-term follow-up (Savic et al., 2017). The results from Study II thus extend previous findings in the field with the use of a functional paradigm, suggesting that frontostriatal engagement during working memory processing is modulated by burnout severity, and that the striatum in particular may be responsive to stress recovery. This corroborates the notion that cognitive control deficits may be a key characteristic of cognitive dysfunction in ED, putatively linking these impairments to functional alterations in the frontostriatal circuitry and potentially also the frontoparietal network.

**Neural correlates of ED in relation to a high effort approach**

Based on the results from Sandström et al. (2012), in which lower prefrontal activation during working memory processing was observed in patients with stress-related exhaustion, we predicted in Study II that higher levels of burnout would be associated with decreased activation in the PFC; however, the opposite pattern was observed. The fact that level of burnout was positively associated with neural activation in working memory-related regions, but unrelated to task performance, could be interpreted as a compensatory neural engagement, in which patients with high levels of burnout need to recruit additional cognitive resources to uphold similar levels of task performance as patients with lower levels. This is particularly interesting in light of the fact that it has been proposed that patients with stress-related exhaustion may adopt a high effort approach, striving to maintain cognitive performance at the cost of increased effort and mental fatigue (Krabbe et al., 2017; Oosterholt et al., 2014; van Dam, Keijsers, Eling, & Becker, 2015). Dysfunction in the striatothalamic-cortical loops connecting the striatum with the PFC has been proposed as an underlying mechanism for fatigue in neurological disorders (Chaudhuri & Behan, 2000),
and, more specifically, increased neural activity in the PFC, the striatum and the superior parietal cortex has been interpreted as a neural correlate of increased cerebral effort and mental fatigue in patients with traumatic brain injury (Kohl, Wylie, Genova, Hillary, & Deluca, 2009). Taken together, the positive association seen between level of burnout and neural activation in the PFC, the PPC and the striatum in Study II may reflect a cerebral recruitment serving to uphold working memory task performance (i.e., a high effort approach), which in turn may be associated with increased mental fatigue. In this context, it is interesting to note that patients with stress-related exhaustion often report substantial subjective cognitive impairments in their everyday lives, as well as high levels of effort and mental fatigue during cognitive tasks, despite generally showing mild-to-moderate impairments in cognitive tests (Eskildsen et al., 2015; Krabbe et al., 2017; Oosterholt et al., 2014; van Dam et al., 2011). Integrating this clinical observation with the results from Study II, it is possible that patients with ED are able to compensate for cognitive control deficits for a limited period of time, when external motivation is high (e.g., in cognitive testing), whereas this strategy may not be viable in everyday life, usually requiring more sustained cognitive performance and self-motivation.

**Neural correlates of cognitive training**

To gain further insights into the mechanisms underlying the training-related effects observed in Study I, in Study II we investigated whether cognitive training induced changes in functional neural response. Results showed that cognitive training was associated with increased neural activation in task-relevant regions, including frontal regions, the striatum and the thalamus. An important caveat when discussing these results is the fact that our sample was small and the analytical approach exploratory and that no behavioural transfer was observed on the in-scanner task. Thus, these results should be interpreted with caution. Nevertheless, the fact that we observed increased neural activation in the striatum deserves consideration, because the striatum has been proposed as central for achieving transfer within the updating domain (Dahlin, Neely, et al., 2008; Salminen et al., 2016), with training-induced changes in the dopaminergic system as a proposed mechanism (Bäckman & Nyberg, 2013; Bäckman et al., 2011). If stress-related exhaustion is de facto associated with frontostriatal functional alterations, the possibility of strengthening this network through targeted training is encouraging. Additionally, it is interesting to note that the positive association between burnout and neural activation in the baseline analysis was most evident in the 2-back condition, whereas cognitive training impacted functional neural response only in the 3-back condition. The responsivity to increasing task demands in the working memory network has been suggested to be an important determinant of working memory performance (Nagel et al., 2011; Nyberg, Dahlin, Neely, & Backman, 2009), and one possible
interpretation of our findings is that the 2-back condition was associated with effortful working memory processing at baseline, whereas following the cognitive training intervention, increasing effort was placed in the 3-back condition; thus reflecting a shift in the allocation of cognitive resources from moderate to high task load. Integrating the results from studies I-III, albeit somewhat speculative, our findings may imply that ED is related to a high effort approach and that cognitive training leads to improved cognitive control and better allocation of cognitive resources, which in turn is reflected by a small improvement across several cognitive tasks.

Psychological health and work ability

When adding elements to stress rehabilitation, the overarching question is whether these additional rehabilitative components give rise to further benefits on the endpoint outcomes of the treatment. Therefore, in Study III we sought to explore the long-term effects of cognitive and aerobic training not only on cognitive performance, but also on variables related to ED recovery, more specifically psychological health and work ability.

The results from the intention-to-treat analysis in Study III showed no additional benefits from cognitive or aerobic training on psychological health, when compared to stress rehabilitation alone. Instead, all patients showed reduced symptoms of burnout, depression, anxiety and fatigue across the course of treatment and the follow-up period. Previous interventional studies in this patient group concur with our results; that is, they reported a general improvement across time but no differences in treatment effects between interventions (e.g., Blonk et al., 2006; de Vente, Kamphuis, Emmelkamp, & Blonk, 2008; Stenlund et al., 2009) and the specific components of rehabilitation that are efficacious in treating stress-related exhaustion are not well-established. With this in mind, the fact that cognitive training was successful in giving additional improvements in burnout symptoms, albeit only when analysed per protocol, is encouraging and it is interesting to speculate about the possible mechanisms of this.

Executive functions are crucial for several aspects of everyday life (Diamond, 2013), and poor executive functioning can influence all stages of the stress process (Williams, Suchy, & Rau, 2009). Difficulties with planning, organizing and flexibly adapting to everyday life situations could increase the risk of stress exposure and lead to less efficient coping. As was described in the introduction, brain models on stress highlight that the influence of stress on several brain regions can lead to a vicious circle, in which initial stress leads to more stress due to reduced top-down control and increased emotional and habitual responses (Arnsten et al., 2015). The ability to handle a threat at hand in a rapid manner
may be adaptive in some situations, but many stressful situations that we encounter today (e.g., in the workplace) require higher level cognitive processing. As suggested by the results from Study II, this negative spiral may be additionally reinforced in patients with ED by their attempts to compensate for cognitive deficits through adopting a high effort approach. Thus, improved cognitive control may help break this vicious circle by enhancing coping efficiency and reducing the need for compensatory mental effort. Another possibility is that improved cognitive control reduces burnout levels through improved ability to regulate stress reactions. The importance of cognitive control in emotional regulation is increasingly being highlighted (Ochsner, Silvers, & Buhle, 2012) and several emotional regulatory strategies such as problem solving and reappraisal rely on cognitive processes. Some indications exist that process-based cognitive training can influence emotional regulatory processes, using emotional (Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013) and non-emotional (N. Cohen et al., 2016) training task material. That said, the long-term improvement in burnout symptoms observed in Study III was the result of a post hoc analysis on a secondary outcome measure, suggesting some caution is warranted when interpreting these results.

The fact that aerobic exercise did not lead to more pronounced effects on the psychological variables is perhaps somewhat surprising, given that engagement in physical activity has been associated with lower levels of mental health problems (Jonsdottir, Rodjer, Hadzibajramovic, Borjesson, & Ahlborg, 2010), including burnout (see Naczenski, Vries, Hooff, & Kompier, 2017 for a review). However, it could be speculated that the relatively brief intervention was not sufficient in giving lasting improvements on the psychological variables, especially when compared to the fairly extensive stress rehabilitation program serving as the control condition. Additionally, the fact that no consideration was made with respect to baseline physical activity level of participants could be viewed as a potential confounder. It has previously been shown that it is possible to increase physical activity levels within the context of MMR using tailored advice on physical activity (Gerber et al., 2015) and that this was associated with a greater improvement in burnout symptoms at long-term follow-up for initially physically inactive patients who complied with the recommendations (Lindegård et al., 2015). However, it was also noted that patients had difficulties maintaining exercise levels across the study period (Gerber et al., 2015). Taken together, perhaps more individualized aerobic training approaches and support for achieving long-term behavioural changes, such as adopting a more physically active lifestyle, may be required to gain additional benefits on psychological health in this patient group.

The results from Study III showed no additional benefits of the added interventions on work ability, either when assessed through sick-leave levels or
through self-reporting. The process of returning to work after sick-leave is a multifactorial concept, involving individual and work-related factors, as well as factors relating to the social and healthcare system (Andersen, Nielsen, & Brinkmann, 2012; Blank, Peters, Pickvance, Wilford, & MacDonald, 2008). Additionally, workplace involvement has been found to be a key interventional element in the rehabilitation process to promote return-to-work (Cullen et al., 2018). Therefore, it is perhaps not surprising that no additional effects on work ability were found from cognitive or aerobic training, since none of the interventions were directed at the workplace. In this context, it is important to take into consideration the fact that the extent to which stress-related cognitive deficits influence work ability is not well established. The idea that they would do so may seem intuitive, as the demands of cognitive skills are extensive in many work situations today. However, work ability is a complex construct and it remains unclear whether the relatively moderate impairments associated with stress-related exhaustion de facto have an effect on work ability, particularly so when this is operationalized as degree of sick leave. It is possible that cognitive impairments associated with ED primarily influence on-the-job productivity or, in line with the high effort approach, that they require increased levels of effort being placed into work tasks. Therefore, cognitive impairments in the work context might be better addressed through adjustments at the workplace, aiming to reduce the negative impact of cognitive deficits, such as support in structuring, planning and prioritizing between work tasks, focusing on one task at a time, and finding an appropriate balance between activity and restitution during the work day (Karlsson, Classon, & Rönnberg, 2014).

**Adherence to treatment**

One of the primary limitations of the studies included in this thesis is undoubtedly the large amount of dropouts within the RECO project. Before discussing the issue of adherence to treatment, it should be noted that a large amount of dropouts was seen also in the control group, suggesting that discontinued study participation was not only related to the added interventions per se, but also to elements of the study design. This will be discussed in the section related to methodological considerations. However, several patients had difficulties adhering to training, resulting in discontinued study participation, as well as moderate attendance rates for those patients who completed the aerobic training intervention¹ (Eskilsson et al., 2017). The most common reason for dropping out was that participating in MMR took great effort and that the added

¹ Due to technical issues, no information regarding number of trained sessions was available for the participants in the cognitive training group.
training was perceived as too strenuous. Therefore, adherence to treatment is important to consider.

Adherence refers to “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (Sabaté, 2003, p. 3). Adherence has been emphasized by the World Health Organization as an important determinant of treatment effectiveness, stressing that improvement of health outcomes requires treatment efficacy as well as treatment adherence (Sabaté, 2003). The World Health Organization outlines five key dimensions of relevance to adherence: (1) social and economic factors; (2) health care team and system-related factors; (3) condition-related factors; (4) therapy-related factors; and (5) patient-related factors. I will centre the lessons learned within the RECO project on these dimensions.

First, our dropout analysis revealed no systematic differences between patients who completed the intervention and those who dropped out on any of the relevant background variables (i.e., age, sex and educational level) suggesting that these sociodemographic factors were not related to discontinued study participation. A more specific factor worth consideration within this dimension, however, is social support. The cognitive and aerobic training were conducted individually, and because the group based format of the MMR program was one of the key elements perceived by patients as beneficial in the recovery process (Eskilsson et al., 2018), drawing on the support of the MMR group also in relation to cognitive and aerobic training might have been of value.

With this follows logically the fact that the added interventions were not well integrated in the overall rehabilitative context, which relates to the second dimension (i.e. health care team and system-related factors). Although participants received some motivational feedback from physiotherapists and psychologists at the Stress Rehabilitation Clinic, the training was conducted individually at home (cognitive training) or at an individually chosen training centre (aerobic training), and some of the pre- and posttest assessments were conducted at the university facilities rather than the Stress Rehabilitation Clinic. Thus, better integration of cognitive and aerobic training within the context of stress rehabilitation might facilitate more systematic approaches to addressing training adherence by the health care providers.

The third and fourth dimensions, condition-related factors (i.e., associated emotional and behavioural correlates or comorbid conditions of the disease that might affect adherence), and therapy-related factors (i.e., the duration, complexity and potential side effects of a particular treatment) are perhaps the most important factors for adherence in this particular context. Because the
primary symptom of ED is physical and mental fatigue, adding extra elements to stress rehabilitation may be too demanding for some patients. Supporting this argument is the fact that the large amount of dropouts is not unique to our study; in fact, previous interventional studies in this patient group have struggled with similar issues (Blonk et al., 2006; Sonntag-Öström et al., 2015; Stenlund, Nordin, & Jarvholm, 2012). Within the RECO project, participants were required to conduct the training three times a week for 12 weeks and, arguably, this also could be difficult to attain for a healthy individual. Thus, consideration of the restricted energy resources of patients might be important. One approach could be to provide more individually tailored interventions, adjusting the amount and intensity of training to an individual’s current level of fatigue. Another issue that deserves consideration in this context relates to the timing of the added interventions. The rationale for placing the cognitive and aerobic training during the final 12 weeks of stress rehabilitation was that patients would have recovered sufficiently to be able to conduct the training. However, this also meant that the added interventions were initiated during a period in which many of the patients were in the process of work resumption and possibly were more restricted in terms of time and energy resources. The optimal timing for cognitive and aerobic training in the context of stress rehabilitation remains unestablished; for cognitive training perhaps a better approach is offering the intervention after stress rehabilitation for patients with residual cognitive impairment.

The final dimension concerns patient-related factors, such as the individuals’ capacity for behavioural change in terms of knowledge, motivation and skills. Tools facilitating behavioural change, such as providing information, using individual goal-setting, providing feedback and identifying barriers for change (Abraham & Michie, 2008), could be of value for both cognitive and aerobic training. For cognitive training, patients in the RECO project highlighted factors important for training motivation, such as making training more fun and receiving feedback on training progress (Eskilsson et al., 2018). An avenue for future studies could be to develop the training to make it more engaging (e.g., through adapting more videogame-like formats; Anguera & Gazzaley, 2015).

**Clinical implications**

As has been highlighted throughout this thesis, stress-related exhaustion is associated with selective and potentially enduring cognitive impairments and high levels of subjective cognitive complaints. Despite this fact, interventions that might alleviate cognitive deficits and their potential utility in the recovery from ED has received little attention. Therefore, this thesis sought out to explore the effects of interventions targeting cognitive impairments on both cognitive performance and clinical variables. So far, the results of this thesis have been
discussed in relation to each specific outcome. Here, I will attempt to synthesize the findings and discuss their clinical implications.

The results from this thesis showed that cognitive training was successful in giving a lasting improvement in cognitive performance for patients with ED. The effect size of the cognitive improvement was small; however, this should be interpreted in light of the fact that cognitive impairments in stress-related exhaustion are generally of a small-to-moderate magnitude (e.g., Ellbin et al., 2018; Eskildsen et al., 2015; Jonsdottir et al., 2013), but with large perceived impact on everyday life. The question is, then, whether this small improvement in cognitive performance is of clinical relevance for patients with ED? The fact that our results gave partial support for cognitive training leading to a reduction in subjective cognitive complaints, as well as additional effects on burnout levels, as compared to stress rehabilitation alone, suggests that cognitive training may de facto have merits in stress rehabilitation. However, the latter improvements were only seen for those patients who completed the intervention, and given the large amount of dropouts in the RECO project, an important clinical implication is finding ways to increase adherence.

We further showed that neural activation during working memory processing was modulated by burnout severity, suggesting that patients with high levels of burnout need to recruit additional neural resources to uphold task performance. Thus, patients with ED may be able to compensate for cognitive deficits to some extent, potentially at the cost of depletion of cognitive resources and increased mental fatigue. The tasks we face in everyday life usually require more sustained cognitive performance, thus, the stress-related cognitive impairments and associated fatigue effects may be most evident in the everyday context. With this follows that reducing the demands on cognitive control in everyday life may benefit patients with ED. This could be achieved by the use of compensatory techniques, such as working with explicit strategies for planning, structuring and prioritizing among tasks, as well as the use of external aids, such as calendars and reminders. Additionally, specifically addressing mental fatigue may have clinical value; this could be achieved through gradual exposure to cognitive tasks in conjunction with recuperative activities, as discussed above.

Drawing on models of neuropsychological rehabilitation, which are usually based on a holistic approach including rehabilitative measures directly targeting cognitive deficits, as well as addressing the emotional and psychosocial consequences of cognitive impairment (Wilson, 2008), it could be viewed as somewhat problematic that cognitive training interventions are traditionally implemented outside of the rehabilitative context. From a clinical perspective, better integration of the cognitive training into the MMR program might allow for combining the training with techniques from CBT, as well as the use of more
individualized training approaches. In this context, it is also interesting to reflect upon the fact that tertiary interventions for stress-related exhaustion are mostly directed towards the individual, despite the fact that stress-related illness is dependent on contextual factors. Perhaps reducing the demands for cognitive control in everyday life should not be placed solely on the individual with cognitive impairment, but could be aided by a social support system (e.g., through involving the workplace and family members to a larger extent), to increase knowledge about stress-related cognitive impairments and their consequences, and help make adjustments at the workplace as well as in the home environment.

The results from this thesis did not lend support to a restricted period of aerobic training giving long-term effects on cognitive functioning, nor to any additional benefits in the recovery of ED, as compared to stress rehabilitation alone. Nevertheless, an immediate improvement in episodic memory was observed following aerobic training and our results tentatively suggest that sustained effects on episodic memory may be dependent on the active maintenance of aerobic fitness levels. Since physical activity has been associated with positive effects on physical and psychological health (Penedo & Dahn, 2005), further investigation of the potential benefits of aerobic training for this patient group is warranted. Perhaps the most important contribution of the RECO project in this respect is the lessons learned about potential ways to incorporate aerobic training in stress rehabilitation in ways that make sustained increases in exercise levels attainable to patients.

In sum, the papers in this thesis provide initial evidence of neurocognitive plasticity in patients with ED and tentatively suggest that cognitive improvements following cognitive training may also translate into alleviated clinical symptoms. These results are encouraging and lend support to the argument that interventions targeting cognitive impairments holds a place in the effective rehabilitation of ED. Figure 10 provides a schematic model of how cognitive impairments could be addressed in stress rehabilitation, summarizing the issues that have been discussed throughout this thesis. The model is based on the proposition that cognitive impairments in ED could contribute to a vicious circle, associated with increased mental fatigue and impaired coping of daily stressors. As shown in Figure 10, different interventional approaches could potentially be used to break this circle by targeting different aspects of the chain. These include the use of restorative techniques, which are the focus of this thesis, but also compensatory techniques and rehabilitative measures focusing on recuperation.
**Figure 10.** A schematic model for how cognitive impairments could be addressed in stress rehabilitation. In ED, impaired cognitive function and mental fatigue could contribute to a vicious circle, associated with insufficient coping of daily stressors and increased stress reactions. Cognitive impairments could be targeted by interventions aiming to strengthen the impaired cognitive and neural functions (i.e., restorative techniques), such as cognitive or aerobic training. Mental fatigue could be addressed through interventions aiming to restore the balance between cognitive activity and psychophysiological relaxation (i.e., techniques focusing on recuperation), such as graded cognitive activity and combining cognitive challenges with recovery behaviours. Additionally, impaired coping of daily stressors could be addressed by interventions aiming to reduce the negative impact of cognitive deficits in everyday life (i.e., compensatory techniques), such as teaching explicit strategies for planning, structuring and prioritizing everyday tasks, the use of external aids such as calendars and reminders, and workplace adjustments.
Limitations

Attrition
The primary limitation of this thesis is the fact that the RECO project suffered from high attrition rates. The poor adherence is important from a clinical and a methodological point-of-view and a critical discussion is warranted. The clinical implications have been touched upon throughout this thesis (particularly so in the section relating to adherence to treatment), and here, I will focus on the methodological implications. The fact that many patients discontinued study participation arguably puts some constraints on the generalizability of the results. However, it should be noted that the fairly extensive drop-out analyses showed no systematic differences between completers and drop-outs, suggesting that discontinued study participation was not related to ED symptom severity. The small number of participants may also imply that the study was underpowered to detect potential training effects. This issue is not unique for our study; because the effect sizes of cognitive improvements following cognitive (e.g., Soveri et al., 2017) and aerobic (e.g., Smith et al., 2010) training are generally small-to-moderate, resource-demanding interventional trials in the field often suffer from weak statistical power. This further led to the decision not to correct for multiple comparisons, due to increased risk of making a Type II error. In light of these limitations, the results from this initial study need to be replicated in a larger study group to make firm conclusions. On a final note, a large amount of dropouts was also seen in the control group, suggesting that discontinued study participation was not only related to the added interventions, but also to the fairly extensive pre- and posttest assessments, which required investment of time and effort. Thus, future studies might consider a more streamlined assessment procedure to increase study participation.

Assessing cognitive function
A second limitation relates to the use of single tasks to assess cognitive function. Due to the task impurity problem (i.e., that cognitive tasks generally tap into several cognitive processes) cognitive functions should preferably be assessed using multiple indicators for each targeted cognitive construct and a latent variable approach (e.g., Noack et al., 2014). Because the study did not include enough participants to allow for a latent analysis of transfer, we tried to mitigate the problem somewhat in Study III by using composite scores for each cognitive domain. However, single tasks were still used for some of the cognitive domains (e.g., episodic memory). Also, as previously mentioned, the global cognitive score consisted of tasks from several different cognitive domains, however, the emphasis of the cognitive test battery was on executive function and working memory tasks, making the global cognitive score weighted towards these abilities.
Thus, the global cognitive score used in Study III should not be viewed as reflecting general cognitive functioning in the broader sense, but rather effects which span across the different cognitive domains that were the focus of investigation. The use of multiple indicators for each cognitive domain would have been preferred to increase validity and reliability of the cognitive assessments, potentially allowing for firmer conclusions regarding the range and specificity of transfer. This approach could also allow for moving beyond the traditional division of transfer on the near-to-far continuum, and instead attempt to differentiate between performance improvements due to knowledge acquisition (e.g., task-specific strategy attainment or perceptual expertise), increased process efficiency (e.g., improved cognitive control), and nonspecific factors (see Lövden et al., 2010; Soveri et al., 2017 for discussions). However, conducting such a detailed analysis of transfer was beyond the scope of this clinical trial, as it would require a more extensive cognitive test battery and a larger number of participants.

Assessing clinical relevance
As was alluded in the introduction, the issue of transfer following cognitive training interventions in clinical populations ultimately relates to whether training leads to changes in outcomes that are clinically meaningful for patients; the same line of reasoning also applies for aerobic training. However, what constitutes a clinically meaningful outcome is not entirely straightforward. The primary symptom in ED is burnout, and this could be argued to be the most clinically relevant outcome in any interventional study for this patient group. However, in the present project, the added interventions constituted a small part of an extensive stress rehabilitation program and because burnout symptoms are quite distal to what is actually being targeted by the added interventions, the potential additional effects on burnout symptoms could be expected to be small. Perhaps a more viable candidate is subjective cognitive complaints, which is more aligned with the interventional targets. Problems with memory and concentration are part of the diagnostic criteria for ED and patients frequently report substantial cognitive problems in their everyday lives, with effect sizes far exceeding what has been observed for performance-based measures of cognition. This supports the notion that improvements in subjective cognitive complaints are of potential clinical relevance for patients with ED. However, the association between subjective cognitive complaints and cognitive performance is generally weak and may also be influenced by depressive symptomology (see Burmester, Leathem, & Merrick, 2016 for a review). Perhaps what is required to better address the issue of clinical relevance of cognitive interventions are the development of more ecologically valid cognitive tasks, to better capture the cognitive problems faced by patients in their everyday lives.
**Defining an active control group**

In the cognitive training literature, the importance of using an active control group is often stressed, to disentangle improvements in cognitive functioning from the effects of nonspecific factors such as social contact, motivation or expectancy effects (Noack et al., 2014; Shipstead et al., 2012). An active control group usually involves conducting a version of the training without the hypothesized active ingredient, such as a non-adaptive version of the cognitive training tasks (e.g., Brehmer et al., 2012), or, for aerobic exercise, the use of non-aerobic training as control condition (e.g., Jonasson et al., 2017). However, considering the limited energy resources of patients with ED, the use of an active control group is somewhat problematic, because it would require patients to spend time and effort on a training regimen that is not believed to have an effect. In the RECO project, we therefore used a treatment-as-usual control condition, and although the MMR program consisted of fairly extensive treatment, it did not constitute an active control group in the more stringent sense. The control condition used in the RECO project allowed us to control for confounders such as retest effects and social contact, however, we cannot exclude the possibilities of motivation or expectancy effects influencing the results. In this context, however, it is worth mentioning that authors of recent meta-analyses have indicated that the differences between the results of cognitive training trials using active and passive control groups are slim (Hill et al., 2017; Lampit, Hallock, & Valenzuela, 2014).

**Brain imaging analysis of training-related effects**

The limitations of the brain imaging analysis in Study II have been discussed in the original paper, however, some additional comments are worth making here. Specifically, with respect to the investigation of the neural mechanisms of cognitive training for patients with ED, a variety of circumstances somewhat restricted the conclusions from this analysis. The main problem was that large attrition made the final sample of participants who completed the cognitive training intervention, as well as the pre- and posttest fMRI-scanning sessions, very small. This had several implications. First, the power of the analysis was restricted, allowing only for an exploratory analytical approach. Second, no near transfer effect was observed for the in-scanner $n$-back task in the fMRI-subsample. A related problem was that no trained task was included as an in-scanner task. Relying solely on a near transfer task in the scanner is problematic, considering that transfer effects following cognitive training are not as reliably reported in the literature as training task improvements (as reflected also by the results from Study II). Without behavioural transfer, the conclusions that can be made regarding neural changes following training are limited, and a better approach would perhaps have been to include both trained and transfer tasks as in-scanner tasks. Inclusion of a trained task in the scanner would also have
facilitated comparisons with previous research, which has primarily focused on neural changes related to training tasks (Salmi et al., 2018), possibly allowing for somewhat firmer conclusions from the exploratory analysis in Study II.

Future directions
The RECO project is the first systematic evaluation of interventions targeting cognitive deficits within the context of stress rehabilitation. Thus, this thesis provides some important insights into the possibilities of harnessing neuroplastic mechanisms in the treatment of ED. However, the results from this relatively small clinical trial also raise several questions warranting further investigation.

First, the improved cognitive performance following cognitive training was general, rather than specific, and the lack of a clear, theoretically plausible pattern of transfer restricts firm conclusions regarding the underlying mechanism of the cognitive improvement. This raises the question of whether the positive effects on cognitive performance was specifically related to process-based cognitive training (e.g., through improved cognitive control) or if other, more general mechanisms, such a reduction in mental fatigue or other factors, offers a more parsimonious explanation. Future studies should address this issue, preferably with a larger study group and the use of multiple indicators for each targeted cognitive construct.

Second, although no long-term effect was seen following the aerobic training intervention, an improvement in episodic memory was observed immediately after the intervention, suggesting it was possible to induce neuroplasticity to some extent. An interesting venue for future research could be to investigate the effects of more extensive training on cognitive performance and psychological health. To do so, perhaps more individualized training approaches and explicit support to adhere to the training regimen (e.g., through supervised training) might be required, as well as consideration of the baseline physical activity levels of participants.

The compensatory neural engagement suggested by Study II raises several interesting questions. Future studies should explore the relationship between cognitive impairment, compensatory effort, motivational processes and mental fatigue in patients with ED, in particular in relation to healthy controls. Additionally, the results from Study II highlight the need for more sensitive measures to better capture the cognitive deficits associated with stress-related exhaustion, including more ecologically valid executive tasks.
Looking more closely at individual differences in variables such as baseline cognitive performance and aerobic fitness levels, as well as motivation and engagement in training, might give insight into who benefits from training and how interventions may be tailored to the individual patient.

Finally, emerging new treatment approaches such as the combination of cognitive and aerobic training (e.g., through active videogames) or cognitive training with emotional material offer intriguing treatment possibilities for this patient group.
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