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General Introduction
Fatigue is a common symptom in adults worldwide, varying in length (acute to chronic) and severity [1]. Occurrence of fatigue can be medically explained (e.g. related to chronic disease), but in some cases fatigue (physical and mental) symptoms are medically unexplained, i.e. cannot be adequately explained by organic causes. Unexplained fatigue is considered to be chronic (chronic fatigue - CF) if it lasts for at least 6 months.

Persistent and severe unexplained fatigue is not alleviated by rest, is debilitating, and leads to functional and social impairment (e.g. inability to work). Commonly, these patients experience additional rheumatologic and neuropsychiatric symptoms, namely pain and cognitive impairment [2, 3]. When at least four of these symptoms are present it is diagnosed as Chronic Fatigue Syndrome (CFS), according to the US Centres for Disease Control and Prevention (CDC) criteria [4], which is the most widespread criteria in research and clinical practice. Another case-definition commonly used is based upon the Oxford Criteria [5], a less restricted set of criteria not requiring the presence of additional somatic symptoms. Table 1 presents the characteristics of these case definitions.

A panel of experts has recently proposed a new international consensus case definition [6], which does not establish a timeframe for the presence of fatigue, but requires the presence of postexertional malaise (i.e. increase in fatigue following intense effort) as well as additional clusters of symptoms related to neurological, immune, gastro-intestinal, genitourinary, and energy production/transportation impairments. One of the problems with diagnosing CF or CFS is that the primary symptom, fatigue, is difficult to define and to measure due to its subjective nature; there is no biological marker for CF(S) [7, 8]. The diagnosis of CF or CFS is thus exclusionary [9]. In terms of terminology, another name also used for CFS is Myalgic Encephalomyelitis/ Encephalopathy (ME). Some researchers consider this term to be more appropriate to characterize the complex nature of the disease [8].

CFS is considered to be a heterogeneous clinical condition. Patients may present with different levels of (mental and physical)
fatigue, psychological distress, additional somatic symptoms, impairment and disability [3, 10]. Co-morbidity between CFS and psychological distress (depression and anxiety) was found in several studies, although the relationship remains unclear [3, 11]. Patients with CFS also experience a great number of other somatic complaints [8, 12]. In addition, studies report a percentage between 35% to 70% of CFS patients that present with both CFS and Fibromyalgia [8, 13].

### Table 1 Criteria of the main CFS case definitions

<table>
<thead>
<tr>
<th>CFS criteria</th>
<th>Oxford</th>
<th>CDC (1994)</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Fatigue is the principal symptom. Definite onset that is not lifelong. Fatigue is severe, disabling, affects physical and mental functioning. Fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time. Other symptoms may be present, particularly myalgia, mood and sleep disturbance.</td>
<td>Medically unexplained, persistent fatigue lasting for at least 6 months, of new onset, not due to ongoing exertion or organic disease, not substantially relieved by rest, and leading to a significant reduction in activity levels.¹ Presence of four or more of the following symptoms: • lengthy malaise after exertion • impaired memory or concentration • unrefreshing sleep • joint pain without swelling or redness • muscle pain • headaches of a new type or severity • tender cervical or axillary • lymph nodes • sore throat</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Medical conditions known to produce chronic fatigue. Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder, proven organic brain disease.</td>
<td>Medical conditions known to produce chronic fatigue. Patients with a current diagnosis of Major depressive or bipolar disorder, psychotic disorder, dementia, eating disorders, alcohol and substance abuse, and severe obesity.</td>
</tr>
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¹If symptoms do not fulfil the criteria for CFS, the condition is referred to as idiopathic chronic fatigue (ICF)
Chronic fatigue is reported by about 6% of the general population [14]. Prevalence of CFS has been reported to be in between 0.007% and 2.6% in community and primary care samples. Prevalence rates vary according to several factors such as the setting, country and diagnostic criteria used [14]. Most studies on the prevalence and clinical characteristics of CF and CFS have been conducted in North-Western Europe, North America and Oceania [15], and there are very few international studies that compare patient populations from different countries [16, 17]. It is more prevalent in younger adults (less than 40 years of age) and among women [2, 3, 8]. In terms of prognosis, full recovery rates are low; it is more common for patients to experience improvements in symptom severity [18]. Chronic fatigue is associated with a high use of health care resources and represents an important socioeconomic burden [2, 19].

Aetiology of Chronic Fatigue

The aetiology of CF(S) remains unclear. Still, research points towards a multifactorial nature that consists of a combination of biological/physical and psychosocial factors (biopsychosocial model) operating as predisposing, precipitating and perpetuating factors of chronic fatigue [3, 8, 9, 20].

Predisposing factors are those that make the person more vulnerable to develop chronic fatigue, such as genetics, personality factors, prior psychiatric disorder, and overactive lifestyles, among others [3, 8, 9]. Precipitating factors are those that trigger fatigue, such as acute or chronic physical (e.g. viral infection, surgery) and psychological stress (e.g. serious life events) [3]. Perpetuating factors contribute to the chronicity of fatigue, and can impede recovery from CF(S) [21]. Research has identified several perpetuating factors, such as biological changes (e.g., changes in the hypothalamic-pituitary-adrenal axis), presence of additional somatic symptoms (e.g. pain), social factors (e.g. lack of social support), psychological distress (depression and anxiety), as well as cognitive and behavioral factors, which
are considered to play a major role in the maintenance of fatigue [9, 20, 21]. Regarding cognitive factors, negative or maladaptive illness perceptions (e.g. poor sense of control over symptoms or somatic attributions of symptoms), and coping strategies (e.g. catastrophizing, passive coping) have been identified as perpetuating factors of fatigue [20, 22].

Prolonged physical inactivity (rest) and decreased physiological exercise capacity are considered major perpetuating behavioral factors of symptoms in CF(S) [23, 24]. It has been suggested that prolonged inactivity can result in physical deconditioning as well as in other physiological and psychosocial consequences that may perpetuate fatigue severity and physical disability [23, 25, 26]. On the other hand, high levels of physical activity that exceed personal physical capacity can cause overexertion and perpetuate fatigue symptoms [23, 27-29]. It is therefore common to find a “all-or-nothing” (or “boom-and-bust”) behavior pattern in these patients, which is the systematic alternation between periods of over-activity (when feeling good) and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time [9, 23, 30]. Some patients continue to perform their daily activities even when symptoms get worse (overactive pattern), but most patients present reduced levels of daily activity [23, 31]. Patients’ perceptions and expectations with respect to symptom exacerbation as a consequence of physical exertion (postexertional malaise) can also lead to an avoidance and fear of physical activity [3, 26, 27] that does not correspond to the actual level of physical disability.

Available research shows that patients with CFS have at average lower levels of physical activity, less muscle strength and a worse physiological exercise capacity [24, 25, 31], than healthy sedentary control subjects. It has therefore been recommended that patients with chronic fatigue engage in (balanced) physical activity instead of refraining from it.

Research is still limited with respect to the most appropriate type of physical activity for chronic fatigue management but recent literature points at the beneficial effect of aerobic activities (e.g. walking), performed at mild and moderate levels of intensity [23].
Current behavioral and psychological treatments

Treatment approaches for CF(S) focus on perpetuating factors, especially on behavioral (physical activity) and psychological factors, in view of reducing severity of fatigue and other symptoms as well as improving functioning and quality of life. Graded Exercise Therapy (GET) and Cognitive Behavioral Therapy (CBT) are the current recommended non-pharmacological treatments for chronic fatigue management [3, 8, 32]. Based on a physiological model of deconditioning, GET is an aerobic exercise therapy, consisting of supervised exercise sessions and/or home-based exercise prescription (e.g. walking). In GET, physical activity is initiated at a level that (a) takes into consideration patients’ initial level of exercise capacity and (b) doesn’t exacerbate symptoms. Exercise is then gradually increased in frequency and intensity until patients reach an optimal level of activity. GET focuses on avoiding overexertion by advising patients not to exceed the recommended levels of physical activity/exercise. At the same time, patients are encouraged not to reduce or stop doing physical activity when symptoms get worse. Graded exercise programs follow the exercise prescription guidelines from the American College of Sports Medicine [33], tailored to each patient’s level of physical capacity [34]. GET has shown to have moderate beneficial effects upon chronic fatigue management [35-37].

CBT and other psychological approaches consider not only behavioural factors, but also cognitive and affective factors that may contribute to the maintenance of fatigue symptoms. The primary focus of CBT for these patients is on challenging cognitions related to the perpetuation of symptoms and distress (e.g. somatic illness attributions, perceived lack of personal control, focusing on physical sensations) as well as on planning work and functional recovery [38, 39]. Because of the empirically established benefits of physical activity in CFS, a large number of Cognitive Behavioural Therapy (CBT) trials have incorporated a graded physical activity/exercise component. Focusing on a cognitive model of avoidance of physical activity, patients are encouraged to engage in a gradual
increase of physical activities and balance daily activities [3]. Some CBT approaches distinguish between relatively-active (characterized by an alternation of over-activity and rest) and low-active patients [3, 39]. In the first case patients are initially encouraged to balance their daily activities and rest, but for both groups of patients the intervention focuses on a gradual increase of physical activity levels. Cognitive-behavioral therapy (CBT) has also demonstrated to have beneficial effects on chronic fatigue management [36, 37, 40].

Some recent GET, CBT and combined approaches (e.g. multidisciplinary rehabilitation treatments) [41] also use pacing strategies, either by allowing flexibility in graded exercise goals or programs (e.g. duration of session) according to individual tolerance levels (e.g. stop if symptoms get worse) [27, 42] or by promoting a balance between physical daily activities and rest according to patients own symptoms and capability [27, 41].

Two meta-analyses comparing GET and CBT have not found differential effects between both treatments on fatigue management [36, 37]. Despite the fact that physical activity seems to be an important component of both treatment approaches, there is little research on the effects of GET and CBT on physical activity, with some studies showing only marginal or trivial effects [43, 44]. One of the problems with both GET and CBT is that both interventions are resource-intensive [36, 37]. Recent randomised controlled trials have tried to overcome this limitation by conducting minimal contact interventions based on self-guided instruction manuals and remote contact showing promising results [45-47]. These brief interventions have the advantage that they can be more easily implemented in standard health care, e.g. in a primary care setting. Other non-pharmacological treatments such as complementary and alternative therapies, as well as pharmacological immunological treatments have been developed but results from these trials are inconclusive [48].
Promoting (balanced) physical activity: The Role of Self-Regulation

Adopting a health behavior change framework can contribute to the understanding and long-last promotion of physical activity in chronic fatigue patients. One of the most prominent perspectives on health behavior change is Self-Regulation (SR) theory [49-52]. According to this theory, behavior is a goal driven process [50]. SR can thus be defined as a “sequence of actions and/or steering processes intended to attain a personal goal”[49]. This dynamic-goal guided process occurs in phases, consisting of a goal selection and goal setting phase, an active goal pursuit or action phase, and a goal attainment and maintenance or disengagement phase, in which motivational and volitional aspects interact [49]. A central aspect in SR is that individuals set personal important and meaningful goals [49, 52]. Research points out that formulating self-chosen and personally important goals to guide behavior (goal ownership), as well as autonomously regulate one’s own behavior, increases the likelihood of goal achievement and maintenance [49, 53]. Goals are hierarchically structured and interconnected, with more abstract long-term goals (e.g. be healthy), generating input for the formulation of short-term concrete goals such as specific actions (e.g. exercise three times a week) [52]. This hierarchical goal structure is important for health behaviour change interventions as it considers that specific actions or concrete goals such as doing physical activity will only be formulated and pursued by individuals if they are linked to higher hierarchical goals such as being healthy. At the same time it stresses the importance of increasing the personal relevance of health goals in order to increase the likelihood of adopting physical activity goals. One of the triggers of motivation and intention to change behavior is the perceived discrepancy between an individual’s current state (input value) and a desired state (the reference value), leading to the formulation of a specific goal [52]. The significance of these SR processes for interventions in chronic fatigue is that they cannot only contribute to our understanding of the influence of life goals on chronic fatigue patients’ behavior and treatment adherence [54], but interventions based upon these models may also contribute to
change the reference value from symptom avoidance to well-being and encourage patients to change their personal goals to more active and positive goals [54, 55].

Additional SR cognitions and skills are considered to play an important role in the phases of the goal guiding process, and thus in promoting long-lasting health behaviour change [49]. Goal self-efficacy, formulation of self-chosen and personally important goals (goal ownership), planning, control over competing goals, self-monitoring, feedback and anticipatory coping, as well as attention and emotion control, are considered to add great value to the transition from a motivational phase (goal selection) to action phases of goal pursuit. Relapse prevention strategies such as coping planning, as well as satisfaction and ownership of the changed behaviour or goal reformulation are additional SR factors that can contribute to long-lasting health behaviour change [49].

Self-regulation based interventions have demonstrated to be effective in promoting long-lasting health behaviour change in chronic disease populations [56-59]. In a recent meta-analysis, Michie et al. [60] found that interventions combining self-monitoring with other skills derived from Self-regulation theory (i.e. Control Theory [52]), such as goal setting, provision of feedback, planning and goal revisiting, were more effective in promoting changes in PA and healthy eating in the general population than other intervention not using these techniques. The moderation effect of SR-skills in interventions effect were also found in other meta-analysis of trials conducted with chronic diseases patients [61-63]. For that reason, a self-regulation perspective was adopted to develop an intervention for CF(S) patients.
Aims of the thesis

Several behavioral and psychological treatments have been developed for chronic fatigue patients, focusing on physical activity, which is considered a key factor in chronic fatigue management. Research is however limited with respect to the effects of these interventions on physical activity. Furthermore, many of these interventions focus on establishing/prescribing structured exercise plans and less on the role of motivational and self-regulatory factors in the successful adoption and regulation of physical activity and other behaviours that can lead to a reduction of fatigue severity and improvement of patients’ functioning and quality of life.

The objectives of this thesis are to:
1. Adapt the Checklist of Individual Strength (CIS20), a valid and reliable measure of fatigue severity, for a Portuguese population in order to measure fatigue according to international standards.

2. Investigate the differences in clinical characteristics and behavioral and cognitive determinants on chronic fatigue in a Dutch and a Portuguese patient sample.

3. Examine the effects of behavioral and psychological treatments containing a graded exercise component in chronic fatigue management as well as to examine potential moderator effects of trial characteristics.

4. Develop and evaluate post treatment and medium-term effects of a self-regulation based intervention (4-STEPS), combining motivational interviewing and self-regulation skills training, on physical activity and chronic fatigue management.

5. Analyze whether changes in physical activity and use of self-regulation skills explain observed effects of the 4-STEPS intervention on fatigue severity.
Outline of the thesis

This thesis consists of eight chapters. This first chapter (Chapter 1) provided a general introduction on chronic fatigue, its management and the contribution of a self-regulation perspective to available behavioural and psychological treatments targeting physical activity. The following six chapters (Chapters 2 to 7) correspond to empirical studies either published or submitted to peer-review journals in the field of psychology and health.

The first of these studies (Chapter 2) describes the psychometric properties of the Portuguese version of the Checklist of Individual Strength (CIS20-P;[64]). The CIS20 is a well-validated multidimensional measure assessing fatigue severity that has been used in several observational and intervention studies conducted in chronic fatigue patients [45, 65]. Fatigue severity is the primary endpoint in many interventions conducted in chronic fatigue patients, including the trial presented in this thesis. Hence, in research studies conducted in Portuguese speaking populations it is crucial to use a Portuguese validated measure to assess fatigue severity.

Chapter 3 explores cross-cultural similarities and differences in clinical characteristics and behavioral and psychological determinants of CFS between a Portuguese and a Dutch CFS patient sample. Due to the fact that there is no published research conducted with CFS patients in Portugal, and that most trials targeting these patients are done in Northern European countries, this comparison is important in view of developing culture relevant behavioral and psychological treatments for CFS.

Chapter 4 presents an updated systematic review and meta-analysis of the effects of behavioral and psychological interventions with a graded physical activity component on fatigue severity, physical functioning, physical activity, and psychological distress, among patients with ICF/CFS. Potential moderator effects of trial characteristics were examined in order to identify factors of success that can improve interventions’ design and effectiveness.

Chapters 5, 6 and 7 describe the development, implementation and evaluation of a randomized controlled trial (RCT) for
patients suffering from chronic fatigue, the “Four steps to control your fatigue (4-STEPS)” trial. This RCT, conducted in Portugal, compared a brief self-regulation based physical activity program consisting of motivational interviewing and self-regulatory skills training (4-STEPS) to a control condition (usual care + general information on physical activity).

Chapter 5 presents the protocol of the 4-STEPS trial. The protocol describes in detail the trial rationale, study design and procedures, description of the intervention content and materials, as well as the outcomes assessed.

Two studies (Chapter 6 and 7) present the results of the 4-STEPS implementation. Chapter 6 reports the post-treatment (3-months) effects of the 4-STEPS intervention on fatigue severity (primary outcome) and impact on daily life, physical activity, health-related quality of life, psychological distress and somatic complaints. Intervention effects at follow-up (12-months) are reported in Chapter 7. In addition, this last study examines the mediation effects of the intermediate targets of the intervention (physical activity and use of self-regulatory skills) on medium-term changes in fatigue.

The last chapter (Chapter 8) integrates and discusses the findings from the different empirical studies. Directions for future research and practical implications are formulated.
References

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