Brittle Brain Power

Post-stroke fatigue, explorations into assessment and treatment.

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Voor Michiel

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“Fatigue has always been an elusive creature”

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Chapter 1. General Introduction

"We are continually faced with a series of great opportunities, brilliantly disguised as insoluble problems"

John W. Gardner (1912-2002)

Introduction

Stroke is a common and devastating neurological disease with far reaching consequences. It is one of the leading causes of death in developed countries and survivors of stroke often face lasting physical, cognitive, psychological and social disabilities as a result of their illness.[1-4] In the Netherlands each year about 41.000 people suffer a stroke, of which 20% do not survive the first year after the attack.[5] Due to the ageing of the population and improved healthcare facilities for patients in the acute phase of stroke,[4] the amount of patients surviving a stroke is increasing, as is the number of patients who have to cope with the chronic consequences of stroke. It is estimated that from 2000 to 2020 the number of stroke survivors in the Netherlands will increase from about 118.000 to 152.000.[6] For these patients the consequences of stroke will have to be managed as a chronic disease.

A stroke may be accompanied by a large series of consequences and co-morbidities. Frequently encountered co-morbidities include hypertension, diabetes, pulmonary and heart disease.[7] Complications that arise as a consequence of the brain injury itself exhibit a wide diversity of clinical signs and symptoms. These can be broadly classified into: (1) sensorimotor, (2) cognitive, and (3) emotional and behavioral symptoms. Sensorimotor sequelae of stroke may include: muscle weakness (paresis), increased muscle tone (spasticity), loss of sensibility, tinnitus, (central) pain, loss of smell, and visual field deficits. Cognitive problems often encountered after stroke are: mental slowness, attention deficits, memory deficits, language disorders, visuospatial neglect, and impaired executive functions.[8] The emotional and behavioral consequences can include: depressive symptoms, anxiety, irritability, emotional instability, apathy and, as a result, changes in personality.[4, 8] Furthermore emotional and behavioral problems can arise in response to the consequences of the stroke, the ensuing impaired functioning and altered social roles in everyday life.[9]

A frequently voiced complaint by stroke patients is fatigue. Unfortunately, fatigue was not considered a core symptom of stroke until rather recently, in the 1990's. Current research has established that it is indeed a distinct symptom after stroke requiring medical attention.[10] Two main causes for this long lasting neglect of fatigue have been suggested. First, fatigue is a subjective feeling which is difficult to define.[11-13] The second cause is its non-pathognomic nature, as fatigue is a non-specific complaint accompanying many (neurological) diseases.[11] As this has had long reaching effects on the general view of fatigue after stroke, these causes will be discussed in more detail in section 1 of this chapter. Furthermore, in the above-mentioned classification of consequences after stroke, fatigue seems to comprise all three elements: the sensorimotor, the cognitive as well as the behavioral and emotional. It is sometimes seen as a diminished ability to concentrate or a diminished activity level, whereas on the

other hand, it can negatively influence mood and vice versa. After stroke, fatigue is a frequently mentioned symptom with about 29 to 77% of patients even experiencing severe levels of post-stroke fatigue (PSF). Furthermore, the impact of PSF on daily life is vast with 29 to 50% of the patients rating fatigue as one of their worst symptoms.[10, 14, 15] Moreover, PSF has been found to have a negative effect on quality of life,[16-18] rehabilitation outcome,[19] functional independence in daily life[18, 19] and even mortality.[20, 21] It is thus of great importance to not only recognize PSF in patients, but also to treat this symptom in order to improve overall rehabilitation outcome and the general wellbeing of patients with stroke.

Investigations of PSF and especially of treatment options for PSF are still in their infancy. Recent reviews stress that, although PSF is a common and debilitating symptom after stroke, many of its aspects still need to be studied[20] and no guidelines for clinicians have been established until now[21-23]. Moreover, several researchers have stressed that PSF is disregarded in scientific research as well as in clinical practice. Articles entitled "Fatigue after stroke: a major but neglected issue" by Staub and Bogousslavsky (2001)[22]; "Post-stroke fatigue: an important yet neglected symptom" by Morley et al (2005)[23]; and "Post stroke fatigue-where is the evidence to guide practice?" by Barker-Collo et al (2007)[24] exemplify this idea. Thus, extensive research into the field of PSF is still greatly needed.

Unfortunately, research into PSF is subject to several complicating issues. Fatigue is by nature a subjective feeling and, therefore, difficult to define and measure.[13, 25] To complicate matters, the existing research into PSF (as discussed in further detail in paragraph 1.1) has largely focused on either the cognitive *or* the emotional aspect, with or without interest in the physical component. Thus, the multi-dimensional nature of fatigue has been disregarded.[10] Not surprisingly, there is a lack of a generally accepted unambiguous definition of PSF, let alone an unambiguous assessment procedure to measure it. Consequently, a wide variety of assessment tools to measure PSF are in use, often ill-defined and only moderately correlating with each other. Studies using different PSF-assessment tools often find conflicting evidence with regard to associated variables, as discussed in more detail in paragraph 1.3. This impedes the comparison of studies and the generalization of findings.

In conclusion, the neglected status of PSF, the division of focus of the tripartite consequences of stroke (e.g. physical, cognitive or emotional) and the use of a wide variety of assessment tools have not only hampered the development of a comprehensive theory of the etiology of PSF, but also hindered the development of clear guidelines for health care professionals in the recognition and treatment of patients with PSF. Hence, the central objective of this dissertation is to provide first directions for researchers and clinicians faced with patients that suffer from PSF. Herein, the three perspectives on PSF will be incorporated. In addressing these issues, and in order to gain understanding of

the current standing and knowledge of PSF, the latter part of this introduction and the core of this thesis are divided into two main sections. The focus of the first section is on the symptoms of fatigue, its ambiguous definition, its neglected status, its diverse assessment tools and its many equivocal associations. The second section is then dedicated to the treatment of PSF. References of all chapters are provided on page 149.

Section 1. The trouble with fatigue

Fatigue in general is a well-known feeling. Normal fatigue can often be related to increased mental or physical activity. It does not systematically impede activities and it is alleviated after sufficient rest. On the other hand, severe and pathological fatigue is a familiar symptom accompanying many diseases, such as cancer, heart disease, pulmonary disease and the flu. Here fatigue is 'too normal a symptom' to aid in the differential diagnosis of the primary disease itself and is almost never a primary treatment target. On the other hand, fatigue is one of the diagnostic criteria of clinical depression as stated in the DSM-IV-TR.[26] Therefore, it is not surprising that fatigue has often been assessed in the framework of depression[10] and, consequently, has been referred to as "pseudo-depressive symptom" by Bogousslavsky in his W. Feinberg Lecture.[27]

The prevalence rates of fatigue amongst all neurological afflictions are high, but hardly any effective treatment is available.[11, 21] Fatigue is a highly subjective experience and its unambiguous assessment poses great challenges for the clinician. It is not surprising that, when faced with fatigued patients, researchers and clinicians have seen fatigue as one of many symptoms of a disease or a common non-specific disease symptom[13] that does not need further attention or is untreatable. Thus, fatigue has often been neglected in research and in medical practice.[28]

Several qualitative studies undertaken in developed countries have emphasized that fatigue is neglected in general health care.[29-31] Flinn & Stube (2009)[30] formed three focus groups of stroke survivors in the United States in order to gather experiences of fatigue and its subsequent impact on daily life. Common themes among these groups were the lack of information that patients and their families had received, as well as the continuous search for the cause of fatigue and its social validation.[30] In interviews held with 15 patients in Sweden, Bendz (2003)[29] reported that while the patients' experience of fatigue and loss of control influenced their rehabilitation process, the health care professionals ignored these aspects in their recordings.[29] Furthermore, in a longitudinal study in Australia, White et al (2012)[31] did not only show that PSF led to role loss, but also that the lack of information on PSF caused confusion and distress, elongating the time needed to adjust to fatigue.[31]

In summary, patients have an urgent need to understand their experience of fatigue, aspire to have it properly assessed and explained, so that they feel less overwhelmed and know what to do about it.[30] However, in order to inform and treat patients, health care professionals first need to know what PSF is, how to diagnose it, and what treatment strategies are available. A first prerequisite then is a uniform definition of PSF.

1.1. The definition and experience of fatigue

As mentioned before, defining the subjective feeling of fatigue proves to be difficult.[9, 30-33] This is probably the reason that many different definitions of fatigue in neurological disorders, and specifically for PSF, are in operation as summarized in **table 1**. It is striking that these definitions can be broadly classified into descriptions of 'subjective emotional' fatigue or 'more objective' measures focusing on limitations in mental or physical work-output. Research following these different views of PSF will evidently have different foci and use different operationalisations and assessments. In the subjective approach researchers will rely on self-report assessments of 'experienced fatigue', whereas studies applying the 'objective fatigue' line will use behavioral tasks in which attention or work output is measured.

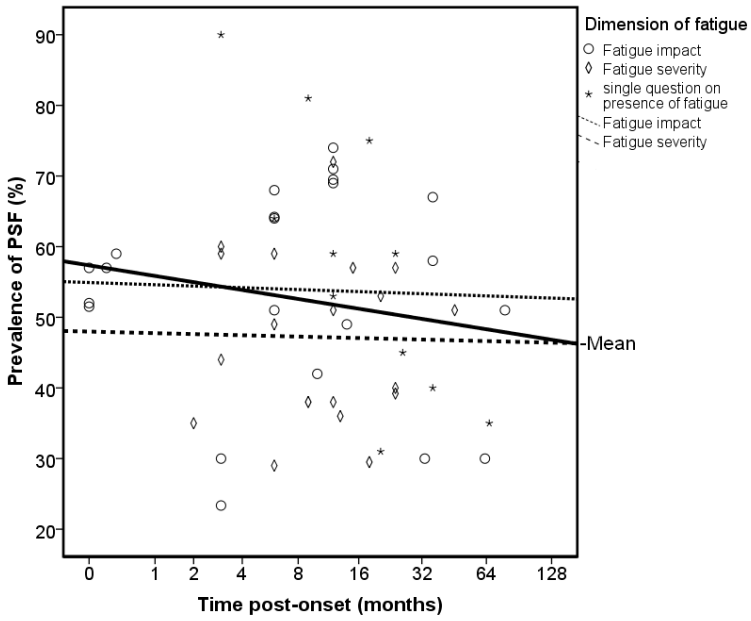
The problem with these different approaches is that the 'subjective experience' of fatigue seems to be a different construct than the constructs involving either mental and/or physical activity. Studies investigating both views have shown that feelings of PSF as assessed with self-report measures are not directly associated with physical fitness[34] and correlate only moderately at best with the 'objective measurements' such as attentional tasks.[35-38] More pressingly, valid biological markers of fatigue have still to be found[33, 39] and assessment tools to be developed and validated.[36, 37, 40]

However, there are common features to the 'subjective' and 'objective' definitions of PSF. These involve a distinction between 'normal' and 'pathological' fatigue after stroke: several studies have shown that patients describe PSF to be qualitatively different from fatigue before stroke.[30, 31, 41, 42] While normal fatigue and exertion occur after energy expenditure, have a short duration and improve with rest,[30, 43, 44] PSF is characterized by early exhaustion, more severe fatigue, and an aversion to effort. PSF is not directly related to visible effort, may elicit difficulties in sustaining actions, and is not typically ameliorated by rest.[20, 43] In addition to this description, as mentioned previously, PSF seems to be a multi-factorial concept [e.g. Lerdal et al, 2009[20]]. The subjective feeling of fatigue, the physical and mental activity could be different components. This is exemplified by the findings that patients differ greatly in their experience of fatigue including a more emotional, cognitive or physical feeling[31, 41] as well as in the fluctuation[41] and impact of their experienced fatigue on daily life.[31, 42]

Various studies have also shown that PSF is a persistent complaint, starting directly post onset for most patients.[16, 41] Although some prospective studies have reported declining prevalence rates of PSF over time,[35, 45] others have not found any difference over a time course of several years.[46, 47] Furthermore, relatively consistent prevalence rates (between 29% and 77%) of PSF have been found from admission up to 6 years after stroke as shown in **figure 1**. Since the long-term duration seems to be such an intrinsic feature of PSF, this warrants the incorporation of persistence into the definition of PSF.

In summary, as so-called biological markers of fatigue are still lacking, a 'subjective' definition of PSF is adopted in this thesis, incorporating both physical and mental fatigue as well as the persistence of fatigue: "a subjective experience of extreme and persistent tiredness, weakness or exhaustion after stroke, which can present itself mentally, physically or both, and is unrelated to visible previous exertion levels". Herein, the impact of fatigue on activities or daily life is not addressed, since this may vary considerably,[31, 42] and is possibly even more sensitive to the effects of personal disposition towards experienced fatigue.

Figure 1. Prevalence rates of post-stroke fatigue (fatigue severity and fatigue impact) observed at different times post stroke onset.



1.2. General assessment procedures

As mentioned above, a uniform definition of PSF is lacking and no derived and well-validated assessment instruments have been specifically developed for this population. As objective markers are still lacking, assessment of PSF is hitherto mainly restrained to the use of questionnaires. It is has been

reported that more than 250 self-report devices, of which 150 have been only used once, exist in the general literature on fatigue.[48] Also for PSF, many different questionnaires have been proposed, as can be seen in **table 2**. To name a few, there are linear analogue scales (visual analogue scale, VAS)[44,49]; single questions requiring a yes/no answer and questionnaires: vitality domain in the Short-Form 36 (VIT SF-36)[50]; Brief Fatigue Inventory (BFI)[28]; Fatigue Assessment Scale (FAS)[50, 51]; Checklist Individual Strength-20R (CIS-20R)[52, 53]; Fatigue Severity Scale (FSS)[54]; Multidimensional Fatigue Inventory (MFI-20)[28]; and the Multidimensional Fatigue Symptom Inventory (MFSI)[28]. These scales differ from each other in several regards. First, the construct that is assessed varies considerably, as there is no guiding definition of PSF. Whereas some scales focus on energy levels (SF-36), others take physical and/or mental fatigue into account (CIS-20R; MFI-20) and again other questionnaires seem to focus mainly on the experienced impact of fatigue on daily life (FSS). Furthermore, some questionnaires assess multiple domains of fatigue (e.g. CIS-20R; MFSI), whereas others regard fatigue as a uniform construct (e.g. SF-36 and FSS).

The wide variety of scales used has led to major problems in comparing studies and standardizing data,[33, 39] since no scale measures the exact same construct as the other.[28, 51] This is probably one of the main reasons for the substantial differences found in the prevalence rates of PSF (29 to 77%), but also for the variability in associations found with other variables. Furthermore, studies that used identical tools have used different cut-off scores to determine PSF **(see table 2**), compromising the comparability of data even more.

1.3. PSF and its associations

In an effort to disentangle its content and etiology the majority of studies have focused on the associations of PSF with pre-clinical, demographical and psychosocial variables (**see table 2**). The findings of these studies are summarized in what follows, starting with pre-stroke, stroke, clinical and socio-demographical variables. Thereafter, the main findings will be summarized of previous studies regarding depression and other psychological variables. Finally, an overview of the relationship between cognitive performance and PSF will be given.

1.3.1. Pre-stroke variables

Few studies have systematically taken pre-stroke variables into account, such as pre-existing morbidities, pre-stroke depression or pre-stroke fatigue. To our knowledge six studies have investigated whether hypertension, cardiac disease, diabetes mellitus or handicap prior to stroke had a relation with PSF. Of these, one study reported prior myocardial infarction to be more prevalent in patients with than in patients without PSF.[55] The other studies did not report associations with pre-stroke variables.[14, 49, 56-58] Two studies took pre-stroke

fatigue into consideration and found that it increased the risk of PSF. Controlling for pre-stroke fatigue decreased the association between PSF and post-stroke depressive symptoms.[16, 49] The reported prevalence rates of pre-stroke fatigue were 61%[49] and 30%.[16] Two other studies questioned patients about pre-stroke depression. One reported an association with PSF,[55] whereas the other did not.[47]

Thus, so far, the only pre-stroke variable found to be consistently related to PSF is pre-stroke fatigue. This relation can be explained in several ways. As higher levels of exhaustion have been found to be a risk factor for a subsequent stroke,[20] PSF might be one of the tell-tale signs for a forthcoming stroke. On the other hand it is plausible that for those patients who experience fatigue as an expression of psychological distress, it is this expression that manifests itself after the disturbing experience of stroke.

1.3.2. Stroke variables

Stroke variables have rarely been found to be associated with fatigue. This is true for severity of stroke, number of strokes, neurological deficits, location and type of stroke. Three studies examined the differences between patients with a transient ischemic attack (TIA) and those with a definite stroke. It was found that stroke patients, even those with a minor stroke (NIHHS score=0)[59], were significantly more fatigued than those with a TIA.[55, 57, 59] This effect is not evident for number of strokes. Whereas one study reported that patients who had suffered recurrent strokes were more prone to fatigue than those with only a single stroke,[19] another study did not find this association.[17] Also, conflicting findings on the relationship between neurological deficits and PSF have been reported. Whereas some studies found a significant association,[18, 47, 49, 59, 60] others did not.[14, 47, 55, 56] Furthermore, several studies failed to find an association between severity of stroke and PSF.[19, 47] Yet, white matter lesions proved to be related to fatigue in two[55, 60] out of three studies.[47]

Of the studies investigating the relationship between stroke type and PSF, only one reported increased levels of fatigue (assessed with the FSS) in patients after an ischemic attack in comparison with an intracerebral hemorrhage.[61] Other studies found no significant differences between different stroke types.[14, 19, 46, 56, 62] Although subarachnoid hemorrhage (SAH) was not included in most of these studies, prevalence rates of severe fatigue after SAH are similar to those after other types of stroke.[63-65]

No study found global localization or type of stroke to be associated with PSF,[14, 18, 19, 46, 47, 49, 56, 58, 62] except for infratentorial lesions that have been associated with a greater risk of PSF.[47] Some studies have focused on more specific brain regions. Significantly higher incidences of PSF were found in patients with lesions in the internal capsule[66, 67] and the basal ganglia than in patients with other stroke locations.[66] Furthermore, studies classifying lesions on the basis of the artery involved have shown mixed results with regard to basilar

infarctions.[55, 58] Whereas in one study, no association with fatigue was reported,[55] in the other study patients with basilar infarctions and little residual disability reported less fatigue impact than patients with severe disabilities as assessed with the modified Ranking Score. The authors thus argue that, opposed to the relative insensitivity of PSF to the severity of cerebral hemisphere ischemia, the extent of the basilar artery infarction might influence PSF.[58] However, in a later study by the same researchers, no association between basilar infarctions and PSF was substantiated.[55]

The results of the studies on localization and stroke type seem to fit with the concept of 'central fatigue' as proposed by Chaudhuri and Behan (2004; 2004).[68, 69] There are several functional circuits in the brain involving the basal ganglia, the thalamus, the anterior cingulate cortex, and frontoparietal cortex, consisting of both dopamine and serotonin systems.[68, 69] Damage to each of these areas can affect the circuits and feedback loops involved, causing problems in e.g. movement control, attention and speed of information processing. The authors propose that central fatigue is caused by disruptions in the striatal-thalamic-frontal loops, connecting the neostriatum with the prefrontal cortex. Herein, the basal ganglia have a key position because they subservice higher order aspects of motor control that regulate the motivation to undertake an activity and, thus, may relate to central fatigue: "the failure to initiate and/or sustain attentional tasks ('mental fatigue') and physical activities ('physical fatigue') requiring self-motivation (as opposed to external stimulation)".[68, 69]

Thus, according to the above-mentioned theory, infarctions of the basal ganglia as well as of other regions involved in the striatal-thalamic-frontal loop may cause PSF. One study has indeed found an association between PSF and basal ganglia infarction.[66] Most other studies, however, did not report the specific lesion sites of the patients included, so that this relationship could not be further substantiated. Still, this theory might explain the absence of a relationship between lesion size and fatigue, not only in stroke patients but also in patients with MS.[11]

Recently, the hormonal origin of PSF has been emphasized. Activation of the cytokine system has been associated with inflammation after stroke,[32] and peak levels of proinflammatory cytokines have been found to correlate with infarct volume, functional outcome and mortality after one year.[33] Furthermore, cytokine-receptors can be found throughout the hypothalamic-pituitary-adrenal axis (HPA-axis) which in turn plays a central role in stress responses. Specifically, after stress, HPA-axis functioning as well as increase in proinflammatory cytokines can induce sickness behaviors such as social withdrawal, apathy and sleepiness in order to allow the individual to recuperate from the stress. However, chronic alterations in these systems have been reported as more detrimental and subsequently, as possible causes for chronic fatigue in

neurological afflictions such as traumatic brain injury (TBI) and multiple sclerosis (MS).[32, 70-72]

In addition, HPA-axis deregulation such as putative abnormalities can affect the striato-thalamo-cortical loop[68, 69] and, thereby, central fatigue as mentioned previously. Until now, only two small studies on this subject have been conducted in stroke and SAH patients.[39, 73, 74] One study with SAH patients concluded that, since only three out of 10 patients showed some degree of pituitary dysfunction, impaired pituitary capacity may contribute but is not necessary to develop PSF.[73] The other study found that, after excluding patients with high depression scores and pre-stroke fatigue, patients who fulfilled the criteria for PSF had markedly higher levels of serum C-reactive protein levels than patients without PSF.[74] Thus, although these studies did not show direct links with fatigue, it is plausible that alterations of cytokine levels and HPA-axis deregulation might (partly) explain fatigue in patients with stroke.

In summary, it is evident that PSF can occur after any kind of stroke with any kind of severity, and that multiple causation of fatigue as a result of brain injury may be a distinct possibility. Furthermore, severe fatigue has been found to be as frequent in stroke patients as in patients with other types of progressive and non-progressive brain damage, such as multiple sclerosis (75%),[75] Parkinson's disease (33-81%),[76] traumatic brain injury (50%-80%)[76, 77] or brain tumors (40%).[78] Despite these commonalities regarding fatigue in neurological patients, some reviews have concluded that, since direct associations between lesion sites and fatigue are weak, PSF is not directly caused by the brain damage suffered.[20] Thus, not surprisingly, many studies have focused primarily on clinical and psychological variables as possible direct causes for PSF. Although fatigue is undoubtedly related to a number of these variables as discussed below, it is unfortunate that the central origin of PSF has been largely disregarded in these studies, since this could have provided a more comprehensive view on this extensive problem.

1.3.3. Clinical variables

Amongst the clinical variables related to PSF, sleep disturbances, pain and physical disability have received most attention. Some studies have also taken into account current co-morbidity and medication. Although associations between these clinical variables and PSF have been found, the relationships are often complex and uncertain.

Sleep disturbances are frequently found in stroke patients. Sleep-related breathing disturbances, for example, are found in 50-70% of the patients and sleep-wake cycle disturbances in 10-50%.[79] These sleep disturbances might provoke sleepiness and low rest levels. Therefore, a high concurrent prevalence of PSF and sleep disturbances can be expected. Yet, only a surprisingly small amount of studies on PSF have taken sleep disturbances into account (see table

2). Five out of seven studies found a weak relationship between PSF and sleep disturbances, such as insomnia or frequent awakening.[16, 49, 55, 56, 80] However, these associations found in two studies disappeared when controlling for depression[49] or when entered in a multivariate analysis.[16] Unfortunately, the majority of the studies used questionnaires[16, 80] or even single questions[46, 49, 56] to assess sleep disturbances. These tools are probably not adequate to assess the full scope of common sleep disturbances after stroke, especially milder forms of sleep apnoea. Even though sleepiness is different from fatigue,[28] sleep apnoea seriously affects rest and may thus exacerbate PSF.[41]

Chronic pain after stroke is increasingly recognized, with reported prevalence rates ranging from 11% to 53%.[4, 81] Furthermore, stroke patients often report other bodily pain and headache. Although one study reported no relationship between PSF and pain, in this study only one question to assess fatigue and one to assess pain were used.[56] The few other studies covering both PSF and pain are quite consistent in finding small to moderate associations (see table 2),[19, 82, 83] but one study found a strong relationship between pain and fatigue impact.[61]

There are a few studies in which the relation of PSF with concomitant diseases and medication use was investigated. Although patients with stroke consistently showed more concurrent diseases and higher use of medication, only weak associations between these variables and PSF have been found. No associations between fatigue severity and concurrent cardiac disease, diabetes or angina pectoris have been reported.[20, 46, 49, 56, 58, 80] Only one study reported a significant relationship between diabetes mellitus and fatigue impact.[55] In a study investigating the relationship between blood pressure and PSF, the results showed that both hypertension and hypotension were related to PSF, as was the use of antihypertensive medication.[57] However, two other studies did not find hypertension to be related to fatigue impact.[55, 58]

Studies relating PSF to physical disability are few and difficult to compare, since the assessment tools and methods used vary considerably. A noteworthy difference seems to lie in the use of either the Barthel Index (BI) or the modified Ranking Scale (mRS) as a measure of disability or ADL-dependence. In general, no associations have been found between the BI and several different fatigue scales (FSS[16, 80]; FIS[84], CIS-f[47], SF-36[17] and AED[18]) except for one study using the MFI-20[45]. The opposite seems to hold true for the mRS which has almost consistently been found to be associated with PSF. Associations were found with the FSS,[58, 82] VAS-f[49] and a single question on fatigue,[56] but not with an interview of Astheno- Emotional Disorder.[18] It has been suggested that the BI has a substantial ceiling effect[63] and, furthermore, that the mRS seems to be more sensitive and responsive as compared to the BI in assessing disability after stroke.[85] Thus, it seems that the mRS is preferable in PSF research.

Other studies taking into account physical disabilities also show conflicting findings. Two out of three studies using the Motricity Index (MI) as an assessment tool for paresis did not find an association between the severity of paresis and the FSS score.[35, 46, 80] Physical functioning as assessed with the Short Form-physical functioning (SF-phys) was not related to SF-vitality in a large cross-sectional study,[86] but it was associated with FSS scores in two other studies.[16, 17] Lastly, less reported assessment tools such as the Sickness Impact Profile-ambulation and single questions regarding ADL or speech impairment have all resulted in finding associations with fatigue, regardless of the fatigue scale used.[15, 19, 87-89] Overall, prevalence rates of PSF were found to be high, even in patients with minor physical disabilities.[14, 22]

Recently, a systematic review was conducted on the association between PSF and physical fitness. Based on three studies, the authors concluded that there was no significant association between PSF and the efficiency of gait, peak exercise capacity, number of steps per day, or self-reported exercise level.[34] This conclusion is congruent with two other studies (not included in the review) on walking efficiency[89] and aerobic fitness.[44]

Although there appears to be no unambiguous relationship between PSF and physical disability, some aspects of ambulation capacity and physical fitness may still be relevant, because physical disability might induce physical deconditioning leading to fatigue. On the other hand, severe fatigue might have a negative impact on functional ability and general health.[19] It is possible that the lines of causality differ between patients and for various activities. For instance, basic activities, such as dressing and toileting, are generally less affected by fatigue than activities that are more dependent on choice and demand greater initiative, such as sexual intercourse,[49] shopping[18] and vocational activities.[18, 20, 90] It is likely that fatigued patients can get themselves to do basic daily life tasks, but spend too much energy on these basic tasks to feel sufficiently fit to engage in other activities. However, as of yet, this is no more than a hypothesis that, although it seems to have substantial face validity, needs to be thoroughly examined.

1.3.4. Sociodemographical variables

Associations with demographical variables do not aid in the identification of patients at risk of developing PSF. As some studies have found older age to be related to PSF,[19, 46, 84] others found an association with younger age,[43, 47] or no association at all.[14, 16-18, 56-58, 62, 66, 91] With regard to sex, some studies have found female gender to be related to PSF,[17, 19, 46, 62, 66] but others have not.[14-16, 18, 47, 49, 56-58, 91] Level of education is not associated with PSF either according to a majority of studies.[16, 17, 49, 91] Employment status, especially being unemployed, showed an association with PSF,[49, 58, 90] but in a study by Naess et al (2005) this relationship disappeared when functional outcome was taken into account.[58]

Studies focusing on social functioning found that there was an association between PSF and diminished social functioning as measured with the SIP-68,[82] or the social functioning subscale of the SF-36.[83] A study taking into consideration the social relationships of patients found that there was a negative association of PSF with sexual functioning as well as with social contacts with friends and acquaintances (but not with partner or family).[18] A plausible explanation for this finding is that PSF limits the amount of energy that can be spent on social interactions and that, as a result, patients choose to spend their energy to those people that are closer to the home and heart. Furthermore, living alone (or not being married) was associated with PSF only in one study,[19] but not in others.[16, 46, 56, 92]

Studies taking lifestyle into consideration found no conclusive evidence for cigarette smoking,[49, 56, 58] use of alcohol,[49] or Body Mass Index[16, 58] to be related to PSF. In a pilot study in Sweden, the relationship between nutrition, mood and fatigue was studied in 89 elderly stroke survivors 6 months after discharge from hospital,[93] since eating difficulties and nutritional deficits are frequent problems after stroke. It was found that being female and feeling fatigued was related to poor nutritional status as assessed with six questions of the Mini Nutritional Assessment-Short Form. The authors argue that this relationship may be bidirectional. On the one hand, fatigue may cause difficulties in preparing food and may impede motivation to eat, leading to a lack of nutritional intake. On the other hand, poor nutritional intake may exacerbate fatigue.[93]

Thus, although demographical variables and lifestyle seem to have little relationship with PSF, it is evident that PSF can have a negative impact on social relationships and nutritional intake. For the clinician it is important to take the latter aspect into consideration, since it can easily be overlooked.

1.3.5. Psychological variables

Depression is a common problem after stroke with an estimated prevalence of about 30%.[94] Since fatigue is a symptom of depression, as stated in the DSM-IV-TR, an overlap between both symptoms is unavoidable.[9, 20, 22] Indeed, moderate to high associations between PSF and depressive symptoms are a consistent finding in the literature, not only in stroke patients,[14, 15, 19, 35, 46, 49, 58, 66, 80, 82, 95] but also in patients with TBI,[96] MS,[97] and in healthy subjects.[82, 96] Yet, in the studies that specifically looked at stroke patients who suffer from depressive symptoms and/or fatigue, a clear dissociation between the two phenomena was always present in some patients.[14, 15, 46, 49, 57, 58, 98, 99] This dissociation indicates that, although a co-occurrence of fatigue and depressive symptoms is common, these symptoms cannot be viewed as a unitary construct or affliction.

Anxiety after stroke is also commonly reported. It is estimated that approximately 20% of all patients with stroke will experience serious anxiety at

some point in time.[100] A few studies have reported a weak association of anxiety level with fatigue severity[19, 47] and fatigue impact.[57, 62]

Studies on the relationship between PSF and other psychological variables are scarce. Although merely very limited and specific psychological constructs were found to be related to PSF (increased locus of control towards powerful others[46] and emotion-oriented coping[84]), these findings have had relatively far reaching consequences in the field. For one, these findings have been repeatedly referred to as evidence for a psychological basis of PSF. They have even led some authors to conclude that PSF is associated with personality.[20] Undoubtedly, this possibility still needs further research. Since interventions on a psychological level are quite feasible and because the relationship between PSF and psychological factors is still elusive, a study on the psychosocial profile of patients with PSF was conducted in this thesis **(chapter 3).**

1.3.6. Cognitive performance

A number of studies on PSF has focused on cognitive impairments. Most of these studies used the Mini Mental State Examination (MMSE) to asses cognitive performance, and none of these found an association with PSF.[18, 46, 47, 58, 66, 80] However, the MSSE is a rather coarse instrument and does not detect subtle cognitive impairments after stroke, such as mental slowness or attention deficits.[101] Furthermore, in the MSSE ceiling effects are known to occur. Likewise, another study found no relationship between performance on the Trail-Making Test (TMT) and fatigue impact.[35] The TMT is a short test and, used in isolation, not suitable to measure the whole array of executive processes, let alone other cognitive functions.[101] Thus, it can be concluded that no associations between PSF and 'crude' measures of cognitive functioning have been found.

In contrast, studies using more extensive[65, 67] or in-depth neuropsychological assessment tools[102] do support the notion of an association between PSF and cognitive (dys)functioning. The results of these studies suggest that (subtle) attention deficits seem to be related to fatigue.[67, 102] This suggestion is in line with the findings of other studies that subjective concentration problems are associated with PSF.[15, 82] Because in daily life stroke patients are confronted with many more attention demanding situations than in the structured and distraction-free setting of a clinical test situation, even relatively small attention deficits can become problematic, for example during conversations or when driving a car. If patients compensate for such attention deficits by mobilizing more attentional resources, they may experience more fatigue. Thus, it can be expected that fatigue will increase during the day in PSF-prone patients more than in healthy controls, who do not have to recruit such additional mental resources.

The above-mentioned mechanism regarding attention and compensation has been proposed by Van Zomeren et al (1984) and referred to

as the 'cognitive coping hypothesis'.[103] This hypothesis postulates that fatigue is mainly due to the additional (compensatory) effort made by brain injured individuals to meet the attentional demands of everyday life as a result of their cognitive deficits.[103] As these cognitive deficits are ubiquitous after stroke, in this thesis the view is adopted that the primary cause of fatigue is the recruitment of attentional resources according to the cognitive coping hypothesis (**chapter 5).**

Section 2: The management of fatigue

In 2009, a Cochrane systematic review of interventions for PSF was published.[21] Herein, McGeough et al reviewed the few available disease-specific treatments and concluded that there was insufficient evidence to alleviate PSF, either by pharmacological or by non-pharmacological means. The few possible treatment options included the administration of fluoxetine, investigated in a randomized double blinded controlled trial, which did not improve PSF but decreased depressive symptoms.[104] In a small trial, patients after SAH were less exerted when receiving tirilazad mesylate,[105] however, more than half of the patients were not available for follow-up.[21] A chronic-disease self-management program, not specifically aimed at fatigue, was not effective in reducing fatigue after stroke.[106] Furthermore, a small study of modafinil showed that this drug decreased fatigue severity by a very small margin in patients with brain stem and thalamic strokes, but not in patients with cortical infarctions.[107] Lastly, a study on the treatment of sleep disordered breathing by continuous positive airway pressure showed a decline of fatigue only in those patients suffering from sleep apnea syndrome.[108] More importantly, this treatment seemed to have negative effects on some aspects of functional health. In summary, these studies provide little basis for the development of clinical guidelines. It has however repeatedly been suggested that tailored educational programs might aid fatigued stroke survivors.[42, 46]

Unfortunately, the literature on other neurological conditions, such as TBI or MS, does not yield more conclusive evidence. In systematic reviews of the literature Belmont et al (2006)[109] and Lee et al (2008)[110] concluded that there is only little evidence-based advice that can be offered to patients with TBI and MS, respectively. A handful of studies on the benefit of pharmacological agents, such as modafinil, suggested some effectiveness in reducing daytime sleepiness without improvement of overall fatigue and with a risk of undesirable side effects. One study suggested positive effects of an energy conservation course[111] aimed at teaching MS patients to cope with fatigue by implementing rest, energy efficient planning of activities, efficient use of body mechanics and effective communication.

In short, at the start of the present project, no evidence-based treatments or guidelines for PSF were available, nor was there strong evidence available from studies of patients with other neurological diseases. Yet, in the St. Maartenskliniek in Nijmegen a treatment module specifically targeted at PSF had been evaluated in a pilot study with positive effects on fatigue severity.[10] This treatment module consisted of a combination of exercises, patient education, goal setting, energy compensation strategies and some elements of cognitive behavior therapy. It was then decided by the Cognitive Rehabilitation Consortium in the Netherlands that this treatment should be evaluated thoroughly.[112] Thus, the description and the evaluation of this treatment form the core of this thesis. The central objective is to provide first directions in dealing with this common, chronic and debilitating affliction called PSF.

Research questions, and outline of the thesis

As described above, there are several important issues regarding PSF. First, it is a highly prevalent and troublesome consequence of stroke, requiring medical attention. However, qualitative studies have suggested that PSF is still a neglected problem in healthcare, even though patients report that receiving insufficient information on the subject causes significant distress. Second, no consensus on the definition or diagnostic criteria for PSF exists. As a consequence, many different assessment tools tapping into different constructs are being used. This hampers not only the comparison of research results, but it also confuses clinicians as to which tool to use in practice. Although the FSS is the most frequently applied tool to determine PSF, it assesses fatigue impact rather than fatigue severity, and there is no consensus on which criterion to apply for the diagnosis PSF. A third problem concerns the still poorly understood etiology of PSF. A better understanding hereof would be of great value in the development of targeted treatments. Many researchers presume that altered brain mechanisms might constitute the direct cause of fatigue after stroke. On the other hand, somatic problems and psychological distress have consistently been found to be related to PSF. Yet, the direction of these associations is still unclear and knowledge of other possible psychological factors is scarce. Taken together, considering the current lack of knowledge concerning diagnosis and treatment of PSF, the following research questions form the outline of this thesis:

1. *Is there a problem of underdiagnosis of PSF in the Netherlands? Do patients receive sufficient information about PSF in Dutch healthcare and is this related to personal or clinical characteristics?*

2. *Do patients with PSF have specific psychological or social characteristics? If so, could knowledge of these characteristics aid in the development of effective treatments?*
3. *How does the one-dimensional FSS psychometrically compare to the multi-dimensional CIS20-R? To what extent do both commonly used fatigue scales assess the same construct?*
4. *What components should be part of a comprehensive treatment protocol for PSF, taking into account the emotional, cognitive and physical aspects of fatigue?*
5. *Is such a comprehensive treatment approach effective to reduce PSF in the chronic phase after stroke?*

These questions are addressed in seven chapters divided into two sections:

Section 1. The trouble with fatigue.

Chapter 2 addresses *research question one* and presents an internet-based study on the information about PSF provided to patients in the Netherlands. It reports on the data of 538 participants who completed a questionnaire containing questions about whether they had received information on PSF as well as questions about their fatigue (impact, severity, onset time and nature of fatigue), their perceived need for treatment, demographic characteristics and the perceived difficulty level of the questionnaire. It is also investigates whether this provision of information is related to personal or clinical characteristics, as it is conceivable that elderly patients or patients with a low educational level may receive less information compared to younger and higher educated people.

Chapter 3 addresses *research question two* and presents a study on the psychological and social characteristics of patients with severe PSF. Herein the data of 88 outpatients is used. These patients completed a relatively extensive array of questionnaires regarding psychosocial aspects. Thus, a profile consisting of symptoms of depression, anxiety, psychological distress, somatic complaints, coping styles, social support and self-efficacy is obtained. These data are compared to reference groups of healthy controls and patients with other chronic diseases. Fatigue is assessed by the FSS and the CIS20-R and associations between these fatigue scales and the psychosocial variables are calculated. Moreover, it is discussed whether targeting these associated variables might aid in reducing fatigue.

In **chapter 4** investigates the psychometric properties and underlying constructs of two widely used fatigue assessment tools: the CIS20-R and the FSS (*research question three*). Both questionnaires were filled out by 196 patients with stroke and 112 age-matched controls. The internal consistency and

convergent validity are calculated. Next, factor analysis is conducted to examine the item structure and underlying constructs of these questionnaires.

Section 2. The management of PSF.

Chapter 5 deals with *research question four*. In this chapter the treatment protocol "COgnitive and GRaded Activity Training for post-stroke fatigue (COGRAT)", based on the treatment module "Dealing with fatigue" developed in the Sint Maartenskliniek, is described. The treatment comprises two complementary ingredients. The first is a COgnitive treatment (CO), teaching patients cognitive strategies that allow them to make more efficient and sagacious use of their energy. The other part consists of GRaded physical Activity Training (GRAT) aimed at improving physical strength and stamina. Both treatments are offered in parallel during a twelve-week period. Although the general outcome of a pilot study of the "Dealing with fatigue" module showed a decline of fatigue and psychological distress, several adaptations were deemed necessary. First, patients often suffer from attentional problems and are, therefore, easily distracted and, subsequently, fatigued. For this reason, the maximum group size was scaled down from eight to four patients. Second, because Cognitive Behavioral Therapy (CBT) has been found effective in non-neurological patients with fatigue, CBT was more strongly incorporated into the treatment. A third major adaptation included the development of a graded activity training protocol based on the recommendations of the American Heart Association[113].

In **chapter 6** the results of a multi-center randomized controlled trial evaluating the effectiveness of the COGRAT treatment as described in chapter 5 are reported for patients in the chronic phase after stroke (*research question five*). In this study, after a qualification period of three months, 83 chronic stroke patients suffering from severe PSF are randomized to either the cognitive treatment (CO) alone or a combination of cognitive treatment and graded activity training (COGRAT). The patients are assessed at four time points, two prior to treatment, one immediately after treatment, and the last time at 6 months follow-up. Fatigue is assessed with two fatigue scales. It is hypothesized that COGRAT is more effective in reducing fatigue than CO alone.

Finally, **chapter 7** summarizes the main findings of this thesis and provides a general discussion. The results of the studies presented in the previous chapters are discussed in the context of the existing literature on PSF as well as the most important methodological issues related to the studies. In addition, recommendations for future research are made and first practical directions for researchers and clinicians faced with patients that suffer from PSF are provided, specifically regarding assessment and treatment techniques.

Table 1. Definitions of post-stroke fatigue and fatigue in neurological disorders.

	Definition	Affliction	Applied by
1	Difficulty in initiation of or sustaining voluntary activities requiring self motivation. Pathological fatigue is thus best understood as an amplified sense of normal (physiological) fatigue that can be induced by changes in one or major variables regulating work output.	Fatigue in neurological disorders	Chaudhuri & Behan [68, 69](2000;2004)
2	Subjective fatigue can be described as a feeling of early exhaustion developing during mental activity, with weariness, lack of energy and aversion to effort. Objective fatigue being: a failure to maintain a required output (physical or mental) during a task.	PSF	Staub et al [12, 22](2001a; 2001b) Staub & Carota [9](2005) Barker Collo, 2007[24]
3	A reversible decrease in or loss of abilities associated with a heightened sensation of physical or mental strain, even without conspicuous effort, due to an overwhelming feeling of exhaustion, which leads to an inability to sustain, or a difficulty in sustaining, even routine activities.	PSF	Bogousslavsky[27] (2003) White et al 2012 [31]
4	Pathological fatigue is a state characterized by weariness unrelated to previous exertion levels and is usually not ameliorated by rest: A feeling of physical tiredness and lack of energy that was described as pathological, abnormal, excessive, chronic, persistent, or problematic.	PSF	De Groot et al[43] (2003); Lerdal & Bakken[20](2009) Kutlubaev et al (2011)[39]
5	Subjective sensation of fatigue is defined as: an overwhelming sense of tiredness, exhaustion, lack of energy, or difficulties of sustaining routine actions.	PSF	Naess et al (2005)[58]
6	A condition accompanied by subjective feelings of physical and psychological exhaustion making daily living activities impossible or difficult. It may be reversible or chronic, unrelated directly to effort.	PSF	Jaracz et al (2007)[84]

Table 1. Continued

7	A feeling of lack of energy, weariness, and aversion to effort.	PSF	Mead et al (2007) [50]; Lewis et al (2011)[89] Barbour & Mead (2012)[41] Duncan et al (2012) [34]
8	A subjective experience, that includes symptoms as rapid inanition, persisting lack of energy, exhaustion, physical and mental tiredness and apathy	PSF	Valko et al (2008)[91]
9	The subjective lack of physical or mental energy to carry out usual and desired activities as perceived by the patient.	PSF	Tang et al (2009; 2010)[17, 66]
10	A reduced capacity for work following a period of mental or physical activity: 2 different kinds of fatigue: motor fatigue and cognitive fatigue: motor fatigue refers to a decrease in motor performance during sustained attention, whereas cognitive fatigue refers to a decrease in performance during sustained cognitive activity.	PSF, fatigue in patients with MS and healthy controls	Claros-Salinas (2010)[102]
11	A sense of exhaustion, lack of perceived energy or tiredness distinct from sadness or weakness	PSF	Lerdal et al (2010)[16]
12	Fatigue is a psychophysiological state that acts on the subject's motivation to engage in and/ or to continue strenuous physical or cognitive activities. Fatigue as a subjective condition, which can be assessed by specific questionnaires, must be strictly distinguished from fatigability, which is defined as reduction of a physical or mental performance during a prolonged task.	PSF & fatigue in neurological disorders	Romani et al (2008)[71]
13	A subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities	Fatigue in patients with MS and PSF	Barrit & Smithard (2011)[33]

Table 1. Continued

14	A profound sense of tiredness, lack of energy, and feeling of exhaustion following acute stroke	PSF	Kirkevold et al (2012)[42]
15	Over the past month, there has been at least a 2-week period when the patient has experienced fatigue, a lack of energy, or an increased need to rest every day or nearly every day. This fatigue has led to difficulty taking part in everyday activities.	PSF, case definition	Lynch et al (2007)[62]
16	Astheno emotional disorder is a psycho-organic syndrome, termed by Lindqvist-Malmgren, which includes in mild forms; increased fatigability, impaired concentration, memory difficulties, irritability and emotional instability. In more severe forms it also includes impoverishment and sluggishness, slowness of thought, lack of overview and reduced capacity for abstraction.	Astheno-emotional disorder	Carlson (2003)[18] Rödholm (2001; 2002)[114, 115]
17	General exhaustion, lack of initiative and increased sleep demand	Post-aneurismal SAH fatigue	Brandt et al (2004)[73]

Table 2. Studies of post-stroke fatigue: study design, patient samples, time post stroke, questionnaires used, and associations found.

Authors	Study design, Population, N, Mean age (yrs)	Time post stroke	Fatigue Assessment Questionnaire, cut-off, prevalence of PSF	Associations with fatigue
Andersen 2011[90]	Longitudinal, Cohort, Stroke, N=83 <60 yrs, employed prior to stroke Mean age 54	10 days, 1 year & 2 years	MFI-20 (PSF: MFI-20 general fatigue ≥ 12) At 2 years 57% PSF (scores and percentages at other assessment dates are not specified; part of the study of Christensen 2008[45]).	- Fatigue at 10 days, and at 1 and 2 years post-stroke, was an independent determinant of the chance of returning to work after stroke at 1 and 2 years post-stroke.
Appelros 2006[56]	Cohort, first –ever stroke, N= 253 Mean age 74.5	1 year	Single Question (yes/no): 53% indicated fatigue	- Fatigue was associated with neurological deficits (NIHSS: OR=1.1) and physical disability (Modified ranking scale: OR=1.4). - No associations with pain, depressive symptoms, age, gender, stroke type or pre-stroke risk factors (hypertension diabetes, heart disease, smoking) were found (all p>.05).
Carlsson 2003[18]	Longitudinal, First – ever mild stroke < 75 years, and living together with spouse. N =75 Mean age 60	1 year	Interview on astheno-emotional disorder (AED) including specific question on fatigue 72% indicated fatigue	- Of the patients with AED (71%) 51% were depressed (DSM-IV criteria), and 49% were not depressed. - AED correlated with life satisfaction, leisure situation, vocational situation, sex –life, contact with friends and symptoms of depression (all p<.05). - AED was not related to ability to self-care, financial situation, partner relationship, family life, neurological impairment (SSS), cognitive deficits (MMSE), ADL (BI), age, sex, handicap (OHS) or stroke localization (all p>.05).

Table 2. Continued

Choi-Kwon 2005[49]	Cross-sectional, First-ever stroke, between 40 & 80 yrs, mRS<4, MMSe>23, N=220	3-27 months Mean:15 months	VAS-f (1-3: mild; 4-6: moderate; 7-10 severe fatigue) 57% (70.4% mild; 18.4 % moderate 11.2% severe PSF) FSS mean score: 3.0 ± 1.4 FIS (Fatigue Impact Scale) mean score: 1.4 ± .5 Question on frequency of PSF: 44% 20-29 days a month Question on daily duration of PSF: 88% < 6hrs a day, 12% 6-24 hrs a day.	- Pre-stroke fatigue was frequent (38%) and associated with PSF (OR=33.46) - Association between PSF and depressive symptoms (GDS; OR=2.67), however of patients without depression (GDS ≤10) 50% had PSF. - PSF was associated to mRS (OR=3.25) and decreased sexual activity (OR=2.46). - PSF was not related to specific lesion location, lesion size, medication use, gender or age.
Christensen 2008[45]	Cohort, longitudinal, First ever stroke, N=165 Mean age 65 HC, N= 653 chronic disease N= 416 Mean age 48	10 days, 3 months, 1 year & 2 years	MFI-20 (cut-off: MFI-20 general fatigue ≥ 12) At 10 days; 59% PSF, mean score 12 ± 5 At 3 months; 44% PSF, mean score 11 ± 5 At 1 year; 38% PSF, mean score 10 ± 4 At 2 years 40% PSF, mean score 10 ± 4 HC and chronic disease combined, 32% above cut-off, mean score of 10 ± 4	- Functional outcome (BI<60) was associated with PSF - No associations found for lesion site

Table 2. Continued

Eskesen 1984[116]	Longitudinal, cohort, SAH, N=42 Mean age: 51	3-64 months Mean:36 months	Single question (yes/no) 41% indicated fatigue	
Glader 2002[19]	Cross-sectional, longitudinal, Stroke, N=3667	2 years	Single Question: do you feel tired: Always: 10% Often: 29.2% 39.2% PSF	- Dependency and not returning to home was related to PSF (PSF often, OR= 2.44.- PSF always OR=5.15), as was self-reported general health, feelings of anxiety, pain and depression (all p<.005). - Patients with PSF at year 2 were more likely to die before year 3 than those without PSF(OR= 1.64) - Patients with speech impairment, living in an institution prior to stroke, dependent on ADL prior to stroke or with worse general health had more fatigue (all p<.001). - PSF was not related to number of strokes or stroke type.
Harbison 2009[57]	Cross-sectional, Stroke, N=69 TIA, N= 31 Independent (MRS>2) Mean age 69	1-6 months	FSS (cut-off: FSS > 4) Stroke pt 51% PSF, mean score: 3.8 TIA pt 23%, mean score: 3.0	- Fatigue impact was higher and more prevalent in stroke pt than in TIA pt - Hypertension (OR:3.1; p=.05) and low daytime diastolic blood pressure (OR: 4.2; p=.004) were both associated with fatigue impact, as was blood pressure medication. - FSS was associated with anxiety (HADS-A:*r=.37; p=.009)* and symptoms of depression (HADS-D; *r=.42; p=.002)*. - Double dissociation was found: 23% of non-depressed (HADS-A &HADS-D ≤ 7) had FSS>4. And 31% of pt with FSS<4 had higher depression scores (HADS-A &HADS-D > 7). - No associations were found for age, gender, mean daytime or night-time blood pressure (systolic and diastolic blood pressure).

Table 2. Continued

Hellawell 1999[64]	Longitudinal, cohort, SAH, N=28 Mean age: 50	6, 12 & 24 months	HISC (Head Injury Symptom Checklist) Single question on whether fatigue is present as a symptom. Prevalence of symptom at 6 months 64%, 12 months 59% and 24 months 59%	- Fatigue was the most common problem reported by patients, followed by passivity 61%-47%-46%, and memory problems 50%-52%-56%.
Jaracz 2007[84]	Cross-sectional, First-ever stroke N=50 (60% mild, 40% moderate stroke) Mean age: 55	3 months	FIS (3 subscales: physical, psychological and social) No clear cut-off specified 30% of pt indicated to experience severe and very severe fatigue impact in several domains.	- Most severe fatigue impact was found for physical functioning domain, but no association with functional deficit (BI) was found. - Depressive symptoms (BDI) were associated with psychological fatigue impact only - Emotion oriented coping (CISS) was associated with higher fatigue impact, whereas task oriented coping was associated with lower fatigue impact - No associations with fatigue impact were found for sex, and side of lesion (R/L)
Koopman 2009[82]	Case-control Prospective, N=44 CVT (cerebral venous thrombosis) and 44 HC, (functionally independent) Median age: 31	median 63 months (range 12-124)	FSS Stroke pt 30% PSF (FSS>5), mean score: 4.2 HC 7% FSS>5, mean score: 2.8	- Associations in patients were found for fatigue impact with headache (*Headache Impact Test: r=.47, p<.001*), depressive symptoms (*CES-D: r= .43, p=.004*) subjective concentration problems (*EuroQuol cognition: r=.59, p<.001*), functional outcome (*mRS; r=.75, p<.001*) and the psychosocial impact (*SIP; r=.69, p<.001*). - No associations with fatigue impact were found for age, sex, symptoms at admission and time post-onset.

Table 2. Continued

Lewis 2011[89]	Cross-sectional, Stroke N=66 independent ambulatory Mean age: 71	Median 160 days (range: 84-280 days).	SF-36 vitality subscale (SF-VIT) PSF-prevalence not specified Mean score: 53.6±20.6	- Physical fitness (Lower limb extension power; Nottingham Power Rig) was related to VIT *(r=.38, p=.003, N=58)*. - Walking economy (VO2) was not related to SF-VIT
Lerdal 2011[16]	Longitudinal, Acute stroke (<15 days), N=115 Mean age 68	Mean 5 days	FSS FSS<4=low/no fatigue; FSS 4-4.9=moderate fatigue; FSS ≥ severe fatigue PSF: 33% moderate fatigue; 24% severe fatigue Mean score is not given.	- FSS was related to declared pre-stroke fatigue (overall prevalence 30%; r=.39), physical ambulation (SF-physical, r=-.4) and depressive symptoms (BDI-II, r=.31, all p<.05) in multiple linear regression. - FSS was not related to sex, ADL (BI), sleep quality, body mass index, respiratory disease or use of sleep medication when controlled for in multiple linear regression (all p>.05).
Mead 2011[86]	Cross-sectional, Longitudinal, Stroke , N=1080 Mean age: 71	Mean 64 weeks (Sd:30) weeks	SF-36 vitality subscale (SF-VIT) Median SF-VIT: 37.5	- Vitality was higher in males than in females (median SF-VIT 40 vs 35). - Increasing age, worse emotional role function (SF-36; r=.38, p<.001) and worse mental health (SF-36; r=.20, p<.001) were associated with less vitality. - Less vitality was associated with reduced long-term survival rates in 2/4 models. - SF-VIT at follow up was not independently predicted by stroke-(sub)type, baseline atrial fibrillation, baseline systolic blood pressure, and other SF-36 subscales: physical function, bodily pain, general health and social function.

Table 2. Continued

Michael 2006 [117]; Michael 2007[118]	Cross-sectional, Hemiparetic Stroke, N=53[117] N=79[118] Mean age 65	Mean 10 months (6-120 months)	FSS: (cut-off: FSS > 4) PSF 46%[117] PSF 42%[118] Mean score 3.28 ± 1.36[118]	- FSS was not related to ambulatory activity or fitness (stride counts, step activity intensity and VO2 peak) [117, 118] - FSS was related to lessened balance (Berg balance scale) and poorer falls efficacy (both p<.01).
Naess 2005[58]; Naess 2006[83]	Cohort, controlled Longitudinal, Young stroke, N=192 HC, N=212 Mean age: 48	Mean: 6 yrs (range: 1.4-12.3)	FSS [58, 83] 52% PSF (FSS>4) Stroke pt mean score: 4.1 ± 1.7 HC mean score: 3.44 ± 1.3 SF-36-vitality[83] Stroke pt mean score: 57 HC mean score: 61	- Fatigue impact was independently associated with being a stroke patient depressive symptoms (Nottingham Health Profile-emotional reaction), diabetes mellitus and migraine (all p<.001)[58]. - In stroke patients FSS was independently related to depressive symptoms, reduced functional state and basilar artery infarctation through an interaction with functional state (mRS; all p<.001)[58]. - Anxiety (1 item of MADRS) was associated with FSS in patients with depression (MADRS>6; 39% of patients), but not in patients without depression (MADRS<7)[58]. - FSS was related to unemployment in patients[58] however SF-36-VIT was not[83]. - FSS in patients was not related to sex, age, MMSE, lesion site, severity of neurological deficits at admission, BMI, myocardial infarctation, angina pectoris, smoking, hypertension or post-onset time.[58] - SF-36-VIT was lower in women than in men[83]. - FSS in patients was independently related to SF-36 subscales: vitality (r=-.56), role physical (r=-.31), physical functioning (r=-.30), general health (r=-.44), social functioning (r=-.29; all p<.001) and mental health (r=-.19, p<.05)[83]. - SF-36-VIT in patients was not related to age, sex, marital status, education or mRS[83].

Table 2. Continued

Naess 2010[61]	Prospective, longitudinal, Ischemic stroke N=328 Hemmorhage N=29 TIA N=51 Mean age 68	Mean: 372 days (range 185-757 days)	FSS No prevalence rates of PSF are specified ICVA mean score 4.4 Haemorrhage mean score: 3.0 TIA mean score: 3.5	-	FSS was independently related to pain (VAS-scale: OR=3.4,p=.001).
Noble 2008[119]	Longitudinal, cohort, SAH, N=105 Mean age at start 52	3 & 13 months	MFSI-SF (Multidimensional fatigue symptom inventory-short form). Cut-off and mean scores not stated. At 3 months: 59% pathological fatigue At 13 months: 36% pathological fatigue	-	Variance of fatigue was predicted for 57% by PTSD-symptom severity scale (p<.001). In this study 37% of participants met the criteria for PTSD.
Ogden 1997[120]	Cross-sectional, SAH, N=123 Mean age: 49	4-7 yrs Mean time not specified	Single questions on fatigue and on daytime sleepiness. Separate items not specified. 35% of pt indicated fatigue/daytime sleepiness.	-	Daytime sleepiness/fatigue correlated significantly with difficulties maintaining sleep at night(*r= .34, p< .001*), personality changes *(r = .30, p<.001*), and complaints of poor memory (*r = .32, p<.001*).
Ones 2005[121]	Cross-sectional, controlled, Stroke, N=88 HC, N=40 Mean age 63	> 6 months Mean time not specified	Nottingham Health Profile – energy score Stroke mean score: 66.4 ± 32.7 HC mean score: 20.5 ± 30.7		

Table 2. Continued

Park 2009[80]	Cross-sectional, Stroke, N=40 Mean age 60	Mean: 33 months ± 27	FSS 30% PSF (FSS≥4) mean score: 3.6 ± 1.5	- -	FSS was associated with depressive symptoms (BDI, r=.47, p<.05) and fatigued patients had more often sleeping problems (interview) than none fatigued (p,.05). FSS was not related to Motricity index, BI or MMSE.
Passier 2010[88]; Passier 2011[65]	Cross-sectional, SAH, N=111 Mean age 53 Longitudinal, SAH, N=108 Independent Mean age 53	3 months 12 months	Single question (yes/no) in questionnaire: 90% indicate presence of fatigue[88] FSS[65] 71% PSF (FSS ≥4) Mean score: 4.8	- - -	FSS was higher in patients with physical impairments (GOS < 5, FSS=5.5 vs GS=5, FSS=4.3), an in patients with cognitive impairment (impaired, FSS=5.5, no impairment, FSS=4.4) [65] Main associations were found between FSS, anxiety (STAI), passive coping style (UCL), depressive symptoms (BDI-II) and level of impairment (GOS). [65] No differences were found for age (below and above 52yrs), sex, education (High vs low), location of aneurysm (anterior vs posterior), treatment procedure (coiling vs surgery), or the presence of complications. [65]
Powell 2004[87]	Longitudinal, case-control, SAH, N= 48 Mean age 47	9 & 18 months	Single question with 3-point scale Prevalence fatigue SAH pt 9 months: 62% mild-moderate, 19% severe fatigue Prevalence fatigue SAH pt at 18 months: 65% mild-moderate, 10% severe fatigue	-	Fatigue was associated with lower independence (Brain Injury Community Rehabilitation Outcome).

Table 2. Continued

Rodholm 2002[115];	Longitudinal, cohort, SAH, N= 63[115] Mean age at start 51; SAH, N=119[114]	3,6 & 12 months[115]	Astheno-emotional disorder (AED) diagnostic tool At 3 months: 60% At 6 months: 49% At 12 months (N=63): 38 %[115]	-	AED was associated with pre-existing arterial hypertension. [115]
				-	AED was not associated with age or worse brain injury (RLS85 levels and Fisher grades). [115]
Rodholm 2003[114]	Mean age 52	12 months[114]	At 12 months(N=119):51% [114]		
Schepers 2006[46]	Longitudinal, First ever Supratentorial stroke, N=167 Mean age at start 56	Admission, 6 & 12 months	FSS (PSF: FFS>4) At admission: 51.5 % PSF, mean: 4.1 ± 1.3 At 3 months: 64.1% PSF, mean: 4.5± 1.2 At 12 months: 69.5% PSF, mean 4.7± 1.3	-	Independently related to FSS at 12 months were depressive symptoms (CES-D: β=.34, p<.001) and age (β=.17, p=.02). Locus of control (MHLC-powerful others), was associated with FSS in univariate analysis (r=.24, 0=.002), but not in multivariate (p=.09).
				-	FSS at 12 months was not predicted by sex, co morbidity, marital status, lesion side and type of stroke, motricity index, MMSE, trail making test or sleeping problems.
Schuiling 2005[122]	Longitudinal, cohort, SAH, N= 83 Mean age 53	1-3.4 yrs Mean: 1.7 yrs.	- Single question in Sleep Diagnosis Questionnaire: 31% of pt indicate feeling very tired - SF-36, question on vitality: 53% indicate feeling often tired.	-	Sleep disturbances were associated with tiredness.

Table 2. Continued

Snaphaan 2011[47]	Longitudinal, Stroke, N= 108 Mean age at start 65	2 & 18 months	CIS-f (PSF: CIS-f>35) At 2 months: 35% PSF, mean: 30.3 ± 14.6 At 18 months: 33% PSF, mean 29.5 ± 13.9	- At 2 and 18 months, younger age (OR 0,95), depressive symptoms (HADS-D; OR 1.4; OR 1,3), Anxiety symptoms (HADS-A; OR 1,2, and infratentorial lesions (only for CIS-f at 2 months: OR 4.7) were associated with CIS-f. - Fatigue at 2 months was related to fatigue at 18 months (OR 1.2). - Not predictive of fatigue at 18 months were sex, marital status, education, MMSE, Barthel Index, mRS, NIHSS, lesion location, a history of depressive symptoms or Age-related white matter changes (all p>.05).
Tang 2009[66]; Tang 2010 [17]	Cross-sectional, Stroke, N= 334[66] N=458[17] Mean age 66	3 months	FSS (PSF: FFS>4) [66] 23.4% PSF [66] Mean score 3.1 ± 1.4 [17] SF-VIT Mean score 64.6 ± 21.3 [17]	- In patients with PSF, there were more basal ganglia infarcts, and internal capsula infarcts, whereas brainstem and cerebellar infarcts were less common (p<.05).[66] - FSS was related to SF-VIT score (r=-.61, p<.001), and other HRQOL scales of SF-36: mental health (r=-.50), role-emotional (r=-.43), general health (r=-.40), social functioning (r=-.40), bodily pain (r=-.37), role-physical (r=-.31) and physical functioning (r=-.30; all p<.05). [17] - SF-VIT was related to depressive symptoms (GDS, r=-.60, p<.001), but not to Barthel Index, MMSE, Age, NIHSS, marital status, education, or previous stroke. [17]

Table 2. Continued

Valko 2008[91]	Cross-sectional, Stroke, N= 235 Mean age 63 MS, N=188 HC, N=454 Sleep-wake disorders N=429	For stroke pt mean post-onset time: 1.2± .6 yrs (range .33-2)	FSS (PSF: FFS≥4 / FSS>5.2) Stroke: FFS≥4=49%, FSS>5.2=31% mean score: 3.9 ± 1.9 MS: FFS≥4=69%, FSS>5.2=45% mean score: 4.7 ± 1.6 HC; FFS≥4=18%, FSS>5.2=3.5% mean score: 3.0 ± 1.1 Sleep-wake: FFS≥4=62%; FSS>5.2=36% mean score: 4.3 ± 1.6 VAS-f Stroke mean score: 4.7 ± 2.6 MS mean score: 4.8 ± 2.5 HC mean score: 3.5 ± 2.2 Sleep-wake mean score: 5.1 ± 2.4	- For stroke pt No associations were found for FSS with age, post-onset time, gender or educational status. - The association between FSS and VAS-f was high (in stroke, r=.70, in MS: r=.79, in sleep wake r= .71, in HC r=.52; all p<.01).
Van der Port 2007[35]	Prospective, cohort, First ever (supratentorial) stroke, N= 223 Mean age at start 57	6, 12 & 36 months	FSS (PSF: FFS≥4) At 6 months: 68% PSF, mean: 4.4± 1.2 At 12 months: 74% mean 4.7 (SD not given) At 36 months: 58%, mean 4.3 (SD not given)	- FSS between 6 and 36 months was related to motor function (MI), perceived HRQOL (SIP68), and depressive symptoms (CES-D; all p<.05). - FSS was not independently related to IADL (Frenchai Activities Index) and ADL (BI) when controlled for motor function and depressive symptoms. - FSS was not related to age, gender, co morbidity, or time to complete the trail making task (all p>.05).

Table 2. Continued

Van der Werf 2001[15]	Cross-sectional, Case-control, stroke outpatients >1 yr post-onset, N=90 HC, N=50 Mean age 62	mean 3.8 years (±2.9 yrs)	CIS-f (PSF: ≥ 40): Stroke, 51% PSF, mean score 35.4 ± 14.6 HC: 12% severe fatigue, mean score 21.2 ± 13.1	-	CIS-f was related to perceived disability (SIP7, in patients r=.65, in HC r=.78, both p<.001). Stepwise regression: in stroke most variance of CIS-f was explained by physical impairment (SIP-ambulation, 34%), then depressive symptoms (BDI-PC, 11%), then cognitive complaints (SIP-alertness). In HC, most variance was explained by depressive symptoms (56%). CIS-f was not related to post-onset time
Visser-Meily 2009[123]	Cross-sectional, SAH, N=141 Mean age 51	23–52 months Mean: 36 months	FSS (PSF: FFS≥4) 67% PSF Mean score: 4.6	-	Fatigue impact was related to Health related quality of life (Stroke Specific Quality of Life) in bivariate comparisons (r=.73) and in multivariate analyses.
Wendel 2008[124]	Cross-sectional, Stroke, N= 84 Mean age 74	Mean: 26 months (range: 18-36)	Single question (yes/no) 45% indicated fatigue and poor concentration		
Winward 2009[59]	Cohort, Minor stroke, N=73, median age 74 TIA, N=76 Median age 73	6 months	Chalder fatigue scale (cutoff=3) Stroke: 59%, median score: 4 TIA 29%, median score: 1	-	Fatigue was more prevalent in stroke than in TIA (OR: 3.14) even when controlling for anxiety, depression, medication and even in stroke patients with minor stroke (NHHS=0). Within stroke group, prevalence of fatigue increased with stroke severity (NHHS, p<.001).

Table 2. Continued

Abbreviations: BI: Barthel Index, BDI: Beck Depression Inventory, BDI-PC: Beck Depression Inventory-Primary Care, CES-D: the Center for Epidemiologic Studies Depression scale, CIS-f: Checklist Individual Strength-fatigue scale, FIS: Fatigue Impact Scale, FSS: Fatigue Severity Scale, GDS: Geriatric Depression Scale, GOS: Glasgow Outcome Scale; HADS-A: Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; HC: Healthy controls, HISC: Head Injury Symptom Checklist, HRQOL: Health Related Quality of Life, MADRS: Montgomery-Asberg Depression Rating Scale, MFI-20: Multidimensional Fatigue Inventory-20, MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form, MHLC: Multidimensional Health Locus of Control, mRS: modified Ranking Scale, NIHSS: National Institutes of Health Stroke Scale, OHS: Oxford Handicap Scale, PSF: Post-Stroke Fatigue, PTSD: Post Stroke Depression, SAH: Subarachnoid haemorrhage, SF-36: Short form health survey-36, SIP: Sickness Impact Profile, SSS: Scandinavian Stroke Scale, STAI: State-Trait Anxiety Inventory, UCL: Utrechtse Coping Lijst, VAS-f: Visual Analogue Scale-fatigue.

Chapter 2. Post-stroke fatigue is still neglected

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"The cure for boredom is curiosity. There is no cure for curiosity"

Dorothy Parker (1893-1967)

Abstract

Objective. To evaluate the need for information and treatment of post-stroke fatigue (PSF) in community dwelling patients with stroke in The Netherlands.

Methods. Data were obtained from a Dutch internet-based questionnaire. The amount of information received about PSF, self-management and other treatment options, and the perceived need for treatment were scored. PSF was assessed with two Visual Numerical Scales of fatigue severity (VNSF), the Fatigue Severity Scale (FSS7), and by scoring the nature (physical versus mental) and onset time of PSF.

Results. Data were available of 538 stroke survivors (mean age 52 years, 45% men, and mean time since onset 2.7 years). Severe fatigue (both VNSF items ≥7; 48%) and severe fatigue impact (FSS7 > 5; 68%) were frequent. Most participants (57%) experienced both physical and mental fatigue. Only 17% of the respondents indicated to have had received sufficient information about PSF and 7% about treatment options, whereas 56% expressed a substantial need for treatment. The need for treatment was moderately associated with fatigue severity and fatigue impact, whereas information status was not related to any demographical, fatigue, or stroke characteristic.

Conclusions. PSF is a significant symptom after stroke requiring medical attention and treatment. The results of this survey indicate that patients do not receive adequate information on PSF.

Introduction

Persisting fatigue is a common and debilitating consequence of stroke even in patients with good recovery.[18, 20, 27, 43] Prevalence rates of post-stroke fatigue (PSF) are substantial, varying between 38 and 73%.[20] These rates seem to be stable over time, with no marked decline after the post-acute stage to even years following the injury.[15, 44-46, 58] As no unequivocal associations with clinical or demographical variables, such as stroke type, age, sex or education, have been found, all patients who have experienced a stroke may be at risk to develop this symptom.[20] Furthermore, PSF has been found to have a negative effect on quality of life,[18, 35] rehabilitation outcomes[29] and even mortality.[19, 55, 86] However, PSF is often misdiagnosed[29-31] and evidence-based clinical guidelines for dealing with PSF are scarce.[21, 125]

The pathogenesis of PSF is still poorly understood[20, 34, 39, 86] but believed to be multifactorial.[16, 20, 39, 46, 55, 86, 92] Although direct associations with biological markers have been demonstrated only in a few studies,[39] the brain damage itself is suggested to be a primary cause for the experienced fatigue.[69, 80, 102] Furthermore, associations with psychological distress such as depressive symptoms and anxiety have been repeatedly found.[20] The direction of this association has not been established, but somatic complaints seem to mediate this association.[92] Moreover, the consistent finding of double dissociations between these symptoms underscores the distinction between these syndromes.[27, 92, 104] However, psychological distress may certainly exacerbate fatigue and vice versa.

It has been accepted that PSF is a multifaceted phenomenon, including the severity of fatigue and the impact of fatigue on daily life.[20] Although no uniform definition of PSF exists, it is generally defined as ‘a subjective experience of extreme and persistent tiredness, weakness or exhaustion after stroke, which can present itself mentally, physically or both and which is unrelated to previous exertion levels’.[22, 125] Since this definition is intrinsically subjective and no derivative assessment tools have been specifically constructed for patients with stroke, a large variety of fatigue rating scales have been used in research and clinical practice.[33, 39] Some of these tools assess the dimension of fatigue severity, such as Visual Analogue Scales[51] or the Checklist Individual Strength.[52] Others, such as the Fatigue Severity Scale, measure the impact of fatigue in daily life.[54] The assessment of both aspects is needed to comprehensively assess PSF and to warrant the comparability of different studies.

A few qualitative studies in small focus groups have demonstrated that patients with PSF report a great need for information on the syndrome[30, 31] Patients reported that the lack of information led to confusion and distress, which in turn elongated the time needed to adjust to the fatigue[31] They want to understand their experience of fatigue, have it diagnosed or explained so that

they are less overwhelmed by it and can know what to do about it.[30] Studies on the treatment of fatigue in patients with stroke and in patients with other neurological disease suggest that patient education, teaching energy conservation strategies and graded activity training can be helpful in the management of fatigue.[111, 125, 126]

Despite the importance of education and treatment for patients with PSF, little research has been conducted to quantitatively identify the need for education and treatment possibilities amongst stroke survivors.[21, 125] Furthermore PSF is often not accurately recognized.[29-31] The aim of the present study was to investigate the current provision of patient information and healthcare in the Netherlands, by an internet-based questionnaire, and to relate these needs to demographic, fatigue and stroke characteristics.

Methods

Data were obtained from a Dutch internet-based questionnaire. External links to the website were placed on the Dutch Wikipedia site about Stroke and on the website of the Netherlands Brain Foundation (*Hersenstichting).* All participants who spontaneously completed the questionnaire consented with its use for scientific research. No feedback about results or financial reward was given and data were anonymously collected.

To identify current information and need status, questions about the amount of information received with regard to (i) PSF, (ii) self-management techniques, and (iii) treatment had to be answered on a 5-point Likert Scale (ranging from none to ample information) as well was the need for treatment of PSF (from none to a great need). The sum of the information scores was used (range 0-15) to indicate information status.

A Visual Numeric Scale was used to assess the severity of fatigue (VNSF). The VNSF consisted of questions about perceived fatigue severity (ranging from *0: no fatigue* to *10: extreme fatigue*) at present (question 1) and over the past 2 weeks (question 2). A score above 6 on both VNSF items was regarded as severe fatigue.[127] The mean of both items was used for statistical analysis.

The Fatigue Severity Scale-7 (FSS7)[16] is a well-validated tool to assess fatigue impact. It contains the last 7 items of the original 9-item FSS,[54] to be scored on a 7-point Likert Scale. A mean score was calculated and a higher score than 5 indicated severe fatigue impact (range: 1-7).[16, 54]

Additional questions about the nature of PSF (physical versus mental) and post-onset time of fatigue had to be answered on a 5-point Likert Scale. Furthermore, data were collected regarding date of stroke, age, years of education, marital status and employment. Questions on the assessment itself were posed last, with regard to the amount of help participants received during

the assessment, the time needed to complete the questionnaire and the perceived difficulty of the questionnaire.

Data analysis

Double and faulty entries were identified by comparing, demographic and stroke characteristics and subsequently discarded. Questionnaires not independently completed were analyzed separately. Of all the correct entries, descriptive statistics were calculated. The association of information status, fatigue severity (VNSF) and fatigue impact (FSS7) with demographic data, age, sex, education, time post-stroke, onset time of fatigue and nature of PSF was tested using Pearson's correlation coefficient for continuous and χ^2-tests for categorical variables. All analyses were conducted using SPSS version 18 for Windows, with Sidak correction for multiple analyses ($p<.004$).

Results

Between April 2009 and June 2011 the website drew 9,204 unique visitors. The questionnaire was completed 575 times. Of these 538 could be included, since 33 respondents sent in multiple questionnaires and 4 participants had not had a stroke. Primary analyses were then performed on 479 questionnaires, since 59 entries indicated that they had been filled in with the assistance of another person (50) or had been completed by a proxy (9).

Table 1 list the patients' demographic and clinical characteristics, together with their information status and need for treatment, related to the scores on fatigue severity (VNSF) and fatigue impact (FSS7). Except for younger age, no associations between PSF and demographic variables were found.

Only 17% of the participants indicated they had received sufficient information about PSF and 7% felt they had received sufficient information about treatment options. In contrast, 54% of the respondents expressed a substantial need for treatment. Patients who had no need for treatment (11%) experienced less severe fatigue (VNSF: $M=5.0 \pm 2.0$) and reported less fatigue impact (FSS7: $M=4.8 \pm 1.5$) than those currently receiving treatment (VNSF $M=7.1 \pm 1.8$; FSS7 $M=5.6\pm1.4$) or those expressing some to substantial need (VNSF $M=6.7\pm1.7$; FSS7$=5.5\pm1.2$, $p<.001$). The amount of need for treatment was associated with fatigue severity and impact, but not with any demographical or stroke variable (all $p>.004$).Information status was not related to any stroke, fatigue or demographic characteristic (all $p>.004$).

The experienced nature of PSF on a physical to mental dimension differed greatly between participants $\chi^2(4)=55.33$, $p<.001$, with 57% of the patients expressing both physical and mental fatigue components (figure 1). No

associations were found between the nature of PSF and VNSF, FSS7 or information status (χ^2 tests, all p>. 01).

Regarding the questionnaire, 51% reported having no difficulty at all completing the tool, 30% a little difficulty, 14% some, and 5% had substantial difficulties with filling in the questionnaire. For most participants (53%) completing the questionnaire took less than 5 minutes, 37% needed 5-10 minutes, 8% needed 11-20 minutes, and only 2% needed more than 21 minutes.

Questionnaires that were completed with the help of others or by proxies differed with those completed independently on several accounts. Respondents requiring help were older (61.3 ±1.8 years), less likely to be employed (20%), experienced more severe fatigue (VNSF M=7.7±1.6), took longer to fill in the questionnaire (Median 6 to 10 minutes) and reported more difficulty filling in the questionnaire.

Figure 1. Frequency of experienced nature of fatigue (N=479)

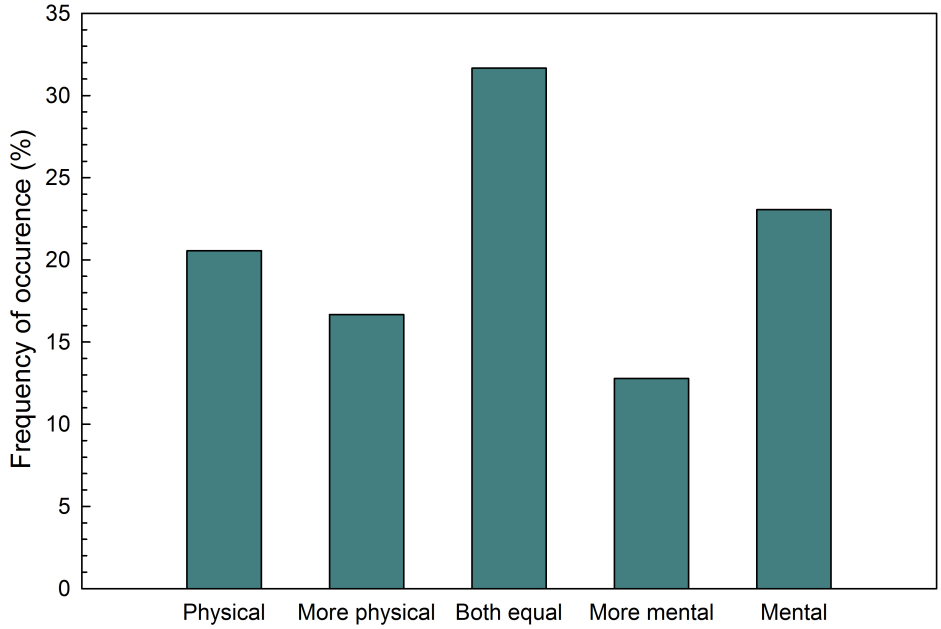

Table 1. Participants characteristics and correlations with VNSF and FSS7 (N = 479)

	Mean ± SD %	VNSF, *r*(p)	FSS7, *r*(p)
Demographic and stroke data			
Age (y)	52.4 ± 10.8	-.15 (<.001)	n.s.
Time since stroke (y)	2.73 ± 4.72	n.s.	n.s.
Gender Male	45%	n.s.	n.s.
Education (y)	12.9 ± 2.5	n.s.	n.s.
Living with partner	74%	n.s.	n.s.
Currently employed	57%	n.s.	n.s.
Fatigue			
Fatigue severity (VNSF)	6.54 ± 1.85		.39 (<.001)
Both VNSF scales ≥7	48%		
Fatigue impact (FSS7)	5.52 ± 1.23	.39 (<.001)	
FSS7 > 5	69%		
PSF (VNSF≥7) since:		n.s.	n.s.
Pre-stroke	18%		
Stroke	53%		
1-6 months post-stroke	19%		
> 6 months post-stroke	10%		
Information and needs			
Sum of information scores	5.87 ± 2.88	n.s.	n.s.
Information received on PSF*		n.s.	n.s.
None	37%		
Some	46%		
Sufficient	17%		
Information on self-management *		n.s.	n.s.
None	50%		
Some	37%		
Sufficient	13%		
Information on treatment*		n.s.	n.s.
None	63%		
Some	30%		
Sufficient	7%		
Need for PSF-treatment*		.34 (<.001)	.31 (<.001)
Currently receives treatment	10%		
No need	10%		
Some	24%		
Substantial	56%		

* Categories are combined to none (none), some (a little & some) and sufficient (sufficient & ample/a great need).

Discussion

This internet-based study was conducted to evaluate the need for information and treatment concerning PSF in community-dwelling patients with stroke in the Netherlands. The results indicate that fatigue is still a neglected symptom after stroke, because most of the participants did not receive sufficient information about (the causes) of fatigue (83%), about self- management techniques (87%) or other treatment options (93%). This worrisome lack of information shows a remarkable contrast with the fact that 54% of participants indicated a substantial need for treatment for PSF.

A large proportion of the participants in the present study experienced severe fatigue as assessed with the VNSF (48%) and reported a severe fatigue impact as assessed with the FSS7 (69%). The moderate association between both scales reveals that different aspects of PSF were measured. Interestingly, fatigue scores were neither associated with sex, time post stroke, nor with the onset time or nature of PSF. Only a small negative correlation with age was found. However, patients who did not complete the questionnaire independently were more severely fatigued and older than those filling in the questionnaires without assistance. These results emphasize the persistence of fatigue complaints after stroke, irrespective of when or by whom they are reported.

Most participants experienced fatigue both physically and mentally, which underscores the notion that PSF includes both components. The finding that the need for treatment was associated with fatigue severity and fatigue impact is understandable and emphasizes the importance of providing appropriate information. The result that the need for information itself was not associated with fatigue scores indicates that even patients with relatively mild fatigue should receive adequate information about PSF and its treatment options. It is possible that patients in fact have received information on PSF and treatment options, but due to their mental fatigue they were unable to remember the information. In this case, the provision of information should be more adequately tailored to the fatigability and the use of written information such as leaflets could be of aid.[128]

This study may have been subject to bias. Most importantly, especially participants with a great need for information and/or need for treatment can be expected to search the internet for information about PSF and its treatment options. As a result, figures about fatigue severity, fatigue impact and lack of information may have been confounded by selection bias. On the other hand, 63% of the participants had received at least some information about PSF and 37% about treatment options. In addition, our respondents were relatively young (52 years of age), highly educated (>12 years), and 57% still were employed, suggesting preserved cognitive functions, which should have enabled them to receive and ask for appropriate information. Another limitation is that PSF scores may have been influenced by pre-stroke fatigue or fatigue as a result of

concurrent disease(s) occurring after stroke. Yet, pre-stroke fatigue was reported in only 18% of the participants with severe fatigue, while 71% experienced the onset of fatigue within 6 months after stroke.

Conclusion

PSF is an important clinical symptom after stroke, requiring attention by medical professionals, as well as treatment and/or care. It is, however, still a neglected phenomenon in the Netherlands.

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Disclosures

None.

Chapter 3. The psychosocial profile of patients with post-stroke fatigue

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« I prefer gazing at the stars still left in my sk,y instead of searching for those lost to me »

Patient XX (in 2010, with permission)

Abstract

Objective. To obtain a psychosocial profile of patients with post-stroke fatigue (PSF), which could aid in optimizing treatment strategies.

Methods. Eighty-eight outpatients with severe PSF measured with the Checklist Individual Strength-fatigue subscale (CIS-f) and the Fatigue Severity Scale (FSS) were selected. Depression and anxiety, psychological distress, coping, social support, and self-efficacy of this group were compared to reference groups of healthy controls and patients with other chronic diseases. Associations between psychosocial characteristics and fatigue were calculated.

Results. Compared to healthy controls, patients with PSF reported more psychological distress, less problem-focused coping, and more positive social support. Minor or no differences were found in comparison with other chronic patients. The CIS-f correlated with somatic complaints and the FSS with cognitive complaints.

Conclusion. Patients with PSF show a psychosocial profile comparable to patients with other chronic disease. Implications for diagnosis and treatment are discussed.

Introduction

In recent years, researchers have become increasingly interested in one of the most common and persisting complaints after stroke, that is, post-stroke fatigue (PSF). PSF is best described as a feeling of early exhaustion with weariness, lack of energy and aversion to effort[22] that develops during physical or mental activity and is usually not ameliorated by rest.[43, 95] The percentages of patients reporting fatigue after stroke ranges from 38% to 77%,[129] and these percentages do not seem to decline in the chronic stage.[15, 46, 129] Furthermore, PSF appears to be related to higher mortality rates and poorer rehabilitation outcomes.[19] However, the pathogenesis of PSF is still poorly understood and, until now, effective treatments are still lacking.[129, 130]

Although the mechanisms leading to PSF are still elusive, its origin is believed to be multifactorial.[129] PSF may be a direct result of organic brain damage,[9] as it has often been reported in other types of brain disease, such as trauma brain injury.[96] However, only a few associations of fatigue with biological markers have been reported in the stroke population.[129] In other words, although stroke severity may play a role, there is little evidence linking lesion size or location to PSF.[43, 46, 49, 129] The origin of PSF could also be related to psychosocial factors, which has been the focus of numerous studies (see Lerdal et al 2009 for an overview).[129] Of all psychosocial factors, the most investigated are depression, anxiety, coping skills, social support and self-efficacy. Nevertheless, also in this area, unequivocal findings are scarce.[129]

Because fatigue is generally considered as a symptom of depression, an overlap between both phenomena seems undeniable.[9, 22, 129] Indeed, an association between fatigue and depressive symptoms is a consistent finding in the literature not only in stroke patients,[15, 19, 46, 49, 66, 80, 82, 95] but also in patients with traumatic brain injury[96] and in otherwise healthy subjects.[82, 96] Yet, in those studies that specifically looked at patients who suffer from depressive symptoms and/or fatigue, a clear dissociation between the two phenomena was also present with groups of patients reporting just fatigue or depression.[15, 46, 49, 98] The same seems to be true for anxiety.[19] The studies that have examined coping style, self-efficacy and social support suggest that emotion-oriented coping,[95, 119] locus of control directed to powerful others,[46] and lack of social support[129] are also associated with PSF. These studies are, however, few in number and cross-sectional in design and did not specifically focus on patients for rehabilitation purposes. As a result, the nature of the psychosocial profile of patients suffering from PSF is still largely unknown, proving only scant clues for optimizing the treatment of PSF.[129, 130]

The aim of this study was to obtain a psychological and social profile of stroke patients, with severe PSF selected for the rehabilitation, to the one of healthy control subjects and patients with other chronic diseases and to

investigate the strength of the association between fatigue and several psychosocial variables. Knowledge about this psychosocial profile can help to optimize PSF treatment.

Methods

Subjects

Data were gathered from patients with PSF who participated in a larger multi-center study (COGRAT: Effectiveness of Cognitive and Graded Activity Training on PSF).[131] In this study 231 patients were recruited via their treating physicians and psychologists (*n*=64), through an article about the COGRAT study in various newspapers (*n*=151), or based on their consent for renewed contact given in earlier studies (*n*=16). The study was approved by the local ethics committee and all eligible subjects signed an informed consent.

For the COGRAT study outpatients in the chronic stage of stroke (at least 4 months post stroke) were identified, according to the following criteria: (1) age between 18 and 70; (2) last stroke episode longer than 4 months ago (either cerebral infarction, or intracerebral or subarachnoid hemorrhage; single or recurrent); (3) severe fatigue (Checklist Individual Strength 20R- fatigue subscale[52] ≥ 40) and (4) ability to walk independently. Patients were excluded from the study if they had (1) severe visual hemi-neglect, Behavioural Innattention Test ≤ 129[132]; (2) severe memory deficits (Rivermead Behavioural Memory Test[132] (screening score > 8); (3) executive impairments (Behavioural Assessment of the Dysexecutive Syndrome[132] < borderline); (4) moderate to severe aphasia (Token Task[132] >12); (5) severe cardiac or pulmonary disease; or (6) co-morbid depression (Hospital Anxiety and Depression Scale depression scale > 10). If the HADS depression scale score was between 8 and 10, a clinical interview (MINI DSM-IV)[133] was conducted to exclude patients with clinical depression.

Of the 124 excluded patients, 47 (54%) were not severely fatigued and 21 had too high levels of depression. The remaining 56 patients met one or more other exclusion criteria, such as memory deficits, mobility deficits or aphasia. Nineteen more patients withdrew consent before complete assessment. Thus 88 patients (38%) were finally included. These participants did not differ significantly with regard to age and gender (alpha = 0.05) from the nonparticipants and those excluded based on too high levels of depression.

Demographic and Clinical Assessment

Data on age, sex, marital status, educational level, stroke type and side, were obtained from the patients and their medical records. Severity of paresis was assessed with the Motricity Index (MI) of the affected lower extremity.[134] The MI was recorded because lower extremity paresis is strongly related to balance[135]

and mobility after stroke[136] and because mobility might be associated with post-stroke depression.[137]

Assessment of Fatigue

Two widely used and well-validated measures of fatigue were used in this study, the subscale fatigue of the Checklist Individual Strength 20R (CIS-f)[52] and the Fatigue Severity Scale (FSS).[54] The CIS-f consists of 8 out of 20 items of the questionnaire, asking about fatigue severity in the two weeks before the assessment, to be indicated on a 7-point Likert scale (range 8-56). Patients with a score ≥ 40 on this subscale were defined as being severely fatigued.[15] In the FSS, individuals rate their agreement with nine statements on a 7-point Likert scale concerning fatigue severity, frequency and impact on daily life. The mean score (range 1-7) is then calculated. The threshold for moderate to high impact of fatigue using the FSS is commonly set at either 4 or 5.[51]

Psychosocial Assessment

To study the psychosocial characteristics of patients with PSF, self-report questionnaires regarding depression, anxiety, psychological distress, coping, social support and self-efficacy were used. Depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS).[138] The HADS is a 14 item self-report measure, with seven items forming a Depression subscale and another seven constituting an Anxiety subscale. Each item is rated on a four-point scale, ranging from 0 to 3, with 3 reflecting the highest distress. Total scores for each subscale range from 0 to 21 and are categorised as normal (0-7), mild (8-10), moderate (11-14) or severe (15-21).[139]

The Symptom Checklist-90 (SCL)[140] measures psychological distress.[141] The scale consists of 90 items scored on a 5-point Likert scale. Nine psychopathology scores can be derived and the total score (GSI) reflects a global severity index of psychological distress. Furthermore, a personality severity index (PSI) to assess personality problems can be calculated.[142] This is done by transferring raw scores to SCL-90R scales, and then comparing the mean scores of the scales interpersonal sensitivity, hostility and paranoid ideation to the mean value of the remaining scales.

Coping strategies were assessed with the Coping Inventory for Stressful Situations (CISS).[143] Forty-eight items are scored on a 5-point Likert scale, resulting in three subscales: Problem-focused coping, Emotion-focused coping and Avoidance-focused coping.

Social Support was assessed with the Social Support List (SSL-12)[144] that consists of twelve statements regarding perceived positive and negative social support from the primary social network. Positive support is described by three subscales: everyday support, support in problem situations, and esteem support.

The Self-Efficacy Scale (SES) was used to assess the sense of control in relation to fatigue complaints.[145] It consists of 5 statements each scored on a 5-point scale. The total scores range from 5 to 25, with a higher score reflecting more sense of control.

Data Analysis

Descriptive statistics (i.e. mean and standard deviation (SD)) were calculated for all psychosocial characteristics. These values were compared to known reference values and derived Z-scores from healthy controls and patient populations (General practice, Traumatic Brain Injury, chronic pain, Multiple Sclerosis, Parkinson's disease, Cancer, Rheumatoid Arthritis, and Chronic Fatigue Syndrome) reported in the literature.[139, 140, 143, 144, 146-148] Based on these Z-scores, different categories were labeled as follows: < -1.28=very low, <-.84=low, <-.525=below average, between -.525 and .525= average, >.525= above average, > .84 high and >1.28 very high.

The presence of personality problems was determined by calculating a PSI from the raw scores of the SCL. Associations between the CIS-f-FFS fatigue scales and gender, marital status, lesion characteristics and PSI were calculated with X^2 analyses. Spearmen rank correlations were calculated with the ordinal demographical, stroke and psychosocial characteristics. Then a stepwise multiple regression analysis was performed on the variables significantly associated with fatigue to establish their unique contribution. All data analyses were computed with SPSS version 17.0 using Holm's correction to adjust for multiple analyses.[149]

Results

Demographic data, severity of paresis, fatigue scores and stroke characteristics are summarized in Table 1. Scores on both fatigue scales indicated on average 'severe fatigue'. On the CIS-f, 92% scored above 40. On the FSS, 92.0% scored above 4 and 69.3% above 5. The mean MI was 90.2 indicating on average mild lower extremity paresis. Mean postonset time since last stroke was 4.3 years, which did not differ significantly between single and recurrent strokes.

Table 1 –Demographic data, severity of paresis, stroke data and fatigue scores (n=88)

Demographics	
Age, mean (SD)	54.6 (8.8)
Gender, male, *no.* (%)	46 (52.3%)
Living together/married, *no.* (%)	71 (80.7%)
Educational level, median (SD), (1=low to 7=high)	5 (1.2)
Severity of paresis	
Motricity Index, mean (SD)	90.2 (13.6)
Stroke	
Time since last lesion, mean (SD)	4.3 (5.3)
Single Stroke, *no* (%)	67 (76.1%)
Ischemic stroke [a], *no* (%)	64 (72.7%)
Hemorrhage [b], *no* (%)	6 (6.8%)
Subarachnoid hemorrhage, *no* (%)	9 (10.2%)
Mixed [c], *no* (%)	4 (4.5%)
Fatigue	
CIS-f, mean (SD); range	45.4 (5.6)
FSS, mean (SD); range	5.2 (1.0)

CIS-f = Checklist Individual Strength subscale fatigue

FSS= Fatigue Severity Scale

[a] ICVA category: 18 left hemispheric, 44 right hemispheric, 4 infratentorial, and 3 bilateral

[b] Hemorrhage category: 4 right hemispheric, 2 bilaterial

[c] Mixed: 4 infratentorial and other lesion.

Psychosocial characteristics

To investigate the psychosocial characteristics of the patients, the scores were compared to reference values obtained from norm groups of healthy controls and patients groups from general practice and with various chronic afflictions (Table 2). The HADS, anxiety scores were comparable to other patient groups, but high compared to the general population. Using the Z-score derived, above-mentioned categories,[139] 60.2% of the patients scored normal, 17% mild, 18.2% moderate and 4.5% severe on HADS-anxiety. On the depression subscale of the HADS, we found high scores compared to both the general population and general practice patients. Still, 64.8% of our subjects had normal and the remaining 35.2% only mild depressive symptoms. The scores on the SCL were generally high compared to healthy controls but, in comparison to other patient groups, the SCL scores were average, except for the subscale 'Obsessive Compulsive' which was above average, reflecting more subjective cognitive complaints. The PSI is a categorical value and could, therefore, not be compared

to reference values. Nevertheless, the incidence rate indicated that 93.2% of the patients were free from personality problems.

As for coping strategies, our patients showed slightly lower levels of problem-focused and avoidance strategies than healthy controls. However, in comparison to other patient groups, they scored average or above average for all strategies. Furthermore, our patients received more positive social support with as many negative social interactions compared to healthy controls and other patient groups. Compared to patients with chronic fatigue syndrome (CFS),[148] they reported to be 'more in control' when assessed with the SES.

Associations of demographic, clinical and psychosocial characteristics with fatigue

Table 3 shows the correlation coefficients of demographic, clinical and psychosocial characteristics with both fatigue scores. No associations with either fatigue scale (CIS-f or FSS) were found for demographics, stroke characteristics or severity of paresis (MI).

The CIS-f scale showed a statistically significant but moderate association with SCL-Somatic and SCL-depression. The FSS was only related to the Obsessive Compulsive subscale of the SCL. No other significant associations were found for any psychosocial measure. The combined Positive social interactions of the SSL were analyzed post hoc, yielding no significant results.

Multiple regression analysis was performed only for the CIS-f with associated variables, since the FSS was associated with just one psychosocial variable (Table 3). SCL-SOM significantly predicted CIS-f scores, $\beta = .54$, $t(86) = 5.89$, $P < .001$. SCL-Dep did not add significantly to the model ($P = .78$) with no concerns for multicolinearity (VIF = 1.56, tolerance = .64).

Table 2 – Means and standard deviations of baseline psychosocial characteristics of PSF patients in comparison with healthy controls and patients with other chronic disease (n=88)

Scale at inclusion	Mean (SD) Study group	In comparison to: *Healthy controls*	*Patient groups*	
Psychosocial characteristics				
HADS		***General population 57-65 years (n=1901)***[146]	***General practice patients (n=112)***[146]	***Traumatic Brain Injury-patients (n=100)***[139]
Anxiety	7.27 (3.76)	High	Average	Average
Depression	7.05 (2.37)	High	High	Average
Psychological distress: SCL		***Healthy controls (n=2092)***[140]	***General practice patients (n=920)***[140]	***Chronic pain patients (n=2461)***[140]
Anxiety	15.08 (4.84)	Above average/ high	Average	Average
Phobic Anxiety	9.13 (3.06)	Above average/ high	Average	Average
Depression	27.44 (7.80)	High	Average	Average
Somatic	22.25 (6.61)	High	Average	Average
Obsessive Compulsive	20.51 (6.47)	Very high	Above average	Above average
Interpersonal Sensitivity	26.98 (8.95)	Average	Average	Average
Hostility	8.36 (2.45)	Average	Average	Average
Sleep disturbances	6.74 (3.21)	Above average/ high	Average	Average
Total (GSI)	149.00 (35.80)	High	Average	Average
Coping styles (CISS)		***Working adults (n=683)***[143]	***Multiple Sclerosis-patients (n=96)***[143]	***Parkinson-patients (n=75)***[143]
Problem focused	51.89 (10.98)	Low	Average	Above average
Emotion oriented coping	35.75 (10.51)	Average	Average	Above average
Avoidance	40.55 (10.66)	Below average	Above average	Above average

Table 2. Continued

Social support (SSL-12)		***Healthy elderly (n=5279)***[144]	***Cancer patients (n=475)***	***Rheumatoid arthritis patients (n=246)***
Everyday support	10.69 (2.08)	Above average		
Support in problem situations	9.76 (2.24)	High		
Esteem support	10.35 (2.10)	High		
Negative social interactions	9.91 (2.92)	Average[147]	Average[147]	Average[147]

Self-efficacy (SES)		***Chronic Fatigue Syndrome- patients (n=292)***[148]
Self efficacy	16.57 (3.32)	Above average

HADS= Hospital Anxiety and Depression Scale, SCL= Symptom Checklist-90, CISS= Coping Inventory for Stressful Situations, SSL-12=Social Support List, SES= Self Efficacy Scale. Reference values were derived from known norm groups or research data from different studies. From research data, means and Z-scores were calculated and categories were described based on Z-scores as follows: <-1.28=very low, <-.84= low, <-.525= below average, between -.525 and .525 = average, > .525= above average, >.84=high, and > 1.28= very high.

Table 3 - Correlation coefficients of demographic, clinical and psychosocial characteristics with PSF (n = 88)

	CIS- f	FSS
Demographic data		
Age[2]	n.s.	n.s.
Gender[1]	n.s.	n.s.
Marital status[1]	n.s.	n.s.
Educational level[2]	n.s.	n.s.
Stroke characteristics		
Single or recurrent stroke[1]	n.s.	n.s.
Lesion side of last stroke[1]	n.s.	n.s.
Time since last stroke[2]	n.s.	n.s.
Severity of paresis (MI) [2]	n.s.	n.s.
Psychosocial Characteristics		
Anxiety and Depression (HADS) [2]		
HADS- Anxiety	n.s.	n.s.
HADS- Depression	n.s.	n.s.
Psychological distress (SCL) [2]		
Anxiety	n.s.	n.s.
Phobic Anxiety	n.s.	n.s.
Depression	0.35*	n.s.
Somatic	0.53*	n.s.
Obsessive Compulsive	n.s.	0.36*
Intrapersonal Sensitivity	n.s.	n.s.
Hostility	n.s.	n.s.
Sleep disturbances	n.s.	n.s.
Total (GSI)	0.34*	n.s.
Personality Problems (PSI)[1]	n.s.	n.s.
Coping (CISS) [2]		
Problem-focused coping	n.s.	n.s.
Emotion-oriented coping	n.s.	n.s.
Avoidance	n.s.	n.s.
Distraction Seeking	n.s.	n.s.
Company Seeking	n.s.	n.s.
Social Support (SSL-I-N) [2]		
Total Positive support	n.s.	n.s.
Negative social interactions	n.s.	n.s.
Self-efficacy (SES) [2]	n.s.	n.s.

[1] X^2 analyses (categorical data)
[2] Spearman rank correlation coefficients
n.s. = not significant
*significant at Holm's correction ($p<0.0011$)
CIS-f = Checklist Individual Strength fatigue severity subscale
FSS= Fatigue Severity Scale

Discussion

The aim of this investigation was to obtain a psychosocial profile of patients suffering from severe PSF in order to tease out options for rehabilitation of fatigue. The results of this study suggest, however, that these patients are not characterized by a distinct psychosocial profile. In comparison to healthy controls, PSF-patients reported high psychosocial distress, high positive social support and low problem-focused coping. However, compared to other chronic patients groups, we found no marked discrepancies with regard to distress, coping styles, social support and self-efficacy. Moreover, independent associations with fatigue were found only for SCL-Somatic Complaints with CIS-f (r=.54; p<.001) and SCL-Obsessive Compulsive with FSS (r=.35; p<.001) but not for any other psychosocial variables or stroke characteristics (e.g. time since stroke, single versus recurrent, nature of lesion and lesion side).

The subscale Obsessive Compulsive of the SCL might mimic the direct neurological consequences of stroke, since it includes items such as 'trouble with thinking', 'mental slowness', 'needing to check things' and 'thinking things over'. Although no direct association between fatigue severity and severity of cognitive deficits has been found,[46, 80, 129] a relationship between cognitive complaints, such as mental slowness, has been substantiated.[82, 150]

A probable cause for the experienced fatigue may be found in this light. Cognitive deficits may temporarily be compensated for by exerting increased mental effort, which may then cause fatigue.[103] Indeed, widespread brain activity has been shown in patients with unilateral lesion of one cerebral hemisphere trying to perform a unimanual task with their affected hand.[151] Such activities typically require a great amount of attentional resources, because subjects act at the limits of (or even beyond) their functional capacities.[152] A parallel can be drawn from studies of traumatic brain injury where affected individuals showed more dispersion and more brain regions activated when engaged in an attention task than healthy controls.[153, 154]

Thus, PSF might be associated with underlying cognitive mechanisms that are independent of the extent of the brain lesion and of psychopathological problems related or unrelated to stroke. If this notion is valid, it would be consistent with the finding that fatigue is almost as frequent in relatively mildly affected patients as in the more severely affected ones,[46, 129] because it will become a problem whenever subjects try to overcome their individual limits. As soon as subjects are able to deal with their functional limitations more effectively, taking into account their limited attentional capacity and mental energy, fatigue may gradually become less severe.

The association between fatigue and somatic complaints could also be seen in line with this hypothesis. Somatic complaints could in part reflect physical consequences of stroke, pain or functional limitations, requiring more attentional

demand from the patient and thereby provoking fatigue. Another part of the somatic complaints could be explained as the physical expression of fatigue. For example, many patients report a heavy feeling in arms and legs, nausea or headaches when they become tired.

As in previous studies, we at first found an association between depression and fatigue on one of the fatigue scales.[15, 19, 46, 49, 66, 80, 82, 95] However, this association was subordinated by somatic complaints in the regression analysis. A variant of this moderation effect has been previously reported, wherein the association between fatigue and depression became weaker when controlled for by sickness and impact on ambulation.[15] This finding emphasizes not only the dissociation of fatigue and depression, but also the need to assess physical complaints in detail.

A rather unexpected but noteworthy finding of this study was that both fatigue measurements used, the FSS and the CIS-f, were associated with completely different variables as shown in table 3. The use of more than one fatigue scale in clinical practice and research might therefore be warranted.

This study holds several limitations. Due to its cross-sectional design we are unable to infer causal relationships. Furthermore, our inclusion criteria restricted the variability of fatigue and mobility, thereby possibly lowering associations. The exclusion of patients with severe cognitive deficits, depression and motor problems might be considered both a strength and a limitation of this study. The major limitation is that it precludes generalization to other stroke patients. On the other hand, this choice enabled us to single out the relationship between fatigue and psychosocial factors, without the influence of these confounding factors.

Conclusions and implications for treatment

By comparing our study group to other reference groups, PSF patients displayed a 'normal chronic patient' psychosocial profile. Only cognitive and somatic complaints were associated directly with fatigue. We therefore propose that (a part of) the fatigue might be a consequence of the inadequate adaptation to diminished and or less efficient attentional resources after stroke.

Our findings suggest the following implications for treatment. Somatic complaints should be directly addressed, whenever possible. Grade physical activity programs might be an important contribution to the treatment of PSF, since exercise has been found to be helpful in improving physical and functional outcomes and to reduce fatigue in other medical conditions.[126, 155] Such programs might help stroke patients to gradually increase physical activity without experiencing bodily symptoms.

Second, cognitive compensation strategies circumventing the limited energetic resources available to patients suffering from PSF might also be

beneficial. These compensation strategies could entail enhanced planning and variation of activities to foster a more regular pattern of activity and rest.[80] Here, patient education and goal setting could be added to improve patient motivation and adherence.[156]

Third, since symptoms of depression and anxiety common in PSF patients, it is important to address these when present, since they may compromise self-management.[157] An augmented form of cognitive behavioral therapy, as proposed by Broomfield et al (2010),[158] is a good starting point to address these issues. It takes into account cognitive deficits and grievance of loss of abilities and could also aid in implementing the behavioral changes needed to apply the compensation strategies. Lastly, our study points to the use of more than one scale to assess PSF, highlighting that fatigue is not only a common but also a complex and multifaceted syndrome.

Conflicts of interest

None of the authors have reported any conflict of interest and all worked independently from the funding source.

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Chapter 4. Psychometrics of the CIS-20r and FSS for measuring post-stroke fatigue

Submitted as: *Dimensional properties, psychometrics and concurrent validity of CIS-20R and FSS for measuring post-stroke fatigue; clinical and research implications.*

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"It is the vague and elusive. Meet it and you will not see its head. Follow it and you will not see its back".

Lao Tzu 60BC-513 BC

Abstract

This study examined the psychometric properties and the underlying constructs of the Fatigue Severity Scale (FSS) and the Checklist Individual Strength (CIS-20r) in 196 patients with stroke and 112 age-matched healthy controls. Since the FSS and the subscale "fatigue severity" of the CIS-20R (CIS-f) claim to measure fatigue severity, the study focused on these (sub)scales. Both (sub)scales were able to discriminate at scale and at item level between patients and healthy controls, except for items 1 and 2 of the FSS. The internal consistency was high for the FSS and the CIS-f (Cronbach's α: FSS = .893; CIS-f = .938). The convergent validity (Pearson Correlation) between the (sub)scales ranged from r_p=.52 in patients to r_p=.82 in healthy controls. Principal Axis Factoring analyses on all items of the FSS and the CIS-f combined were conducted to investigate underlying constructs. These revealed three factors: "Experienced fatigue", "Fatigue impact" and "Physical condition". Since the CIS-f loaded highly on "Experienced fatigue" and the FSS loaded mostly on "Fatigue impact", these (sub)scales seem to measure different constructs that correlate only moderately in patients with stroke. These differences must be taken into consideration when selecting one of these fatigue scales for either diagnostic or research purposes.

Introduction

Post-stroke fatigue (PSF) is a common and debilitating complaint[20, 22, 33] with prevalence rates ranging from 38% to 77%.[20] Even after a minor stroke or a transient ischemic attack, fatigue has been reported in 56% and 29% of the patients at six months follow-up, respectively. [59] This wide variety of prevalence rates can be partially explained by the absence of a generally accepted and unambiguous definition of fatigue[20, 28, 33, 59] and hence by a lack of reliable assessment. Unfortunately, a 'golden standard' for the assessment of PSF is unavailable given the absence of valid biological markers.[33] Currently, fatigue can only be measured at a subjective level. This poses a further challenge to researchers and clinicians when developing measurements and assessing a patient's condition.

Due to the subjective nature of fatigue, self-report measures are the most commonly used instruments to assess PSF.[20, 28] These instruments can be divided into one-dimensional and multidimensional scales.[28] In one-dimensional scales fatigue is viewed as a unitary construct, whereas multi-dimensional instruments aim to measure different aspects of fatigue, such as impact of fatigue, and concentration problems.[28] Two widely used self-report scales to assess PSF are the one-dimensional Fatigue Severity Scale (FSS)[54] and the multidimensional Checklist Individual Strength (CIS-20r).[52, 53]

The FSS is one of the most frequently used scales to assess PSF.[20, 28, 51] It is a one-dimensional scale originally developed for fatigue complaints after systemic lupus erythematosus and in multiple sclerosis. Later it has been applied to measure fatigue in other neurological conditions, such as traumatic brain injury (TBI) and stroke.[38, 159] Until now, the average score on the FSS is most often utilized to assess fatigue severity in stroke patients,[28, 91] although it was originally designed to reflect the impact of fatigue on daily life in persons with suspected fatigue.[28, 54]

The CIS-20r is a multidimensional scale that assesses four dimensions of fatigue on different subscales: fatigue severity, concentration problems, reduced motivation and reduced physical activity level.[52, 53] The CIS-20r is the list of choice in scientific studies of fatigue in the Netherlands and in Belgium. It has been used in different neurological conditions, such as TBI,[160] brain tumors,[161] multiple sclerosis and stroke.[15, 162] Although the total score of the CIS-20r has been reported to reflect fatigue severity in non neurological patients,[163] in patients with stroke, only the CIS- fatigue severity subscale (CIS-f) is used to assess the severity of experienced fatigue.[15, 162]

Although several self-rating scales of fatigue are currently available, including the FSS and the CIS-20r, none of these have been specifically designed for PSF.[20, 28, 50] In addition, few studies have focused on the validity of these measures in patients with PSF. Together with the subjective nature of fatigue, this

gap in previous research poses difficulties to both researchers and clinicians in describing and assessing a patient's condition after stroke.[20, 35] Both the FSS and the CIS-f are utilized to measure fatigue severity[20, 28, 54] and to detect changes in fatigue over time.[51, 52] However, at face value, they seem to measure different constructs. In stroke patients they have been found to correlate with different psychological and neurological variables.[92] In this perspective, the aim of the present paper is to first examine the psychometric properties of the (one-dimensional) FSS and the (multi-dimensional) CIS-20r. An additional goal is to analyze the underlying constructs of both scales.

Methods

Participants and procedure

Data was obtained from stroke patients who entered a study on the effectiveness of Cognitive and Graded Activity Training (COGRAT) for PSF (N=83),[164] and by additional recruitment in three different rehabilitation centers (N= 113). In the COGRAT study the inclusion criteria were (1) being aged between 18 and 70 years; (2) suffering from severe fatigue (CIS-f ≥ 40)[52](3) not having severe cognitive deficits as assessed with the Rivermead Behavioural Memory Test (screening score>8),[165] the Token Test (score>12)[166] and the Behavioural Assessment of the Dysexecutive Syndrome[167] (score < borderline), (4) not having co-morbid depression as assessed with the Hospital Anxiety and Depression Scale[138] (Depression score > 10, and a clinical interview when the score was 8-10),[133] (5) absence of severe pulmonary or cardiac disease and (6) being able to walk independently. Additional 113 patients were outpatients recruited in three rehabilitation centers. The selection of these patients was based on age (over 18 years of age), the presence of a stroke, living independently, and the ability to complete the questionnaires autonomously. For all patients, age, level of education and time since stroke were recorded. Furthermore, the present study included 112 age-matched healthy controls. These were contacted through acquaintances of the researchers. All participants provided written informed consent prior to participation, in accordance with the declaration of Helsinki. The local ethics committees of the centers approved the study.

Measures

The Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) is a one-dimensional scale which consists of nine items that are scored on a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). The fatigue score is calculated by means of nine item scores (range 1-7), with higher scores indicating higher levels of fatigue.[54] In stroke research the cut-off score for severe fatigue is set either at 4 or 5.[51]

The Checklist Individual Strength (CIS-20r)

The Checklist Individual Strength (CIS-20r) is a 20-item questionnaire designed to measure four aspects of fatigue during the previous two weeks: fatigue severity (CIS-f: 8 items), concentration problems (5 items), reduced motivation (4 items) and reduced physical activity level (3 items). Each item is scored on a 7-point Likert scale ranging from 1 (yes, that is true) to 7 (no, that is not true).[52, 53]

In this study we focused specifically on the fatigue severity subscale (CIS-f) to measure PSF (range 8-56), because this subscale is more often used as a measure of fatigue severity than the subscales of the CIS-20r together. The CIS-f cut-off score for severe fatigue in patients with stroke or TBI is set at 40.[15, 160]

Statistical Analysis

Discriminatory analyses, internal consistency and concurrent validity of the FSS and the CIS-20r

To compare the demographic and fatigue data of our groups, t-tests were used for interval and Chi-square-test for categorical variables. Then, Principal Axis Factoring (PAF) analysis with direct Oblimin Rotation was performed on all CIS-20R items obtained from the stroke patients to determine the construct validity of the four subscales for this particular group. To investigate group differences in the FSS and the CIS-20r subscales, independent samples t-test were performed on scale and item levels. Two previous studies investigating the item structure of the FSS in stroke patients with Rash analyses have suggested the exclusion of the first two items. These items clearly lacked discriminatory value and could not distinguish healthy controls from patient groups.[168, 169] Analyses were therefore performed on the 9-item and on the 7-item (FSS7) version of the FSS.

The internal consistency was then calculated using Cronbach's alpha, and Pearson's correlation coefficient was computed to specify the convergent validity between the FSS and the CIS-f. Differences between the patient and control group were calculated by converting the correlation coefficients into z-scores, and determining the difference (z_{diff}) with the accompanying p value.

To compare our data to the prevalence rates of PSF presented in the literature, we counted the number of respondents who scored above 4 and 5 on the FSS, and those with higher scores than 40 on the CIS-f.

Dimensional properties of the FSS and the CIS-fatigue severity subscale

A PAF with direct oblimin rotation was performed on the item scores of the FSS and the CIS-f for all subjects. This PAF was then carried out for stroke subjects and healthy controls separately, to investigate construct validity across stroke patients and healthy controls. Factors were identified according to the following criteria: (1) the bend of the curve in the scree plot; (2) the amount of

variance explained by the factors combined; (3) item loading of more than .4 on a factor; and (4) interpretability by the authors.[170] All analyses were performed using SPSS version 15 for Windows.

Results

Discriminatory analyses, internal consistency and concurrent validity of the FSS and the CIS-20r

Comparisons between demographic variables of patients and healthy controls revealed a significant difference in educational level ($p<.05$) (Table 1). PAF analysis of the CIS20-R in stroke patients largely confirmed the separation of the items in the already existing four subscales, fatigue severity (CIS-f; eigenvalue 7.18, % of variance 33.78, $\alpha=.88$), concentration problems (eigenvalue 2.61, % of variance 11.00, $\alpha=.86$), reduced motivation (eigenvalue 1.43, % of variance 5.3, $\alpha=.82$), and reduced physical activity level (eigenvalue 1.79, % of variance 7.1, $\alpha=.81$). Only the CIS-f item 8 loaded >.4 on both the CIS-fatigue subscale and the reduced motivation subscale. Therefore, the existing CIS-f subscale of the CIS-20r was used as an independent measure of fatigue severity in subsequent analyses. Patients scored higher than healthy controls on the FSS and on all CIS-20r subscales (Table 1). Analysis on an item level of the CIS-f and FSS scales revealed that patients differed significantly from the control group, except for items 1 and 2 of the FSS (Table 2).

Table 1. Demographic and fatigue data of patients and healthy controls.

Variable	Patients N=196 M(SD)	Healthy controls N=112 M(SD)	P
Age, Mean (SD)	55.23 (9.01)	53.46 (9.09)	.098
Time since stroke (years)	3.97 (4.96)		
Gender, male (%)	50.0%	41.9%	.174
Education (1-7), median	5	6	<.001
CIS fatigue severity	38.90 (10.92)	19.53 (11.40)	<.001
CIS concentration problems	22.43 (8.07)	11.04 (6.55)	<.001
CIS motivation	15.31 (6.50)	9.72 (5.05)	<.001
CIS physical activity	12.61 (5.33)	6.16 (3.77)	<.001
CIS-20r total score	89.94 (22.82)	47.35 (22.11)	<.001
FSS7	5.09 (1.39)	2.44 (1.47)	<.001
FSS	4.96 (1.25)	2.82 (1.27)	<.001

The internal consistency (α) of the FSS and the CIS-f was .893 and .938, respectively. For the FSS this consistency increased to .910 after deletion of item 1 and to .916 after deletion of item 2. With both items deleted (FSS7) α increased to 0.933. The Pearson correlation (r_p) between CIS-f and FSS for all participants was .774 and between CIS-f and FSS7 it was .797 (both p<.001). The Pearson correlations for patients and healthy controls and the differences between groups are listed in table 3. Figure 1 shows the scatter plot of both the FSS7 and the CIS-f.

Table 2. Means of individual items of the FSS and CIS-f for patients and healthy controls

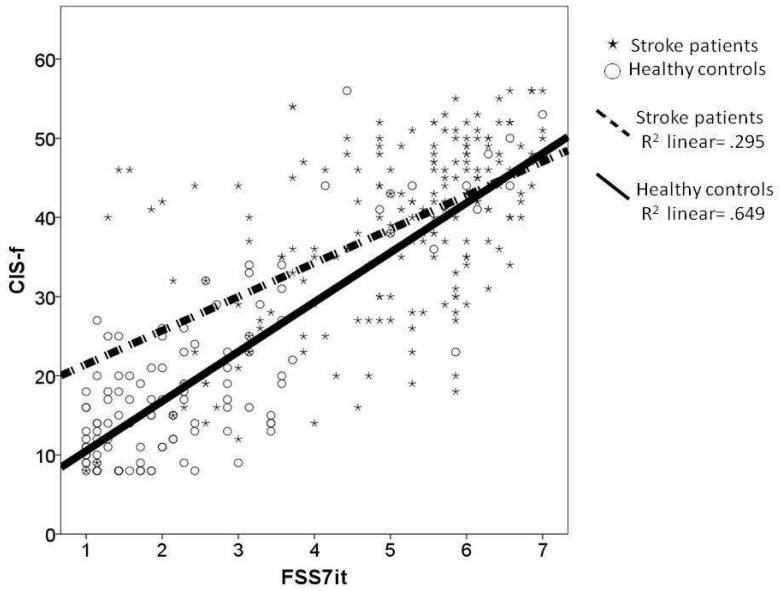
Items	Patients N=196 M(SD)	Healthy controls N=112 M (SD)	*p*	*Mean difference (SD)*
CIS-f				
1. I feel tired	5.3 (1.8)	2.6 (1.9)	<.001	2.7 (.2)
2. Physically I feel exhausted	4.5 (2.0)	2.1 (1.8)	<.001	2.4 (.2)
3. I feel fit (reversed)	4.8 (1.8)	2.4 (1.6)	<.001	2.5 (.2)
4. I feel weak	3.7 (2.1)	1.8 (1.3)	<.001	1.9 (.2)
5. I feel rested (reversed)	5.1 (1.8)	2.9 (1.9)	<.001	2.2 (.2)
6. Physically I feel I am in a bad condition	4.3 (2.0)	2.3 (1.7)	<.001	2.0 (.2)
7. I get tired very quickly	5.8 (1.7)	2.5 (1.9)	<.001	3.2 (.2)
8. Physically I feel I am in good shape (reversed)	5.2 (1.9)	3.0 (1.9)	<.001	2.2 (.2)
FSS				
1. My motivation is lower when I am fatigued	5.4 (1.7)	4.9 (1.6)	.039	0.4 (.2)
2. Exercise brings on my fatigue	3.6 (2.1)	3.4 (1.9)	.427	0.2 (.2)
3. I am easily fatigued	5.3 (1.8)	2.5 (1.7)	<.001	2.8 (.2)
4. Fatigue interferes with my physical functioning	5.3 (1.7)	3.4 (2.0)	<.001	1.9 (.2)
5. Fatigue frequently causes problems for me	4.1 (1.9)	2.0 (1.5)	<.001	2.2 (.2)
6. My fatigue prevents sustained physical functioning	4.6 (2.1)	2.3 (1.7)	<.001	2.3 (.2)
7. Fatigue interferes with carrying out certain duties and responsibilities	5.4 (1.8)	2.8 (2.0)	<.001	2.6 (.2)
8. Fatigue is among my three most disabling symptoms	5.8 (1.8)	2.2 (1.9)	<.001	3.6 (.2)
9. Fatigue interferes with my work, family, or social life	5.1 (1.9)	2.0 (1.6)	<.001	3.2 (.2)

Table 3. Pearson correlations between CIS-f, FSS and FSS7 in patients and healthy controls

	r_p Patients	r_p Healthy controls	Z_{diff}	$P_{two\text{-}tailed}$
CIS-f and FSS	.520*	.783*	1.76	.079
CIS-f and FSS7	.543*	.806*	1.87	.062

* p<.001

Figure 1. Scatterplot of the FSS7 and the CIS-f for patients and healthy controls



Since items 1 and 2 of the FSS did not contribute to internal consistency nor to discriminatory value, we used the score of the remaining 7 items to determine whether participants scored above the cut-off scores of 4 or 5. The percentage of healthy controls scoring above 4 was 12.5% and 8% scored above 5 on the FSS7. In the patients these percentages amounted to 77% and 61.2%, respectively. On the CIS-f 9.8% of the healthy controls scored above the cut-off score of 40, whereas for patients this percentage was 52.6%.

Dimensional properties of the FSS and the CIS-fatigue severity subscale

Since the item to N ratios in patients (196:17) and in healthy controls (112:17) were small, we chose to first analyze the data of both groups and then perform separate group analyses, to investigate whether the original factors of both scales would hold up. In all three analyses, after exploration of the scree plot, the amount of variance explained and the initial eigenvalues, three independent factors were identified explaining more than 51% of the variance. The individual loadings in these analyses were all higher than .4, except for FSS

item 1. The results of these PAF analyses with direct oblimin rotation are presented in table 4.

The PAF analyses revealed item loadings and factors largely similar to those of the original scales across the subject groups, with factor 1 consisting of only CIS-f items and factor 2 of uniquely FSS items. Items that loaded high on factor 3 were CIS-f 6, CIS-f 8 and FSS item 2. Differences across subject groups were found for items 6 and 8 of the CIS-f, and FSS items 1, 2, 8 and 9. In stroke patients CIS-f items 6 and 8 were not clear-cut, both loading over .4 on factors 1 and 3. In healthy controls, CIS-f item 8 loaded only on factor 3 and greater differences were found with regard to the distribution of the FSS items. FSS item 1 did not load on any factor, item 5 was not clear-cut and items 2, 8 and 9 now loaded most strongly on factor 1.

Table 4. Principal axis factoring on FSS items and items of CIS-f in patients and healthy controls

	Patients and Healthy controls (N=308)			Patients (N=196)			Healthy controls (N=112)		
Item	Factor			Factor			Factor		
	1	2	3	1	2	3	1	2	3
CIS-f 1	**.775**			**.831**			**.941**		
CIS-f 2	**.705**			**.688**			**.805**		
CIS-f 3	**.795**			**.633**			**.734**		
CIS-f 4	**.747**			**.642**			**.754**		
CIS-f 5	**.726**			**.663**			**.821**		
CIS-f 6	**.841**		.346	.532		**.540**	.305		**.541**
CIS-f 7	**.687**	.281		**.741**			**.676**		.246
CIS-f 8	**.706**		.283	**.472**		.460			**.742**
FSS1		.361			**.418**		-	-	-
FSS2			**.456**			**.547**		**.436**	
FSS 3	.413	**.524**		.255	**.546**		**.591**		.284
FSS 4		**.566**			**.436**	.225		**.680**	
FSS 5		**.721**			**.598**		.510	**.559**	-.258
FSS 6	.271	**.500**	.266		**.425**	.421		**.557**	.206
FSS 7		**.853**			**.830**		.225	**.667**	
FSS 8	.234	**.747**			**.774**		**.573**	.367	
FSS 9		**.755**			**.752**		**.565**	.380	
Eigenvalues	9.68	1.35	1.03	6.72	1.99	1.43	9.41	1.38	1.05
% of variance	55.2	5.3	3.5	36.9	8.9	5.6	53.6	6.0	3.3
	Rotation converged in 13 iterations.			Rotation converged in 8 iterations.					

Interpretation of the factors was based primarily on the analysis of the patient's data, since both the FSS and the CIS-f have been designed for patients suffering from fatigue, and the constructs seemed to differ between patients and healthy controls. Moreover, in stroke patients the correlations between the factors were moderate at best, allowing the interpretation of different factors (factors 1 and 2 r_p= .44; factors 1 and 3 r_p= .23: and factors 2 and 3 r_p=.31).

Factor 1 consisted largely of items referring to the subjective feelings of weakness and tiredness in patients with stroke (CIS-f items 1: "I feel tired"; 2: "Physically I feel exhausted"; 3: "I feel fit (reversed)"; 4: "I feel weak" ; 5: "I feel rested (reversed)"; and 7: "I get tired very quickly"). Therefore this factor was named "Experienced fatigue".

Factor 2 consisted exclusively of FSS items, except for item 2 in the patient population. This factor mainly contained items covering the impact of fatigue on daily life functioning (items 4: "Fatigue interferes with my physical functioning"; 5: "Fatigue causes frequent problems for me"; 6: "My fatigue prevents physical functioning"; 7: "Fatigue interferes with carrying out certain duties and responsibilities"; 8: "Fatigue is among my three most disabling symptoms" and 9:"Fatigue interferes with my work, family, or social life") and to a lesser degree items on fatigability (item 3: "I am easily fatigued") and motivation (item 1: "My motivation is lower when I am fatigued"). Therefore, this factor was labelled "Fatigue impact". In healthy controls the items covering the debilitating effect of fatigue on daily life activities were included in factor 1. The distinction with factor 2 (fatigue impact or fatigue as a disability) was less clear.

Factor 3 referred to the CIS-f and FSS items covering physical fitness (FSS item 2: "Exercise brings on my fatigue", CIS-f item 6: "Physically I feel I am in a bad condition"). Consequently, this factor was named "Physical condition".

Discussion

In the present study it was found that both the one-dimensional Fatigue Severity Scale (FSS) and the multidimensional Checklist Individual Strength-20r (CIS-20r) have good psychometric properties and adequately discriminate stroke patients with PSF from healthy controls. However, analyses of the (sub)scales that aim to measure fatigue severity (the FSS and the subscale "fatigue severity" of the CIS20-R (CIS-f)) reveal that these scales assess different dimensions of fatigue. The FSS was found to assess the impact of fatigue on daily life functioning, whereas the CIS-f mostly reflected experienced fatigue. Furthermore, the convergent validity of both scales was only moderate in stroke patients. These results indicate that these tools cannot be used interchangeably to assess PSF.

The average score on the FSS is most often utilized to assess fatigue severity in stroke patients.[28, 51, 91] However, the tool was originally designed to reflect the *impact* of fatigue on daily life in patients known to suffer from

fatigue,[28, 54] a distinction that is not always recognized.[51] Moreover, none of the items of the FSS ask about the severity of fatigue. Thus, taken together with the results of this study, it is questionable whether the FSS is a valid scale for the assessment of fatigue *severity* in patients with stroke.

The FSS has its own merits. It is a short, easy to administer self-rating tool, which assesses the impact of fatigue on the daily life of patients with stroke. For diagnostic and research purposes, however, the first two items (1) "my motivation is lower when I am fatigued", and (2) "exercise brings on my fatigue" should be used with caution. In this study, these two items did not distinguish between healthy controls and patients with stroke and both items consistently reduced the internal consistency of the scale. Previous studies using Rasch analyses have suggested the deletion of these two items for use in neurological patients.[168, 169] Most likely, these items are too generic to aid in the differentiation between pathological and normal fatigue.

The results of this study showed that most of the CIS-f items loaded on the factor "Experienced fatigue". However, the meaning of items 6 and 8 was not clear-cut, because they also loaded on "Physical condition". In the preliminary analyses, item 8 did not load on the CIS-f subscale, but on the CIS-20r subscale motivation. This corresponds to the findings by Staub & Bogousslavsky (2001b) who suggested that the CIS-f essentially assesses the *physical* component of fatigue.[12] This is congruent with the findings of a previous study[92] where we found that the CIS-f showed a clear association with somatic complaints in patients with severe PSF. This is an important aspect to be considered in stroke patients when using the CIS-f. Although fatigue is often experienced both mentally and physically, patients with predominantly *mental* fatigue might be at risk of being underdiagnosed with the CIS-f. In contrast, PSF in patients with little physical stamina and or many physical impairments could be overemphasized by using the CIS-f.

This study has some limitations. We assessed the psychometric properties of both scales by calculating the internal consistency and convergent validity in patients with stroke and healthy controls. As we used a cross-sectional design, we were unable to examine the usefulness of the scales to detect changes over time (responsiveness) in stroke patients. Furthermore, 42% of the included patients participated in the COGRAT study[164] in which only patients with a CIS-f score of 40 or above were included. Therefore, it is possible that the variability within our data was restricted and, thus, the generalizability compromised. Nevertheless, the standard deviations of the patient scores were comparable to those of healthy controls, which makes it unlikely that the influence of selection bias was severe.

The findings of this study have implications for both clinical practitioners and researchers. First, the results underscore the multidimensional and subjective nature of PSF. In assessing this complex symptom, researchers and clinicians need

to make sure that they select the most appropriate fatigue scale and are not misled by the name of the scale.[28] When studying fatigue *severity*, the CIS-f is preferable over the FSS. On the other hand, the FSS is more suitable to assess the *impact* of fatigue on daily life. The FSS is shorter and easier to administer, whereas the CIS-20r provides a multidimensional assessment not only of "Experienced fatigue" and "Physical condition" (CIS-f subscale), but also of the influence of fatigue on "Concentration problems", "Motivation" and "Activity" (other subscales). Hence, this difference in the information provided must be taken into consideration when selecting a fatigue scale for either diagnostic and/or research purposes.

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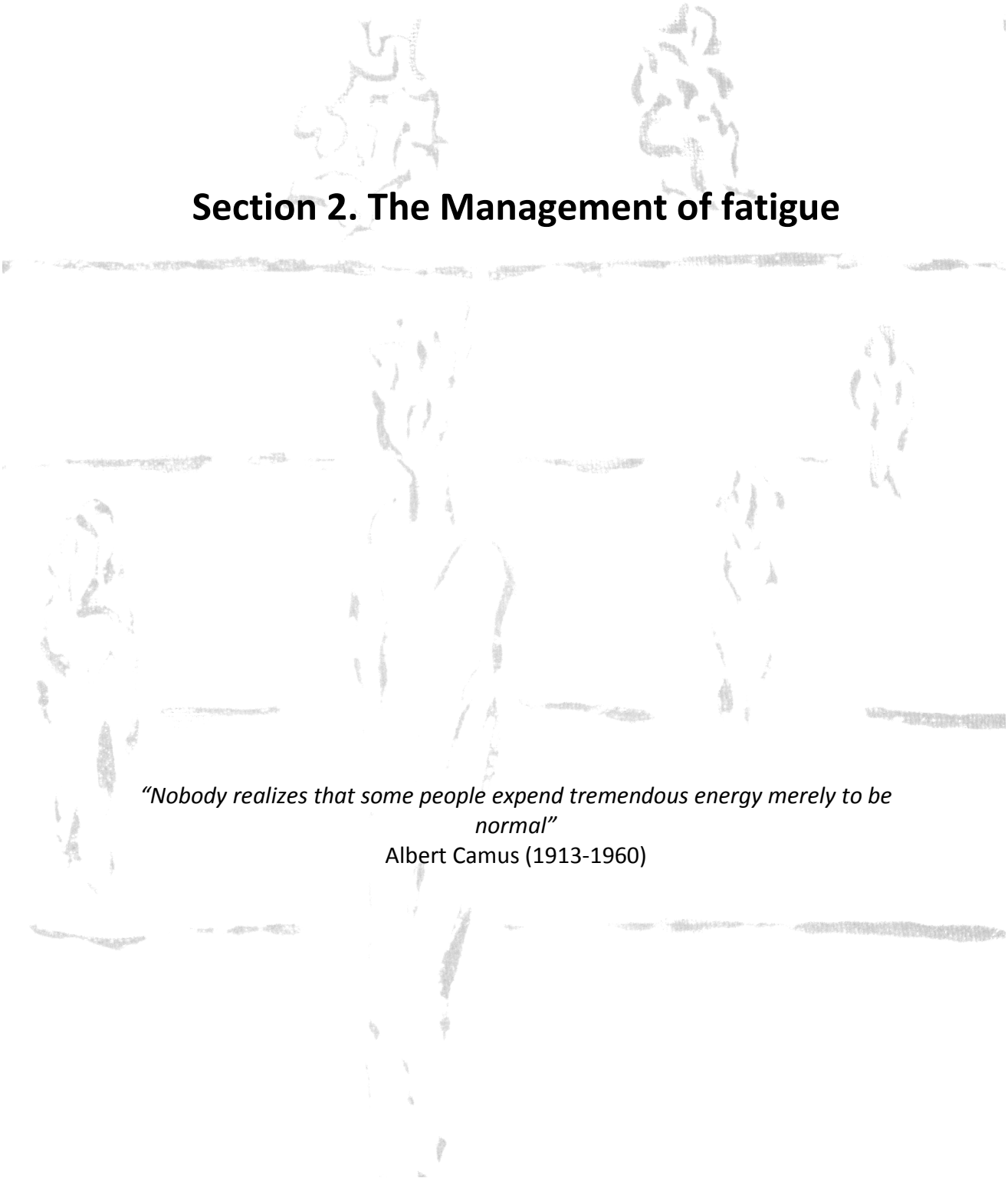

Section 2. The Management of fatigue

"Nobody realizes that some people expend tremendous energy merely to be normal"
Albert Camus (1913-1960)

Chapter 5. COGRAT, a treatment protocol for post-stroke fatigue

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"Creativity is allowing yourself to make mistakes. Art is knowing which ones to keep"

Dilbert, Scott Adams (1957-)

Abstract

Purpose: Post-stroke fatigue is a common and debilitating complaint, which has only recently received attention in clinical rehabilitation. Until now, no evidence-based treatments have been available for the condition. Therefore, a new treatment was designed to reduce post-stroke fatigue complaints: Cognitive and Graded Activity Training (COGRAT).

Rationale: Following the premise that post-stroke fatigue is primarily caused by brain damage, the treatment aims to prevent fatigue and to manage existing fatigue symptoms. The purpose of the added graded activity programme is to reduce fatigue by changing cognitions and enhancing physical fitness.

Theory into practice: COGRAT consists of a cognitive treatment and graded activity programme in small groups over 12 weeks. In the cognitive treatment, patients receive education on post-stroke fatigue and register their activities and fatigue to gain insight into their daily agenda and fatigability. Patients are then taught several compensation strategies. Cognitive behavioural therapy is used to diminish anxiety, facilitate behavioural change and manage fatigue symptoms. The graded activity programme consists of walking on a treadmill, strength training and home work assignments. Maximum heart rate and strength are increased from 40% at the beginning of the training to a maximum of 70%.

Considerations for future improvements: COGRAT is currently being evaluated in outpatients with severe post-stroke fatigue in a multicentre randomized controlled trial. Preliminary data suggest both positive short- and long-term effects. Adaptations for other neurological patient groups suffering from fatigue are suggested.

Introduction

In recent years, rehabilitation professionals and researchers have become increasingly interested in Post-Stroke Fatigue (PSF). PSF is a frequently reported and debilitating consequence of stroke, both in the post-acute and in the chronic stages,[11] occurring in 38% to 77% of the patients.[129] Although an exact definition of PSF is still lacking because of its subjective nature,[9, 129] it is best described as "a feeling of early exhaustion, developing during mental activity, with weariness, lack of energy and aversion to effort" (Staub & Bogousslavsky, 2001; p 75).[22] Rest usually does not ameliorate the fatigue.[43] Moreover, the feeling of physical tiredness and lack of energy is characterised as abnormal, excessive, chronic or problematic.[68, 69] PSF is related to poorer outcomes in rehabilitation, reduced quality of life and increased mortality.[14, 19, 171]

Despite the high prevalence rates of PSF, even in patients that seem to have recovered well,[14, 22] a comprehensive treatment is still lacking.[129, 130] A systematic review of PSF treatments by McGeough et al (2009)[21, 130] concluded that there is insufficient evidence to guide practice, neither by pharmacological nor non-pharmacological means. Until now, only a few cause-specific treatments have been developed.[130] Other fatigue relieving evidence-based treatments have only been aimed at non neurological populations.[71, 129]

Against this background a PSF treatment module "Dealing with fatigue" was implemented in a day clinic specialized in chronic stroke patient rehabilitation. The treatment consisted of a 12-week program in which patients received cognitive treatment once a week from a neuropsychologist, alongside an exercise programme twice a week. Evaluation of pre- and post treatment measurements of 16 patients showed significant decline of fatigue, as measured with the Checklist Individual Strength fatigue scale and psychological distress, as measured with the Symptom Checklist-90 (both $p<.001$).[172]

On the basis of recommendations of this pilot study, the treatment protocol was adapted in several ways. The most important changes include: limitation of group size to four participants, more consistent use of cognitive behavioural techniques and the development of a treatment protocol for graded activity training. This treatment, Cognitive and Graded Activity Training (COGRAT) is currently being evaluated in a multi-centre randomised controlled trial in the Netherlands.[131] Preliminary data of 40 patients showed significant decline of fatigue severity and psychological distress, both on post treatment and on follow-up assessment ($p<.001$), as measured with the above mentioned instruments.[173]

To describe the treatment here, first the underlying rationale and the main principles of COGRAT will be illustrated. Subsequently, a more detailed account of the practice of the treatment protocol will be presented for both the Cognitive Treatment and the Graded Activity Training. Text box case illustrations

of consenting patients in the COGRAT trial are provided to clarify basic concepts. Introductions of the two patients presented are given in Box 1.

Box 1
Case 1: LD is a man aged 56 years who had always been active in many areas. He describes his life prior to stroke as one dedicated to fun and looking for opportunities to ride his motorcycle. Four years ago he suffered a subarachnoid haemorrhage and, since then, he has had to relearn walking. His right arm and leg showed severe motor deficits. Adjusting his life after stroke was a major issue during the first two years. He now still suffers from concentration problems, lack of initiative and severe fatigue.

Case 2: YB is a woman aged 45 years who had sustained a stroke in the left frontal lobe 2 years ago. She still practices her former job as a hospital nurse, but feels she is inadequate to do so due to concentration problems and severe fatigue. After work, she reports being irritable when the phone rings and not having enough energy to engage in activities with her husband and children. She experiences guilt about having to let her husband take over most of the parenting and housekeeping and for no longer being the same "fun" person.

Rationale of COGRAT

The rationale of COGRAT, its aims and treatment elements are shown in Table 1. One of the starting points of the treatment of PSF is that energy levels cannot be restored to the pre-morbid level. In neurological practice it is generally agreed that brain damage is the primary cause for excessive fatigue.[22, 43, 69, 72] Although the mechanisms relating fatigue to cerebral damage are still elusive, a plausible theory is the cognitive "coping hypothesis" proposed by van Zomeren et al (1984).[103] This hypothesis postulates that fatigue is due to the additional compensatory effort spent by brain-injured individuals in meeting the demands of everyday life as a result of their cognitive deficits.[36, 96, 103] Evidence for this notion follows from two sources: (1) studies on the relationship between attention deficits, mental effort and subjective fatigue[37, 38, 174, 175] and (2) imaging studies of patients with Traumatic Brain Injury or Multiple Sclerosis. These patients show higher levels of cerebral activation than healthy controls during attentionally demanding tasks to compensate for their processing deficits, which may increase experienced fatigue.[153, 154, 176, 177]

Thus, the cognitive-behavioural part of COGRAT is principally aimed at providing stroke patients with cognitive strategies that allow them to make a more efficient and sagacious use of their remaining cognitive resources in order to manage existing and prevent forthcoming fatigue. In order to implement these strategies, patients are first educated on the possible aetiology of PSF and fatigue symptoms. Second, patients log their activities and subsequent fatigue. With the

help of analysis and feedback from the therapist, patients then gain insight into their activity and fatigability patterns. Last, three compensation strategies are taught to help patients prevent fatigue: alternation of exerting and relaxing activities, improvement of planning and regular relaxation.

Table 1. Rationale and main elements of Cognitive and Graded Activity Training on post stroke fatigue.

	Rationale	Treatment aims	Treatment elements
1	Primary fatigue is caused by brain damage, therefore energy levels cannot be fully restored	- Prevent fatigue - Manage existing fatigue	- Patient education - Improvement of insight into activity and fatigability patterns - Adaptation of activity patterns to present energy levels by compensation strategies
2	CBT is effective in chronic fatigue syndrome	- Foster behavioral change - Decrease fatigue related anxiety	- Change unhelpful thoughts by means of structural implementation of CBT in sessions and homework assignments
3	Increased physical fitness may decrease fatigue	- Enhance physical fitness - Decrease fatigue	- Graded Activity Training: with training of endurance, strength and flexibility

Furthermore, evidence from studies on treatment in chronic fatigue syndrome [178] suggest that cognitive behavioural therapy (CBT) is helpful in reducing fatigue. In the COGRAT treatment a form of CBT, [179] has been incorporated systematically in the treatment. In this treatment CBT is explained as follows. 'Unhelpful or irrational thoughts about a given situation lead to unhelpful emotions and behaviours. The situation is taken as given. It is the thoughts about the situation which cause our emotions and our behaviour.' These automatic thoughts are identified and challenged with the help of the therapist. Together with the group of patients more suitable and realistic thoughts are then formulated and practiced by the patient in order to facilitate helpful behaviour and decrease unhelpful emotions. The aims of CBT are to foster behavioural change, to decrease fatigue related anxiety and to help accept and manage existing fatigue symptoms.

For example, when a patient sees the pile of laundry still to be ironed, the thought may arise 'I must finish this all now'. When the situation (i.e. the pile of laundry) is taken as given, this thought is not helpful since ironing the entire pile of laundry in one stretch may be too tiresome. When the patient then finds him- or herself too tired to continue, the thought 'I cannot even finish this pile, therefore I am worthless' may lead to depressive feelings and unfruitful behaviour.

Therefore, changing negative thoughts into more helpful and realistic ones such as 'I can stop now and finish this later and that is perfectly ok' will aid the patient in both implementing behavioural change and in accepting fatigue.

Last, a graded activity program is given alongside the cognitive treatment to diminish experienced fatigue through improved physical fitness. Clinical observations show that lack of physical exercise frequently leads to secondary de-conditioning and reduction of cardiovascular fitness in stroke patients.[117] Furthermore, it has been found that exercise therapy effectively alleviates fatigue in numerous other medical conditions.[71, 126, 180-182] Regular exercising may therefore reduce experienced fatigue, which in turn can teach patients that physical activity is trainable and exercise is compatible with life after stroke.[183] In addition, programmes that use graded activity do not only increase the physical fitness of patients, but also have a preventive effect on subsequent stroke or other cardiovascular diseases.[184, 185] The exercises and loads of the program are based on the recommendations for Stroke Survivors of the American Heart Association,[113, 184] taking into account the safety for this patient group in view of their vascular frailness.

Theory into practice

The COGRAT treatment consists of both a cognitive treatment and a graded activity training given alongside for twelve consecutive weeks. It has been specifically designed for patients who suffer from severe fatigue after stroke as their primary complaint. Furthermore to participate in the graded activity training, patients must be able to deambulate independently in order to walk on the treadmill. Several exclusion criteria must be considered, such as cognitive disorders that may limit basic understanding or retention of information (e.g. severe deficits in attention, memory, executive functioning and language skills).

The cognitive therapy takes place once a week for 2 hours and is given by a neuropsychologist with ample knowledge and experience of CBT and PSF. The treatment is given to small groups of four patients in a quiet environment. This choice was based on the findings of our pilot study, where patients in larger groups experienced difficulty concentrating and, thus, benefited less from the treatment than patients in smaller groups. For instance in small groups, patients with mild attention deficits will profit more from the examples brought forward by other group members due to fewer distractions.

The graded activity training is given twice a week for two hours by a physiotherapist with ample knowledge of and experience with stroke patients. This programme may be given to the whole group of four or to pairs, depending on the facilities available (e.g. sufficient treadmills). The organisation of the COGRAT treatment is described in Table 2.

Table 2. Organisation of the COGRAT treatment

	Cognitive treatment	**Graded Activity Training**
Therapist/ Physiotherapist	Neuropsychologist with knowledge of: - PSF - CBT - Group therapy	Physiotherapist with knowledge of: - stroke
Patients	No severe cognitive deficits	Able to walk independently
Group size	Maximum of 4	With 4, or in pairs
Time	Once a week, for two hours For twelve weeks	Twice a week, for two hours For twelve weeks

Cognitive Treatment

The cognitive treatment consists of twelve sessions. All sessions have a specific theme and are uniformly structured. At the start of each session, patients are first made welcome and the sessions' programme is presented. Then the results of homework assignments given in the previous session are discussed. The therapist reinforces positive behavioural change and helpful thoughts verbalised by patients. Next, education on the theme of the session is given, followed by a break of at least 10 minutes. Patients are encouraged to ask for more or longer breaks when needed.

After the break, the second part takes place, in which the session theme is further elaborated. The therapist ensures that all participants understand the tasks at hand and gives personalised examples, whenever feasible. At the end of each session, 15 minutes are reserved to explain the next homework assignment(s). Patients also receive hand-outs of all information and homework assignments and they are encouraged to share their experiences and information with their relatives and close friends.

Furthermore, positive feedback is given to encourage patients in changing their beliefs and behaviours. At all times, the therapist takes great care in creating a safe group environment (e.g. Yalom and Leszcz)[186] to facilitate group cohesion and an open attitude of patients, which is important for an optimal treatment outcome.[187]

During the 12 weeks of the cognitive treatment, three separate stages can be distinguished as shown in table 3.

Table 3. Architecture of the Cognitive Treatment

Stage	Sessions	Therapeutic elements	Homework
1. Education and goal setting	1-3	**A** b c	1, 2, 3
2. Introduction of CBT and insight into personal activity and fatigability patterns	4-6	**A** b c **D**	1, 3, 4, 5
3. Compensation strategies and CBT	7-12	**A** b c **D E** f g	1, 4†, 5, 6
Therapeutic elements *(letters in bold* are the main treatment elements, the other letters are supporting therapeutic actions)* ***A**: Education* *b: Meaningful and personalised information and examples* *c: Feedback, modelling and reinforcement of active behaviour* ***D**: CBT* ***E**: Insightful practice of compensation strategy* *f: Relapse prevention* *g: Assertiveness*		***Homework assignments*** *1: Reading information leaflet of the session* *2: Contemplating treatment goals* *3: Set and practice individual sub-goal* *4: Practice with CBT* *5: Logging activities and fatigue* *6:Practice with compensation strategy set in individual sub-goal* †*CBT homework assignments are given in stage three to those patients who need further change in their beliefs to facilitate the behavioural change.*	

Stage 1: Education and goal setting

The first stage has a psycho-educational character. It consists of the sessions: (1) Introduction, (2) Individual goal setting and (3) Goal setting and presentation. In these three sessions, patient education on the possible aetiology of PSF and fatigue symptoms is repeatedly given. Also since sleep disturbances are common sequelae of stroke[188] that may directly influence fatigue,[56, 80] sleep hygiene is illustrated.

In the first session the organisation of the treatment is explained and the compensatory nature of COGRAT is emphasised. Furthermore, patients are carefully instructed on how to formulate 2 or 3 individual SMART (Specific, Measurable, Attainable, Realistic and Timely) treatment goals.[189, 190]

The second session is an individual session to help patients in wording their goals realistically and attainably, and to manage treatment expectations.

When sleeping disturbances are present, solving these disturbances is always part of the first goal. Every subsequent week, with the help of the therapist, patients formulate an achievable action plan that helps them to realise one of their treatment goals.

In the third session, patients design posters of their goals and present these to their peers. On these posters they indicate their current goal status on a visual analogue scale (VAS) by giving themselves a grade between 1 (not achieved at all) to 10 (completely achieved). Next, they clarify the levels they would like to achieve at the end of the treatment.

Every week, after they have presented their achieved homework results, patients are encouraged to update their VAS-marks on the posters to reinforce positive and active behaviour. The posters are displayed in the treatment room to visualize individual goals and improvements.

Box 2

LD had difficulty adjusting to a life in which he could not participate in pre-morbid activities. He was very impressed with the information given to him about PSF and especially about the possible causes of fatigue. Finally it made sense to him, he said. Because he had trouble initiating activities, he ended up doing nothing but watching TV, which in itself became a straining activity. Incorporating daily duties was formulated as a goal. This involved explicit planning:

"I want to do things, be active. Therefore I will plan my daily activities and resting periods ahead, so that I will know what to do when the time comes. I will use a day planner in order to achieve this."

Although, at first, he was reluctant to plan his life so rigorously, he gradually became aware that his lifestyle was detrimental. Thus, he became motivated to try the 'planning approach'.

Stage 2: Introduction in CBT/RET and insight into personal activity and fatigability patterns.

The second stage consists of the following sessions: (4) Introduction to CBT, (5) CBT and the relationship between activities and fatigue and (6) Activity Registration.

In session 4, CBT is introduced by the simplified formula: 'Event + Thought = Feeling & Behaviour'. This formula is then practiced by matching it to personal experiences. To further help patients apply these principles in daily life, they receive a CBT-workbook in which these principles are illustrated and in which concrete exercises involving fatigue and concrete session themes are incorporated. To enhance the patients' understanding of the close relationship between their activity pattern and fatigue, they are given a homework assignment

in which they log their activities and experienced fatigue on an hourly basis during two weeks.

In session 5, first a repetition and elaboration on CBT is presented. A number of frequent 'unhelping' thoughts are identified and matched with the experiences of the patients. With personal examples of patients 'helpful thoughts' are identified and given to practice as homework assignments. Furthermore, activities and subsequent levels of fatigue that have been logged during the previous week are already considered within the group for possible relationships.

In session 6, a colour coding is introduced in which activities are linked with different colours in order to visualize activity patterns. The coding are: sleep (blue), passive relaxation (brown), active relaxation (yellow) and work/productivity (red). These colours are then applied to the worst and least fatiguing day of the logged weeks. Using the fatigue scores, patients are taught that it is not only the activity itself, but also the duration and intensity level of the activity as well as the intermittent rest that influence and determine fatigue severity (e.g. Box 3).

Box 3
YB had a "moment of epiphany" when she logged all her activities and fatigue during a week. She said she never would have imagined that she was still doing almost as much work and household chores as before the stroke. Furthermore, she noted that she was already exhausted at work after lunch and after meetings. The common denominator was that she developed fatigue during activities with many surrounding sounds and when communicating with more than two persons at the same time. For instance, lunchtime did not bring active (yellow) or passive (brown) relaxation, but resembled strenuous activity (red). As a sub-goal she then chose to allow herself to "drift off" during meetings and, instead of having lunch with all her co-workers, she would take a walk with just one of them. At the next session when YB presented her achievements on this homework assignment, she reported to have more energy due to fewer "red" activities and a more "yellow" lunch. As a result she felt the return of pleasure in her work.

Stage 3: Compensatory strategies

In the third stage, three compensation strategies aimed at implementing behavioural change, are consecutively presented and practised. The modification of activity patterns follows from the insight gained from the colour coding exercises. This stage consists of the sessions (7) Compensation one: Alternating, (8) Mid-term evaluation, (9) Compensation two: Planning, (10) Compensation three: Relaxation, (11) Dealing with surroundings and (12) Evaluation.

In session 7 and the subsequent homework assignments, patients are taught how to incorporate the alternation of activity and rest into their daily activities. Through to the logging exercises, patients have been made more aware

of how long a certain activity may last before they experience fatigue (e.g. 20 minutes). They are then taught to take short resting periods (e.g. 5 minutes), or by engaging in a relaxing activity, instead of completing the task uninterruptedly. Hence, the total time spent on the task can be elongated (e.g. 3x 20 minutes with breaks). Different means of taking small breaks and reminding oneself to rest in time are discussed.

In session 8 all the behavioural changes and achievements up to this point are emphasized and verbally reinforced. Furthermore, this session allows for repetition of previous exercises and information when needed.

In session 9 beter planning, is introduced. Good planning helps to structure and maintain activity patterns that prevent fatigue, to retain an overview of tasks and activities, and to communicate new activity pattern to relatives and close friends (e.g. Box 4).

Session 10 is devoted to relaxation and the role of leisure activities. Patients often have trouble to relax for several reasons. First, energy expenditure has changed after stroke. Activities that were once relaxing may now have become quite demanding. Second, following the cognitive coping hypotheses, the physiological costs of tasks requiring attention are higher after brain damage[36, 38, 96, 103, 177] and these may lead to distress.[9] Furthermore, blood pressure changes significantly during attention-demanding tasks and may remain altered for a longer period of time in patients after brain damage.[37, 175] Both hypertension and hypotension have been linked to fatigue after stroke.[57] In order to normalize blood pressure levels to healthier proportions and reduce the physiological costs, it is crucial for patients to actively bring themselves into a more relaxed condition. To help patients relax, recorded exercises are offered. Patients can then practice these exercises at home.

In session 11, specific attention is given to expressing ones needs and boundaries. Furthermore, patients are taught how to explain their fatigue and fatigue-avoiding behaviours to the people in the direct social environment. This skill equips patients with timely statements regarding their needs and (in)abilities.

Finally, in the last session (12), each patient presents his/her treatment goals and the steps already taken to reach these goals. Finally, the patients award themselves with final points on their Goal-posters for their achievements. All these steps, including the helpful thoughts and the action plans, are written and taken home by the patients.

In sessions 10 through 12, as a part of relapse prevention, the therapist also assists the participants in finding adequate reactions and thoughts to situations in which fatigue is present.

Box 4

LD first greatly opposed to better planning, since he "had never planned in his entire life". However, having learned from the logging exercise that his days were nearly empty and being confronted not only with his inability to initiate activities but also with his memory problems, he agreed that better planning could indeed make his life easier.

LD started by writing down his trips to the clinic and whether he had already organised his transport. He then no longer needed to call the taxi-office to verify whether or not he had already arranged transport. From that point on, he planned adequate rest before and after his visits and on specific occasions during the day, before inserting other tasks and social engagements in his day planner. Because LD always had had difficulty initiating tasks, he was taught to look at his planner regularly, to specify each activity in it, and to plan fixed times to update his agenda. In order to allow for unplanned visits from his friends, LD reserved about 2 hours a day as "unplanned social activities".

After two weeks LD noticed that he needed to think less about what he would do each day. By "just doing" the things that were written down, he experienced that he not only accomplished far more activities, but that he was also less tired than before. Furthermore, he was now able to check which tasks he had already finished and which ones were still due. A week later, LD proudly stated that his friends had now completely approved and accepted his "resting periods" and "social hours", because they had experienced that he had more energy during their common activities.

Physical Graded Activity Training

The graded activity training consists of two treatment sessions per week over 12 weeks. The program focuses on endurance, strength and flexibility. The training follows the principle of progressively increasing intensity of both heart rate and muscle strength[113, 184] as illustrated in the training schedule in table 4.

In order to ensure the proper heart rate and loads used during exercises, measurements of individual heart rate and muscle strength are taken during the first session (baseline) as well as after six weeks to adjust the training intensity for each patient. Ideally, the maximum heart rate (MaxHR) is assessed by a baseline graded exercise test with ECG monitoring.[184]

Endurance is trained by walking on a treadmill using gradually increasing inclination rather than increasing speed [184, 185] and by increasing the total time walking both during the training and at home. When needed, hand rail support or 'unweighting' devices (i.e. harnesses that serve to 'lift' patients) are used to enable patients to walk on the treadmill. At the start of the training, patients walk twice for 10 minutes at 40% MaxHR. The heart rate is then kept constant for two weeks, during which the walking duration increases following a fixed regimen (see Table 4). In the second session patients walk twice for 15 minutes and in the third session for 18 minutes. In the fourth and last session of these two weeks, walking

duration is increased to twice 20 minutes. In weeks 3 and 4, the training heart rate is set at 50% MaxHR, which is gradually increased every two weeks to 70% MaxHR at the end of the 12-week programme.

Another part of endurance training consists of taking walks at home and gradually lengthening these. At the start of the program, patients are asked to walk twice a week for twenty minutes. This increases to twice 40 minutes in week seven, to twice 40 minutes plus twice 20 minutes a week at the end of the programme.

Muscle training is aimed to increase strength. This training consists of core muscle training and weight lifting with upper and lower body limbs. Core muscle exercises are adapted to the individual abilities. In every session three different exercises are practiced with 10 to 15 repetitions each in three sets. Weight training consists of lat pull down, chest press and leg press. As with the endurance training, a graded exercise regimen is specified. Patients start training of upper body limb training with three sets at 40% of maximal muscle strength (1RM), and lower body muscles limbs at 55% 1RM. The specified 1RM is upheld during these two weeks, with only the number of repetitions per set increasing from 10 to 15. The weight is then gradually, with two-week steps, increased to a maximum of 70% 1RM at the end of the program, as illustrated in table 4.

Each session lasts 2 hours and is uniformly structured. First, patients train endurance by walking twice on a treadmill, followed by a resting period of 30 minutes. Then, patients proceed to muscle training. Afterwards, all trained muscles are carefully stretched to improve flexibility. Lastly patients are encouraged to practice their homework; taking walks to promote generalisation of improved physical activity. All individual achievements are registered and made available for patients to optimize their motivation.

It is important to note, however, that some adaptations to the training load may be necessary, especially in patients using beta-blockers. This medication is known to reduce the heart response to exercise, which limits the validity of the heart rate as a measure of physical load [191]. Therefore, Borg's rating of perceived exertion [192] is used in each session to individually adjust the training when necessary. First, the physiotherapist carefully explains the meaning of all scales to promote valid and reliable assessments [193]. When training is perceived as too demanding (BORG > 14), training intensity is temporarily diminished with 5%. When training load is perceived as too low (BORG < 11), training intensity is increased by an extra 5%. The training intensity is, however, always maintained between the 40% and 70% margins to ensure both safety and effectiveness.

Figure 4 Graded Activity Training Schedule

	Endurance training* *(minutes at %MaxHR)*	**Upper body training ** ** *(number of sets x repetitions at %1RM)*	**Lower body limbs **** *(number of sets x repetitions at %1RM)*	**Core muscle training *** *(number of sets x repetitions)*	**Homework ****** *(times a week x minutes)*
Exercise	Walking on treadmill	Lat pull down and Chest press	Leg press	Core muscle exercises	Walking
Week 1-2 *Baseline Measurements*	2 x 10m 40% → 2 x 20m 40%	3 x 10 40% → 3 x 15 40%	3 x 10 55% → 3 x 15 55%	3 x 10 → 3 x 15	2 x 20m
Week 3-4	2 x 10m 50% → 2 x 20m 50%	3 x 10 50% → 3 x 15 50%	3 x 10 60% → 3 x 15 60%	3 x 10 → 3 x 15	2 x 30m
Week 5-6	2 x 10m 60% → 2 x 20m 60%	3 x 10 55% → 3 x 15 55%	3 x 10 65% → 3 x 15 65%	3 x 10 → 3 x 15	2 x 40m
Week 7-8 *Reassessment of MaxHR and 1RM*	2 x 10m 60% → 2 x 20m 60%	3 x 10 55% → 3 x 15 55%	3 x 10 65% → 3 x 15 65%	3 x 10 → 3 x 15	2 x 40m
Week 9-10	2 x 10m 65% → 2 x 20m 65%	3 x 10 60% → 3 x 15 60%	3 x 10 70% → 3 x 15 70%	3 x 10 → 3 x 15	2 x 40m and 1 x 20m
Week 11-12 *Final assessment of achieved results*	2 x 10m 70% → 2 x 20m 70%	3 x 10 65% → 3 x 15 65%	3 x 15 70%	3 x 15	2 x 40m and 2 x 20m

%MaxHR = percentage of Maximum Heart Rate; %1RM = percentage of Maximal Muscle Strength; m = minutes

Graded Activity Training is given twice a week for two hours. During every two-week-period (weeks 1-2, weeks 3-4,… weeks 11-12) there are four sessions in which a gradual increase in minutes of endurance training and number of repetitions of muscle training takes place. Training intensity of endurance and muscle training is monitored with the BORG-scale and temporarily adjusted when appropriate.

***** Endurance training is practiced at the given %MaxHR twice in every session. Minutes walked twice increase from 10 minutes, to 15 minutes the second session, to 18 minutes in the third and 20 minutes in the fourth session. Heart rate is monitored and inclination is adjusted to achieve the desired heart rate.

****** Upper and Lower body muscle training is always practiced in three sets at the given 1RM, with the number of repetitions increasing during the two-week-periods from 10 in the first, 13 in the second, 14 in the third and 15 in the fourth session.

******* Core muscle exercises are adapted to the individual abilities. In every session three different exercises are practiced with 10 to 15 repetitions each in three sets.

******** Homework consists of taking walks. Every week a number of walks and time walked is set and evaluated.

Discussion

Post-stroke fatigue is a common chronic condition after stroke, characterised by persistent and debilitating feelings of exhaustion.[11, 129] However, up to date no comprehensive treatments were available.[130] Therefore, on the basis of a pilot study,[172] we designed a treatment protocol specifically for patients who report chronic fatigue as their major complaint or disability. Since the brain damage is hypothesised to be the primary cause of the fatigue,[22, 43, 69, 72, 103] the treatment is not aimed at restoring pre-morbid energy levels. In contrast it provides patients with several compensation strategies to prevent and manage fatigue. Furthermore CBT is systematically applied to reduce fatigue related anxiety and foster behavioural change. Preliminary data of a multi-centre randomized controlled trial show promising results on both the checklist individual strength fatigue scale and the symptom checklist 90.

The studies on treatments of post-stroke fatigue that have been conducted previously have yielded equivocal results at best. Fluoxetine administration was ineffective for alleviating fatigue in a double-blind randomized controlled trial.[104] Trialiazad mesylate decreased fatigue in a small trial of patients with subarachnoid haemorrhage, however, more than half of the patients randomized were not available for follow-up.[21] A small study on modafinil showed a decrease in fatigue severity in patients with brainstem and thalamic strokes, but not in patients with cortical infarctions.[107] Furthermore, a study on the improvement of sleep-disordered breathing showed decline of fatigue only in those patients suffering from sleep apnoea syndrome.[108] Last, post-stroke fatigue was not reduced by a chronic disease selfmanagement programme not specifically aimed at fatigue.[21]

In conclusion, these studies provide little basis on which to design a comprehensive treatment for post-stroke fatigue. In addition, studies of interventions in other neurological conditions such as traumatic brain injury or multiple sclerosis are scarce or offer little evidence-based advice, [11, 110] other than that exercise may be helpful.[21] Systematic reviews of other nonneurological populations, however, provide a number of fruitful leads. First, in cancerrelated fatigue they show that interventions specifically aimed at fatigue (with education and activity management) are more effective than interventions not aimed specifically at fatigue.[194] Second, in chronic fatigue syndrome CBT has been found to be effective[195] and exercise therapy promising.[182] Therefore, these elements have been incorporated in the COGRAT protocol. Nevertheless, the premise that in neurological patients, fatigue primarily caused by brain damage is upheld and therefore compensation strategies are taught to deal with existing fatigue.

The treatment protocol presented here has its limitations. The proposed treatment has been applied only in chronic stroke patients with relatively mild cognitive, emotional and physical impairments in an outpatient setting. Therefore,

several adaptations might be needed to apply a similar treatment in other types of stroke patients. For instance, when patients are in the subacute phase after stroke, emphasis might be laid on education of the patients, the caregivers and the therapists about fatigue and fatigability in order to properly adjust the training aimed at functional recovery. In patients who are not able to comply with the graded activity training due to physical limitations, personalized adaptations to the training tasks should be sought.

For patients with (severe) cognitive impairments, the cognitive training and education should be tailored to the individual possibilities. In addition, the caregivers should be explicitly included in the treatment to help these patients to gain insight and to restructure their lives. For those patients with problems initiating and stopping activities, the involvement of caregivers could be particularly beneficial. The caregivers may help the patients with external cues on when to initiate and stop certain activities. In patients with communicative problems, the basic principles of clear, repetitive and structured information should be adhered to even more fervently.[196] Furthermore, the treatment protocol should probably make use of a more directive approach by the therapist and of less CBT.

Patients with fatigue due to other neurological conditions could presumably benefit from a similar treatment as presented in this paper. For patients with non-progressive brain damage such as traumatic brain injury or encephalitis, the COGRAT protocol is probably readily applicable. For patients with (potentially) progressive brain disorders such as multiple sclerosis or Parkinson's disease, the same principles can still be upheld, although the graded activity training would need to be frequently adapted to the individual abilities.

Clinical Messages

- COGRAT seems a promising intervention to treat fatigue after stroke.
- Patients receiving COGRAT should preferably have mild cognitive and/or physical impairments
- Therapists giving COGRAT should have knowledge of post-stroke fatigue and cognitive behavioural therapy and be able to adjust treatment to individual abilities.

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Chapter 6. The evaluation of COGRAT, a randomized controlled trial

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"It takes a lot of energy to be negative. You have to work at it. But smiling is painless. I'd rather spend my energy smiling."

Eric Davis (1962-)

Abstract

Background and purpose— Fatigue is a common, persistent consequence of stroke and no evidence-based treatments are currently available to alleviate fatigue. A new treatment combining cognitive therapy (CO) with graded activity training (GRAT), called COGRAT, was developed to alleviate fatigue and fatigue related symptoms. This study compared the effectiveness of the COGRAT intervention with a CO only intervention after a 3-month qualification period without intervention.

Methods— This randomized, controlled, assessor-blind clinical trial was conducted in 8 rehabilitation centres. Eighty-three stroke patients (> 4 months post stroke) were randomly assigned to 12 weeks of CO or COGRAT after qualification. Seventy-three patients completed treatment and 68 were available at follow-up. Primary outcomes (Checklist Individual Strength – subscale Fatigue (CIS-f); self-observation list - fatigue (SOL-f)) and secondary outcomes (Hospital Anxiety and Depression Scale, Stroke-Adapted Sickness Impact Profile, SOL-pain, SOL-sleep-D, 6-Min Walk Test) were collected at baseline (before and after qualification period) and after treatment (immediate and 6-months follow-up).

Results— The qualification period showed stable outcome measures**.** Both treatments showed significant beneficial effects on fatigue (CIS-f: η_p^2=.48, p<.001) and other outcomes (except pain and anxiety) with intention-to-treat analyses. Gains for the COGRAT group exceeded those in the CO group on number of individuals showing clinical improvement on the CIS-f (≥ 8 points: 58% vs 24%) and on physical endurance (η_p^2=.20, p<.001).

Conclusions— A 12-week cognitive therapy program can alleviate persistent fatigue after stroke. The best results are obtained when cognitive therapy is augmented with graded activity training.

Clinical trial registration—URL: http://www.trialregister.nl. Unique identifier: NTR2704

Introduction

Fatigue is a common and often persisting consequence of stroke that negatively affects rehabilitation outcome, functional independency in daily life activities, quality of life and mortality.[20, 197] Although the definition of post-stroke fatigue (PSF) is still subject of debate,[20, 197] it is generally agreed that it is "a subjective experience of extreme and persistent tiredness, weakness or exhaustion after stroke, which can present itself mentally, physically or both and is unrelated to previous exertion levels"[20, 28, 58, 197] Prevalence rates are as high as 38% to 73% without spontaneous amelioration in the chronic phase.[20] Moreover, research on its natural history shows that PSF often does not diminish even years after stroke. [15, 45, 46, 58] The etiology of PSF seems to be multifactorial. On the one hand, direct relationships have been described between the type and extent of the brain lesion, with infratentorial lesions, infarction of the basal ganglia and recurrent stroke yielding a greater risk of fatigue.[20, 47, 58, 66] On the other hand, depression, anxiety, reduced functional health status, sleep disturbances, pain and poor physical fitness have all been associated with PSF.[1] Overall, the exact mechanisms of origin and persistence of PSF are still elusive[20] and no effective pharmacological or non-pharmacological treatment for PSF is yet available.[197]

Evidence from other patient populations with chronic fatigue suggests that tailored cognitive behavioral therapy, exercise therapy [126, 181] and teaching energy conservation strategies[111] are effective means to alleviate chronic fatigue and related psychological and physical symptoms. Against this background, we developed a 12-week group cognitive treatment (CO) tailored to the stroke population, including elements of cognitive behavioral therapy (CBT) and teaching compensation strategies aimed at pacing and relaxation.[198] A Graded Activity Training (GRAT) was offered alongside the cognitive treatment. GRAT consisted of walking on a treadmill, strength training and physical fitness homework assignments. A full description of these interventions has been published previously.[198]

The aim of this study was to compare the effectiveness of a combined intervention (COGRAT) with that of CO alone on fatigue and associated psychological and physical variables. As the long-term beneficial effects of physical fitness training after stroke are still subject to debate and because functional benefits of physical training tend to taper off at a later stage,[199] we did not include a separate GRAT group. We hypothesized that both CO and COGRAT would alleviate fatigue, but COGRAT would be more effective than CO alone, especially with regard to physical endurance.

Methods

Study design

A multi-centre, randomized controlled study preceded by a qualification period was designed using block randomization per treatment center. Outcome measures were administered by blinded assessors and were gathered via self-report questionnaires. Patients did not receive feedback on any of the assessments during the trial.

Eligible patients were first assessed on the primary and secondary outcome measures (T0) and then entered a waiting list period of three months, during which no rehabilitation took place. The benefits of this so called 'qualification period' are that previous therapeutic effects are washed out, that poor compliers can be identified prior to randomization, and that a stable baseline of the outcome measures can potentially be established.[200] Immediately after the qualification period, the outcome measures were administered again (T1).

Thereafter, when 8 patients were available at a center, randomization of individual patients to an intervention group (CO or COGRAT) took place by means of 8 sealed envelopes. If only 4 patients were available at a center, all patients were assigned to one intervention group by means of a sealed envelope. Directly after treatment another assessment took place (T2), while a follow-up assessment was performed after 6 months (T3).

The study was approved by the regional Medical-Ethical Committee for Research Involving Human Subjects and the local Medical-Ethical Committees of the 8 participating Dutch rehabilitation centers. The study was conducted according to the Declaration of Helsinki[201] standards. All patients provided written informed consent.

Patients

Between April 2008 and February 2010, community-dwelling patients who had had a stroke were approached through their treating physicians and psychologists, through newspaper articles or based on participation in previous studies. Patients were eligible if they (1) had sustained a stroke more than 4 months before recruitment, (2) reported severe fatigue (Checklist Individual Strength – subscale Fatigue score ≥ 40 [15, 52]), (3) were aged between 18 and 70 years and (4) were able to walk independently. Patients were excluded if they had severe cognitive deficits (Behavioral Inattention Test ≤ 129 [132]; Rivermead Behavioural Memory Test-screening score <8 [132]; Behavioural Assessment of the Dysexecutive Syndrome < borderline [132]; Token Task >12 [132]) or severe co-morbidity, such as cardiac disease, pulmonary disease or depression (Hospital Anxiety and Depression Scale – depression subscale score > 10,[138] or based on a clinical DSM-IV interview [133] if the HADS depression subscore was 8, 9 or 10). Demographic and neurological data (age, sex, living situation, education level,

previous rehabilitation treatments, stroke type and hemisphere, time post onset of stroke, single vs recurrent stroke, Motricity Index [134]) were obtained from the medical files.

Interventions

Based on the results of a pilot study to test the effects of cognitive treatment (emphasizing pacing and relaxation) on fatigue and psychological distress in patients with stroke, the size of the CO groups was set to a maximum of 4 patients [198]. In addition, a GRAT protocol was designed including walking on a treadmill, strength training and homework assignments. Maximum heart rate and strength were slowly increased from 40% at the beginning of the training to a maximum of 70% at the end of the 12-week program based on recommendations by the American Heart Association.[198, 202] GRAT was given in groups of maximally 4 patients as well. The CO group received weekly two-hour sessions of cognitive therapy for 12 weeks, In addition to group CO, the COGRAT group received 24 two-hour sessions of GRAT twice a week for 12 weeks. During the study interventions, no other treatments were given.

The neuropsychologists giving CO and the physiotherapists giving GRAT were all experienced in the rehabilitation of patients with stroke and worked within an academic setting. The neuropsychologists were also proficient in CBT. All therapists were trained and supervised by the principal investigator (AZ). All participants received daily homework assignments to enhance the therapeutic objectives. After each session, therapists rated patient attendance and patient adherence to treatment and homework on a 5-point Likert scale. Therapists also rated the percentage of the protocol that they had followed after each session.

Primary outcomes

The Checklist Individual Strength – subscale Fatigue (CIS-f)[52] and a fatigue self-observation list (SOL-f)[203] were used to obtain information on patient's fatigue. Both tools are well validated and are widely used in the Benelux countries.[47, 148, 203, 204] The CIS-f contains 8 questions on fatigue severity regarding the two weeks preceding the assessment. The CIS-f has good reliability, is sensitive to change,[28, 52] and has been validated for the stroke population.[15, 47] Questions are answered on a 7-point Likert scale (1-7, summed range 8-56, higher scores represent greater fatigue). Patients with a score ≥ 40 were regarded as severely fatigued.[15, 203] With the validated SOL-f, patients recorded their fatigue severity on a 5-point scale (0-4) four times a day (morning, afternoon, evening and bed time) for 7 days. The daily fatigue score was the sum of these 4 scores (range 0-16). The average daily fatigue score was calculated. [148, 203, 204]

Secondary outcomes

Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS).[138] The HADS has been validated in patients with stroke and it consists of 14 items scored on a 4-point Likert scale (0-3): 7 items on the depression subscale (HADS-D) and 7 items on the anxiety subscale (HADS-A).[205] Subscale sum scores are categorised as normal (0-7), mild (8-10), moderate (11-14) or severe (15-21).[139]

Functional health status was assessed with the well validated Stroke-Adapted Sickness Impact Profile 30 (SA-SIP 30).[206] This tool has 30 items and scores are calculated as a percentage of maximum dysfunction, ranging from 0% to 100%. A higher score indicates poorer functioning. In a well validated self-observation list (SOL) patients recorded the amount of pain they experienced 4 times a day on a 5-point scale (0-4). For each patient a mean pain score per day is available (SOL-pain, range 0-16).[148, 204] A SOL was also used to record the quality of sleep. Patients indicated whether they had slept well, or recorded which of three sleep disturbances had occurred that night (difficulty falling asleep, restless sleep, early awakening). The amount of sleep disturbances was totalled for each day (0-3). Scores were then expressed as the average amount of sleep disturbances per night (SOL-Sleep D, range 0-3). [148, 204]

The 6-minute walk test (6MWT) is a validated tool to assess physical endurance.[207] The total walking distance in meters (m) during 6 minutes was recorded.

Furthermore, after treatment (T2) patients were given a Visual Analogue Scale (VAS: range 0-10) to report patient satisfaction asking the question: “If I had to rate my satisfaction on treatment, I would rate it….”

Clinically important change

Clinically relevant improvement on the CIS-f was determined at follow-up (T3). At a group level, this was defined as a score below 35. This score is situated within two standard deviations of CIS-f scores in healthy controls.[148, 203, 208] At an individual level, a clinically important reduction of fatigue was set at a reliable change index (RCI) greater than 1.96. This corresponds with a CIS-f score decrease of at least 8 points. This decrement has previously been reported as a clinically important improvement in individuals with fatigue.[203, 208]

Statistical analysis

It was calculated that a sample size of 48 patients per treatment group would be needed to detect a clinically relevant difference of 8 CIS-f points with a β-value of .10 and an α-level of .05.[203, 208] Data analyses were performed using SPSS (version 18.0). Holm correction was used to control for multiple outcomes.[149]

Descriptive statistics were used to summarize demographic, stroke and baseline clinical characteristics. We then established whether changes on any of the outcome measures had occurred during the qualification period (T0 versus T1) using paired t-tests. All further analyses were performed on an intention-to-treat basis. Any missing values after treatment were imputed by carrying the last observation forward, adhering a conservative assumption with respect to treatment effects.

As a first step, analysis of covariance (ANCOVA) with the baseline scores as covariate was applied to the data. The interaction between Group and the covariate was significant for all outcome variables, which indicated non-parallel regression. For this reason, multiple analysis of variance (MANOVA) was done to establish treatment effects using Time (T1, T2, T3) as a within-subjects factor and Group (CO, COGRAT) as a between-subjects factor. Effect sizes were expressed in partial eta squared values (η_p^2), which range from 0 to 1.

To establish the percentage of patients with clinically significant improvement in fatigue, CIS-f scores were dichotomized into clinically significant (RCI≥1.96) and clinically non-significant (RCI<1.96).[208] We used χ^2-test and associated contingency coefficients to examine between-group differences.

To test whether any of the baseline characteristics was associated with study withdrawal or drop out, χ^2-tests were used for categorical variables and unpaired t-tests for interval data.

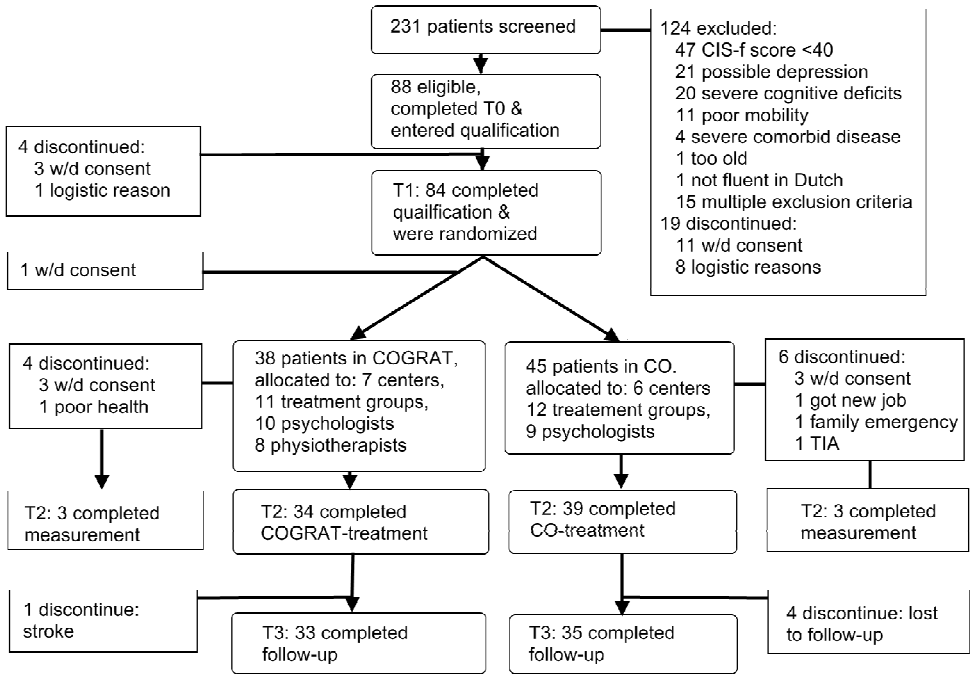
To investigate whether stroke characteristics affected treatment outcome, post-hoc analyses were performed for stroke type (ischemic, hemorrhage, subarachnoid hemorrhage (SAH) and mixed), single versus recurrent stroke, and post-onset time regarding all outcome measures at baseline and follow-up using analyses of variance (ANOVA) or t-tests.

Results

Patients

Patient flow (n=231) throughout the study is illustrated in the consort diagram in figure 1. The main reasons for non-participation were a CIS-f score below 40 (n=47) and symptoms of depression (n=21). Due to insufficient numbers of eligible patients at the different centers, individual randomization of 6 and 7 patients took place in several instances. As a result some treatment groups contained 3 patients. Of the 83 patients randomly allocated to a treatment group, 73 completed the treatment and were assessed at T2 (39 CO and 34 COGRAT). Of the 10 patients who discontinued treatment, 6 were assessed at T2. At follow-up (T3), 68 patients (82%) were still available for assessment.

Figure 1. Consort diagram



Mean post-onset time of stroke in participants was 3.9 years (SD: 3.9). For five patients post-onset time exceeded 10 years. Sixty-three patients had been given prior rehabilitation (75.9%). More than half of all participants had received physiotherapy (61.4%) and/or occupational therapy (50.6%). Demographic and clinical characteristics of both treatment groups are listed in table 1. None of these characteristics was associated with study withdrawal (n=5; 6%) or discontinuation of treatment (n=10; 12%; all p>.05).

Primary and secondary outcomes

Prior to the start of the interventions, after the three months qualification period, no significant change was found for any of the primary or secondary outcome measures. The values of the primary and secondary outcomes after the qualification period, at T1, T2 and T3 are shown in table 2. For the primary outcomes, after the treatment**,** main effects of Time were found (CIS-f p<.001; SOL-f p=.007). Effect sizes were substantial for CIS-f (η_p^2=.48) and less for SOL-f (η_p^2=.12). No interaction effects of Time with Group were found for either fatigue measures. Figure 2 illustrates that Time effects mainly occurred between T1 and T2 and remained stable at T3.

Table 1. Demographic and clinical characteristics of the patients (N=83)

	CO Mean (SD)	COGRAT Mean (SD)
N	45	38
Age (years)	54.8 (9.1)	55.6 (8.8)
% male	48.9%	55.3%
% living alone	24.4%	10.8%
Education (median:1=lowest,7=highest)	5 (1.1)	5 (1.3)
MI	90.2 (15.0)	90.1 (12.1)
Stroke		
Time since last stroke (years)	4.4 (4.2)	3.3 (3.9)
< 1 year post-stroke %	8.9%	13.2%
1-2 years post-stroke %	26.7%	34.2%
2-5 years post-stroke %	40.0%	34.2%
5-10 years post-stroke %	15.6%	15.8%
>10 years post-stroke %	8.9%	2.6%
Range	.8 — 22.2	.4 — 23.0
Single	75.6%	73.7%
Recurrent	24.4%	26.3%
Stroke type		
Ischemic LH/RH/ bilateral	7/23/1	10/18/2
Hemorrhage LH/RH/ bilateral	1/1/1	3/0/0
Subarachnoid Hemorrhage	7	2
Other (infarct cerebellum & mixed)	4	3
Prior rehabilitation	75.6%	76.3%
(mean number of treatments: SD)	(2.6: 1.8)	(2.1: 1.8)
Physiotherapy %	60.0%	63.2%
Occupational Therapy %	51.1%	50.0%
Speech therapy %	26.7%	23.7%
Cognitive Therapy %	31.1%	31.6%
Psychological treatment %	57.8%	36.8%
Specialist counseling %	2.2%	0

MI: Motricity Index[15]
LH: Left hemisphere; RH: Right hemisphere

Small but significant main effects of Time were found for all secondary outcomes, except pain and anxiety. These effects also occurred between T1 and T2 and were stable at T3. Of all secondary outcomes, the 6MWT showed the greatest Time effect and there was a significant interaction effect with Group ($p<.001$, $\eta_p^2=.20$). Figure 3 indicates that after treatment and at follow-up, physical endurance had improved more in the COGRAT group than in the CO group.

Figure 2. CIS-f scores at the 4 time points for the CO and COGRAT groups (N=83)

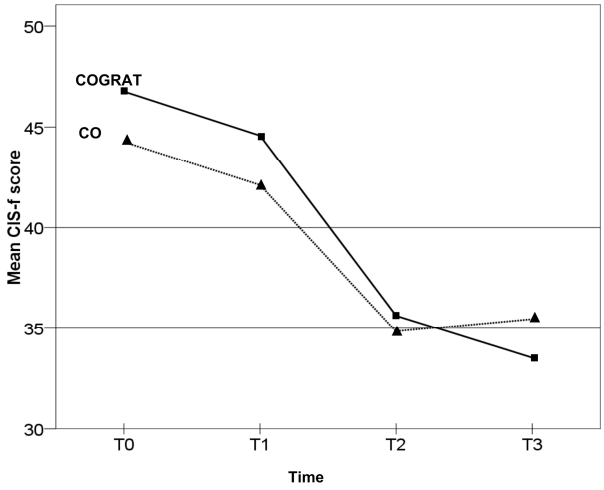
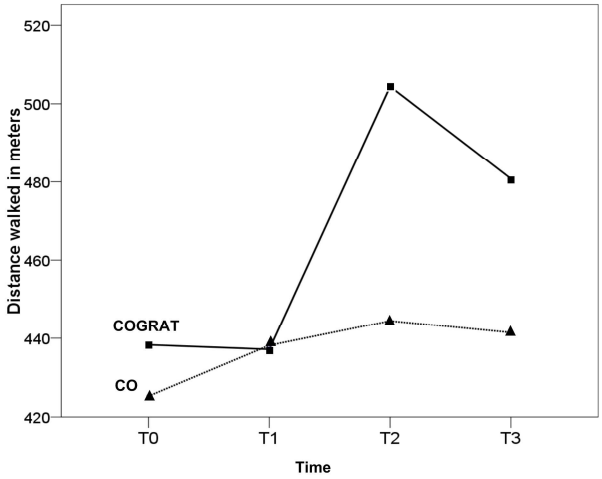


Figure 3. 6-Minute Walk Test, distance walked in meters at the 4 time points for the CO and COGRAT groups (data of one patient are missing on all four occasions; N=82)



Clinically important change

At follow-up, only the mean CIS-f score of the COGRAT group had improved to below 35. In contrast, the mean CIS-f score of the CO group was still (albeit marginally) higher than this cut-off score (table 2). At an individual level, more patients in the COGRAT group showed a clinically relevant improvement on the CIS-f than those receiving CO only (p=.002) (table 3).

Table 2. Outcome measurements (N=83)

Outcome variables	Means (SD)						Analyses						
	CO			COGRAT			Time*			Group*		Interaction*	
	T1	T2	T3	T1	T2	T3	F	*p*	η_p^2	F	*p*	F	*p*
CIS-f	42.1 (8.0)	34.8 (11.1)	35.5 (11.5)	44.6 (7.0)	35.6 (9.5)	33.5 (10.5)	37.74	<.001†	.48	0.06	>.1	2.16	.121
SOL-f	5.8 (2.3)	5.3 (2.6)	5.5 (2.7)	6.0 (2.7)	5.0 (2.3)	5.0 (2.6)	5.24	.007†	.12	1.39	>.1	1.39	.256
HADS-D	6.6 (3.1)	5.6 (3.3)	5.7 (3.3)	7.7 (2.7)	6.4 (2.6)	6.1 (3.4)	6.54	.002†	.14	2.25	>.1	0.12	.884
HADS-A	6.9 (4.1)	6.0 (3.8)	6.1 (4.0)	6.6 (3.9)	5.6 (2.9)	5.8 (3.6)	3.50	.035	.08	0.19	>.1	0.04	.963
SA-SIP	18.2 (10.6)	18.1 (11.5)	16.4 (11.0)	21.1 (13.1)	15.4 (12.1)	15.7 (13.9)	6.69	.002†	.14	0.00	>.1	3.25	.044
SOL-sleep D	.71 (.64)	.58 (.56)	.57 (.56)	.71 (.49)	.60 (.58)	.49 (.51)	5.25	.007†	.12	0.03	>.1	0.67	.516
SOL-pain	2.3 (2.7)	2.3 (2.7)	2.1 (2.6)	1.9 (2.4)	1.8 (2.2)	1.9 (2.7)	0.27	.765	.01	0.41	>.1	0.17	.841
6MWT	438 (123)	444 (112)	441 (123)	437 (107)	504 (94)	481 (92)	14.43	<.001†	.27	1.98	>.1	9.72	<.001†

*df values are omitted to improve legibility

† significant with Holm correction for multiple outcomes: p<.008 for Time and p<.043 for Interaction effect

CO, Cognitive Treatment; COGRAT, Cognitive and graded activity training; CIS-f, Checklist Individual Strength-fatigue severity scale; SOL, Self Observation List (-f: fatigue severity scale; -sleep D, sleep disturbances;) HADS, Hospital Anxiety and Depression Scale (-D, depression subscale; -A; anxiety subscale); SA-SIP, Stroke Adapted Sickness Impact Profile 36; 6MWT, Six-minute walk test.

Table 3. Clinically relevant improvement (N=83)

	CO No.(%)	COGRAT No.(%)
Improvement	11 (24.4%)	22 (57.9%)
No Improvement	34 (75.6%)	16 (42.1%)

Clinically relevant improvement (see text for definition)
Likelihood ratio: χ^2= 9.63, p=.002; Contingency coefficient = .322

Control for confounding variables

Mean patient satisfaction was high (VAS 7.8) and did not differ between the treatment groups. Therapist adherence to the treatment protocol was greater than 98% in both groups. Overall, the patients showed good treatment compliance. There were no statistical differences between groups for the number of CO sessions (median 11 out of 12) or completed homework assignments (nearly always). The median number of GRAT sessions followed in the COGRAT group was 23 out of 24.

Post-hoc analyses revealed no effects of stroke characteristics (stroke type, single versus recurrent stroke, post-onset time) on any of the outcome measures (all p>.05). Separate trend analyses of the outcome measures leaving out patients with SAH yielded the same statistically significant main and interaction effects, except for a non-significant effect of Time on SOL-f ($F_{(70)}$=3.98, p=.023) (non-significant after Holm correction for multiple outcomes).

Discussion

The results of this multi-center randomized controlled trial indicate that a cognitive therapy combined with graded activity training during a 12-week period reduces persistent PSF**.** Furthermore, beneficial effects remain stable at follow up and are not only found on two different measures of fatigue, but also on functional health status, symptoms of depression sleep and physical endurance. To our knowledge, this is the first study reporting significant reduction of PSF and related symptoms after a comprehensive treatment specifically tailored to the needs of this population.

Our results largely support the hypothesis that the addition of GRAT to cognitive therapy leads to a greater reduction of fatigue than when administering CO alone. Although at a group level both treatments resulted in almost similar benefits on the CIS-f, 58% of the COGRAT patients compared to 24% of the CO patients showed clinically relevant improvement at follow-up. In addition, as expected, physical endurance improved more after COGRAT than after CO alone. Directly after treatment, the increment in distance walked after COGRAT had almost reached the minimally important change of 70m.[207] At follow-up, however,

this improvement had decreased to approximately 40m. This pattern of results suggests that (besides the physical benefits) improving physical endurance may help reduce PSF complaints. However, such an improvement is not a prerequisite for lasting beneficial effects of cognitive therapy on PSF.

The major strengths of this study are its multi-center design, the three-month qualification period without any treatment, and the high level of treatment compliance and patient adherence. Although no independent rating of therapist adherence was performed, no conflicts of interest were present and all therapists had prior experience with scientific protocols. In addition, patients were generally satisfied with both treatments and the number of drop outs remained within acceptable limits.[209] Moreover, four out of the 10 patients that did not complete their treatment withdrew for reasons unrelated to the intervention (figure 1), suggesting that both treatments were well tolerated.

This study has, however, several limitations. The specific improvement in PSF due to COGRAT or CO cannot be teased out due to the absence of a sham control treatment. In addition, post-onset times in our study varied considerably, with five patients having suffered a stroke more than 10 years prior to enrollment. As we did not assess the full medical history of co-morbidities, we cannot attribute the presence of persistent fatigue solely to stroke in each patient. Yet, patients with a depression or severe cardiac or pulmonary disease were excluded. In addition, PSF has repeatedly been found to be a chronic condition with prevalence rates remaining relatively stable even years after stroke.[15, 45, 46, 58] Because no significant changes occurred in any of the outcome measures during the qualification period, the beneficial effects observed post treatment are most likely attributable to the intervention.

Two sources of heterogeneity in our study sample may be considered limitations: stroke etiology and previous treatment. As we included not only first-time infarctions, but also hemorrhages, SAH, and recurrent stroke, we cannot relate the observed treatment effects to any type of brain lesion. However, in our data, no influence of stroke type on treatment effects was found and, in the literature, prevalence rates of fatigue do not differ markedly between stroke types. [20, 210] Although more patients with SAH were allocated to the CO than to the COGRAT group (7 vs 2) and prognosis and complications after SAH differ from ischemic infarctions, the patients with SAH in this study did not differ from the other patients on any of the demographic characteristics or outcome measures at any point in time. The fact that the effect of Time ceased to be significant for SOL-f when excluding patients with SAH is most likely due to a loss of power, since all other effects remained unaltered. The etiological heterogeneity can also be considered as a strength for it indicates the effectiveness of COGRAT in a large variety of patients, irrespective of etiology. The strict eligibility criteria with regard

to ambulation and cognition, however, limit the generalizability of the results to other patients.

Patients also differed with regard to the amount and type of prior rehabilitation they had received. We were unable to post-hoc determine the nature and amount of fatigue relieving strategies offered in these treatments. Nevertheless, all patients still had severe fatigue complaints at study entry, and no significant changes were detected during the three-month qualification period.

Future studies should also incorporate (severely) fatigued patients with more pronounced cognitive and/or physical sequelae of stroke. To this aim, the cognitive treatment might be modified by using a more directive approach and by involving the primary caregivers.

In conclusion, this is the first controlled study showing that cognitive therapy can alleviate persistent fatigue **complaints** after stroke. However, the best results are obtained when cognitive therapy is augmented with graded activity training. As fatigue is known to have a negative impact on functional independence and quality of life after stroke, lasting treatment effects on persistent PSF potentially have a major impact on rehabilitation outcome.

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Disclosures

None of the authors have reported any conflicts of interest and all worked independently of the funding source.

Chapter 7. Summary and General Discussion

"There are three methods of gaining wisdom. The first is reflection, which is the highest. The second is limitation, which is the easiest. The third is experience, which is the bitterest. "

Confucius (551-479 BC)

Post-stroke fatigue (PSF) is a common, chronic and debilitating complaint after stroke, experienced by 27% to 77% of the stroke survivors, even in patients showing good recovery. Prevalence rates of PSF show no marked decline even after years, and fatigue has been found to (negatively) influence quality of life, rehabilitation outcomes, functional independency, suicide rate and mortality. Although fatigue has captured growing attention in the past few years, often researchers and clinicians still neglect the subject. In addition, a uniform definition of PSF is still not embraced by everyone in the field and, until recently, there were little directives to guide therapy. This renders PSF a difficult and unattractive symptom to treat. Knowledge of the prevalence, etiology and associations with other impairments could therefore aid in adequate assessment and subsequent treatment of PSF. For this reason, the first part of this dissertation is devoted to these issues. To meet another general aim of this thesis, the second part of this dissertation deals with the management of PSF. Herein a comprehensive treatment of PSF and its subsequent evaluation are presented.

The current chapter starts with a *Summary* of the main findings of both parts of this thesis following the research questions posed at the end of chapter 1. Thereafter, in the *General Discussion,* the findings of the presented studies will be discussed and their most important limitations will be dealt with. In addition, first guidelines for clinicians and researchers faced with PSF will be given.

7.1. Summary

Section 1. The trouble with fatigue

In **chapter 1** an overview of the current literature on PSF is presented. Even though it is evident that PSF is a frequently encountered problem after stroke, no standard or uniform definition of PSF exists. On the contrary, until now, 17 different definitions have been reported. Even more fatigue assessment tools are in use, partly due to the absence of valid biological markers. Fatigue can have mental, emotional and/or physical dimensions. In general, it is assessed with self-report measures that seem to assess different aspects of fatigue. This complicates the comparability of research results. Studies focusing on the experience of PSF show that it is a qualitatively different feeling when compared with pre-stroke fatigue; in particular that PSF is more persistent and severe.

To shed light on the etiology of PSF, many studies have investigated the associations of PSF with various pre-clinical, clinical, demographical and psychosocial variables. Of several pre-stroke variables, only pre-stroke fatigue has been found to be significantly related to PSF. No global stroke characteristics have consistently been related to PSF. Neither severity of stroke, nor stroke type or global stroke location correlates with PSF. However, there is some evidence for a higher prevalence of PSF after lesions of the basal ganglia. These brain areas are part of a central fatigue network proposed by Chaudhuri & Behan (2000

&2004).[68, 69] Moreover, recent research on a possible hormonal origin points towards a role of cytokines and hypothalamic-pituitary-adrenal axis dysregulation in PSF. Amongst the investigated clinical variables, weak associations of PSF have been found with pain, whereas contradictory findings have been reported with regard to sleep disturbances and physical disability. The results of a majority of the investigations seem to depend, at least partly, on the applied assessment tools.

With regard to psychosocial variables, depressive symptoms have consistently been associated with PSF, although evidence for a dissociation between the two also exists. Studies on the relationship between PSF and other psychosocial variables are scarce. In studies using extensive neuropsychological test batteries, strong associations between cognitive dysfunctioning and fatigue have been found. These findings support the so-called "cognitive coping hypothesis" proposed by van Zomeren et al (1984).[103] This hypothesis assumes that fatigue is primarily due to the additional cognitive effort invested by brain-injured patients to compensate for their information processing deficits in order to meet the demands of daily life.

Chapter 1 concludes that PSF comprises cognitive, emotional and physical components. However, many aspects regarding its etiology, assessment and effective treatment are still unclear. Therefore, the following research questions were addressed in this dissertation.

1: *Is there a problem of underdiagnosis of PSF in the Netherlands? Do patients receive sufficient information about PSF in Dutch healthcare and is PSF related to personal or clinical characteristics?*

The notion that PSF is still a crudely assessed and undertreated symptom in the Netherlands can be deduced from the findings reported in **chapter 2**. Herein 538 stroke survivors filled in a web-based questionnaire. Questions were asked about the amount of information received about PSF, self-management and other treatment options, the need for treatment and the nature of the fatigue. The mean age of the respondents was 52 ± 11 years. On average, they reported to be in the chronic phase after stroke (mean post onset time: 2.7 ± 3.4 yrs). Respondents were generally well educated and 57% were still employed. Almost half (48%) of the participants reported to suffer from severe fatigue and 68% indicated that they experienced a great impact of fatigue on daily life. No associations of PSF with personal or clinical characteristics of the respondents were found.

Although in this study some bias towards participants who had received insufficient information was expected, the results were nevertheless surprising. It was found that only 17% of the respondents had received sufficient information about PSF and only 7% had been informed about treatment options, whereas 56%

expressed a substantial need for treatment. As expected, this need for treatment was related to fatigue severity (r=.35) and to the impact of fatigue on daily life (r=.30). These findings are all the more striking, since the data suggested relatively well-preserved cognitive skills in the respondents. Most patients (81%) experienced no problems to complete the questionnaire within 10 minutes. Furthermore, employment status was not related to fatigue severity or information status, indicating that the respondents were capable to search for and understand information about PSF, but that this information was not available.

2. *Do patients with PSF have specific psychological or social characteristics? If so, could knowledge of these characteristics aid in the development of effective treatments?*

In **chapter 3** a cross-sectional study is reported on the psychosocial make-up of 88 chronic stroke patients suffering from severe PSF. In this study fatigue was assessed with the Checklist Individual Strength (CIS-20R) subscale fatigue (CIS-f) and the fatigue severity scale (FSS). Anxiety and depression were assessed with the Hamilton Anxiety and Depression Scale (HADS), psychological distress with the Symptom Checklist-90 (SCL-90), coping styles with the Coping Inventory for Stressful Situations (CISS), social support with the Social Support List (SSL) and self-efficacy with the Self Efficacy Scale (SES). The latter psychosocial variables were correlated with PSF and the average scores were subsequently compared to those of healthy controls and patient groups suffering from other chronic diseases.

Different associations were found for the FSS and the CIS-f. The FSS was associated with the subscale Obsessive Compulsive of the SCL-90 (r=.36), indicating a relationship with cognitive complaints. In contrast, the CIS-f was found to be related to the subscales Somatic Complaints (r=.53) and Depression (r=.35) of the SCL-90. This latter association disappeared when entered in a multiple regression analysis, wherein only Somatic Complaints were related to the CIS-f scores. No other associations were found. Furthermore, PSF was not related to personality problems. When compared to healthy controls, it appeared that patients with PSF showed higher degrees of psychological distress (SCL-90 and HADS) and scored relatively low on the use of problem-focused coping styles. However, hardly any differences were found when the scores of patients with PSF were compared to the normative data of other chronic patients groups.

Overall, these results challenge previous findings that emotion-oriented coping is the main determinant of PSF and that personality plays a significant role in PSF. Moreover, the results show that psychological factors cannot exhaustively explain the presence of fatigue after stroke.

3. *How does the one-dimensional FSS psychometrically compare to the multi-dimensional CIS20-R? To what extent do both commonly used fatigue scales assess the same construct?*

In **chapter 4** the psychometric properties and underlying constructs of the CIS20-R fatigue severity subscale (CIS-f) and the FSS were assessed. The FSS is the most frequently used questionnaire in PSF research, while the CIS-20R (and especially its CIS-f subscale) is the list of choice in fatigue studies conducted in the Benelux countries. Both lists were administered to 196 patients with stroke and 112 age-matched controls.

The results showed that both scales had a high internal consistency (Cronbach's α: FSS = .893; CIS-f = .938), but that the convergent validity of both scales was moderate (r=.52). Furthermore, the first two items of the FSS decreased its internal consistency significantly and were unable to discriminate between stroke patients and healthy controls. Principal Axis Factoring analyses on all items revealed that 6 of the 8 items of the CIS-f loaded high on a factor that was named "subjective feelings of weakness and tiredness", whereas the two remaining items loaded on "physical condition". Eight of the 9 items of the FSS loaded on another factor referred to as "impact of fatigue on daily life".

These results indicated that the CIS-f and the FSS assess different constructs. In accordance with previous psychometric studies on the FSS, it was concluded that the first two items of the original FSS should be skipped in stroke patients, retaining a FSS7, to assess fatigue impact. The FSS does not assess fatigue severity. With regard to the CIS-f, it was concluded that it not only addresses a physical fatigue dimension, but also the severity of a more general subjective experience of tiredness.

Section 2. The management of fatigue

4. *What components should be part of a comprehensive treatment protocol for PSF, taking into account the emotional, cognitive and physical aspects of fatigue?*

Based on the positive findings of a pilot study evaluating the PSF-treatment module "Dealing with Fatigue" at the Sint Maartenskliniek in Nijmegen,[10] this treatment protocol was taken as a starting point and was adapted based on experiences (feedback) from patients and therapists. Notable changes were a more structural incorporation of cognitive behavioral therapy (CBT), a restriction of the treatment group size, and the addition of a graded activity protocol based on the recommendations for Stroke Survivors of the American Heart Association. Based on the experiences from the pilot study, the new treatment was given to small groups of four patients. The complete treatment protocol, called COGRAT (COGnitive and GRaded Activity Training), is presented in **chapter 5**.

In this protocol, the cognitive coping hypothesis was used as a starting point. The primary aim of the COGRAT treatment was to teach patients how to use energy more parsimoniously and how to deal with their limited cognitive resources. In order to accomplish this, patients were requested to register their activities hour by hour for two weeks. Every registration was accompanied by an estimation of its level of fatigue in order to obtain insight into the subject's activity and fatigability patterns. Based on this information, three compensation strategies were proposed: alternation, planning and relaxation. First, patients were taught how to pace and alternate their activities with periods of rest or relaxation in order to avoid fatigue. Second, they were taught to plan their activities more effectively, taking into account the additional time needed to accomplish tasks, the time needed to switch from task to task and, above all, the time needed to recover from fatigue. Finally, patients were coached on how to relax, since many activities that used to be relaxing prior to their stroke had become fatiguing afterwards.

Because adopting these new behaviors was challenging for many patients, basic CBT components were structurally incorporated into the treatment. The goal of CBT was to replace 'disabling thoughts' (that might hinder the implementation of compensation strategies) by 'enabling thoughts'. Furthermore, CBT was used to better cope with feelings of fatigue and the related psychological distress. By performing CBT-homework assignments, patients learned to generate rational and adaptive thoughts with the objective of better coping with the negative emotions related to their fatigue. Besides these fatigue-specific treatment strategies, more general rehabilitation principles of psycho-education, goal-setting and homework assignments constituted a substantial part of the cognitive treatment.

The cognitive treatment was given once a week for two hours, whereas the graded activity training was given in parallel twice a week for two hours. The treatment lasted 12 weeks. During the graded activity training, patients followed an exercise scheme based on specific percentages of their maximum heart rate and maximal muscle strength. They were trained to improve their performance by walking on a treadmill with increasing inclination and by structured weight-lifting exercises.

5. Is a comprehensive COGRAT treatment approach effective to reduce PSF in the chronic phase after stroke?

Chapter 6 reports the evaluation of the COGRAT treatment compared to cognitive training alone (CO), by means of a randomized controlled clinical trial (RCT). This RCT was carried out in eight rehabilitation centers in the Netherlands. Patients were selected based on the following inclusion criteria: severe fatigue (CIS-f >40), able to walk 10 meters independently, no severe cognitive deficits, no

co-morbid depression, and no severe cardiac or pulmonary disease. According to these criteria, 88 out of 231 patients were found to be eligible and 83 finally participated in the study. Primary outcome measures of fatigue (CIS-f and Self Observation List-fatigue / SOL-f) and secondary outcome measures of depression, anxiety, functional health, pain, sleep disturbances and physical endurance were administered at four time points: (1) at the start of the study, (2) after a three-months qualification period without any treatment, (3) after the completion of treatment, and (4) at 6-month follow-up. Randomization to either the CO or COGRAT treatment took place after the second assessment. The three-month qualification period without treatment was used to wash out any possible previous intervention effects and to assess whether patients could be considered 'stable' in terms of fatigue.

The results of this study showed that CO treatment alone was already effective in reducing experienced fatigue, but that more patients showed clinically significant levels of fatigue reduction after COGRAT treatment (24% vs. 58%, respectively). Since all patients were in the chronic phase after stroke (mean: 3.9 years post-onset, ± 3.9) and suffered from severe fatigue at the start of the study, without any decline during the qualification period, it was concluded that persistent fatigue can be substantially alleviated with cognitive treatment. This cognitive treatment should preferably be given in combination with graded activity training. Benefits of both treatments on secondary outcome measures were found for depressive symptoms, functional health and sleep disturbances. No significant improvement was found for anxiety or pain. Physical endurance improved only after the COGRAT treatment.

7.2. General Discussion

In the summary several of the research questions have been briefly answered. In this paragraph, these answers will be discussed in depth. First the issues regarding the neglected status of fatigue and the possible characteristics of patients that could aid in assessment and treatment will be addressed. Herein, the cognitive coping hypothesis and the importance of a differential diagnosis of fatigue versus depression are extensively discussed, since they entail significant clinical implications. Next, in order to broaden the discussion regarding the assessment and treatment of PSF, some unpublished outcomes of the COGRAT study will be presented. This is followed by a discussion on the limitations of the studies reported in this thesis. Last, recommendations for clinical practice and research will be given.

7.2.1 The trouble with PSF in clinical healthcare: professional neglect and lack of clear patient characteristics

The results of the internet based study strongly suggest that patients with PSF, irrespective of personal or clinical characteristics, are underdiagnosed and ill-informed in Dutch healthcare. These findings are congruent with the results of several qualitative studies, where patients reported having received only scant information on PSF and how to deal with it.[29-31] It must be noted that these studies did not take patient characteristics into account. Remarkably, in a recent review on therapeutic patient education programs for stroke survivors, fatigue was not mentioned at all, neither as a symptom of interest nor as a theme within these programs.[211] This underscores the notion of a severe lack of information and education affecting large groups of stroke patients. What is more, these findings do not seem to be limited to patients with stroke. A study of patients with Parkinson's disease showed that in 50% of the consultations with neurologists, non-motor signs such as fatigue were not identified,[212] again indicating that fatigue is often overlooked and undertreated in healthcare.

This professional neglect of fatigue as a cardinal symptom can in part be explained by the absence of a uniformly embraced definition of either fatigue in general or PSF specifically. This void has hindered research as phrased by Harrington (2012, p. 94):[48] "*Optimal would be a definition that allowed objective measures of the state, although we might be content at this point if we can simply agree on a definition allowing consistent self-report measures in human populations; unfortunately there is at this moment no agreement*". This has even led some authors to suggest that it is impossible to treat a condition that cannot be defined.[213] Furthermore, research into valid biological markers that could aid in objective and agile assessment of PSF has so far not yielded clear or unambiguous results.[33, 39, 48]

Another plausible reason for the neglected status of PSF in healthcare is the absence of a simple explanatory (etiological) model[20] that could subsequently aid in the development of treatments. The studies in this dissertation (chapters 2, 3 and 6) may not seem to be directly useful in contributing to this matter. Specifically, no associations between stroke-related, clinical or personal variables and PSF were found, except for cognitive and somatic complaints. With regard to clinical and stroke-related variables, the findings in this thesis are in line with many previous studies. [14, 16, 18, 19, 46, 47, 49, 56, 58, 62, 80] Somatic complaints have consistently been found to be related to fatigue, not only in stroke patients but also in patients with other chronic diseases.[51] This might reflect both a physical dimension of fatigue as well as an emotional component, i.e. dealing with somatic consequences of the disease. Concerning associations with lesion site, it cannot be excluded that the lack of associations found in the literature and the studies in this thesis is due to limited sample size and the inability to obtain detailed information about lesion location. Since the corpus striatum is hypothesised to be part of a central fatigue network it would be recommendable to specifically identify lesions of this brain area in future studies.[68, 69]

Cognitive coping hypothesis

The cognitive coping hypothesis, instead of coupling fatigue to specific locations in the brain, tries to unravel the brain mechanisms leading to PSF. This hypothesis states that fatigue may arise as a result of the extra mental effort required from patients in tasks or demands of everyday life to compensate for their information processing deficits. The coping hypothesis was used as a cornerstone for the COGRAT-treatment. Fatigue is present with approximately the same frequency as information processing deficits across patients with different neurological disorders and it also seems to share similar mechanisms[102]. The association that was found between fatigue impact and cognitive complaints might also be seen in this light and is congruent with findings in other neurological patients. Studies of patients with traumatic brain injury (TBI) and Multiple Sclerosis (MS) have shown a solid relationship between attentional deficits, reaction time variability, mental effort and subjective fatigue.[36-38, 40, 174, 175] Furthermore, several imaging studies using working memory tasks have reported that patients with TBI show increased activation in comparison to healthy controls in several regions of the right hemisphere,[153, 154] more dispersed activations,[153, 214] and altered functional networks.[176, 214, 215] In MS patients also, altered activation patterns have been found, reflecting compensatory reorganization.[177, 216] Furthermore, studies in patients with Chronic Fatigue Syndrome (CFS) have provided evidence for a link between these altered activation patterns, the utilization of more extensive brain networks, and the experience of subjective fatigue.[217, 218] Thus, cerebral reorganization and extra cerebral activation

undeniably reflect increased mental effort. This effort, exerted to compensate for less efficient, less accurate or slower information processing, might significantly contribute to PSF.[11, 176, 216]

In line with this reasoning, Claros-Salinas et al (2010)[102] studied the diurnal variations of fatigue (with a VAS-f scale), tonic attention (with reaction times (RTs)), divided attention and selective attention (with a GoNoGo task) in stroke patients, patients with MS, and in healthy controls. Measurements were performed three times a day on two consecutive days.[102] The authors reported a higher diurnal increase in fatigue for stroke patients than for healthy controls. Moreover, performance on the tasks was not only worse in patients compared to controls (RTs and mistakes), but it also showed a diurnal decline across all tasks. This study has several implications. First, since the stroke group (and to a lesser extent the healthy controls) reported an increase in fatigue during the day, this effect seems to be non-specific. Second, patients performed more or less stably across various difficulty levels. The authors suggest that patients must have engaged compensatory strategies when performing the more difficult attentional tasks. This implies that there could be a clear gap between performance and competence in these patients. On the one hand they seem to be competent enough to accomplish the same attentional tasks as healthy controls, on the other hand their performance seems to imply a much greater energetic cost. Hence, diurnal increase in fatigue is more conspicuous. This is particularly evident in tasks where a speed-accuracy trade-off is possible or in short tasks where additional attentional resources can be recruited. Third, no differences were found between patients with MS and stroke with regard to task performance and fatigue. Hence, fatigue might be produced by similar mechanisms in both groups.[102]

What is more, the cognitive coping hypothesis can be linked to the central fatigue hypothesis. After stroke, the basal ganglia can be directly affected. This in turn can lead to difficulties in executing tasks that require self-motivation, and a much higher perceived effort for task execution. Chaudhuri and Behan primarily present their hypothesis in association with dysfunctions of the basal ganglia.[68, 69] However, the overwhelming prevalence rates of PSF in patients with different lesions suggests that disruptions of other brain areas of the striato-thalamical-frontal cortical system (or possibly the subcortical attentional network)[22] might also lead to fatigue complaints. In addition, one cannot exclude that prolonged stress reactions such as in the case of depression or anxiety might negatively influence these brain networks through the dysregulation of the HPA-axis. This might in part explain the high concomitant occurrence of PSF, depressive symptoms and anxiety.

Personal factors and the necessity of a differential diagnosis with depression

Approximately half of the stroke population does not develop complaints of fatigue. Moreover, stroke-related and clinical characteristics do not seem to entirely explain PSF, while the role of subtle attentional deficits and compensatory mechanisms needs to be further clarified. Thus, psychological and social variables are generally believed to influence PSF.[18, 20, 23, 42, 46, 47, 80, 86, 95] If clearly identified, these could aid in the development of a suitable treatment. However, in our studies no associations of fatigue with psychosocial factors were found and it was concluded that patients suffering from PSF do not differ from other chronic patient populations in this respect. This result can be explained in different ways. Patients with other chronic medical and psychiatric diseases also frequently suffer from fatigue[219], suggesting that physical disease in itself might contribute to fatigue. Additionally, anxiety,[100] depression[94] and medical complications[7] are common after stroke, possibly aggravating PSF. Conversely, inadequate coping styles and insufficient social support might also bring about psychological distress and fatigue. These precipitating factors apply to every chronic illness, but especially to patients with stroke who are confronted with the permanent consequences of their condition in everyday life when they return home from hospital or rehabilitation centre. This might be the reason why a minority of patients (10%) in the internet study reported the onset of their fatigue more than 6 months after stroke, a stage in which these consequences become evident. Furthermore, psychological factors may be present to different degrees in individual patients, thus, it is not surprising that cross-sectional studies have found equivocal results. To be more specific, either too little or too much of one these psychological factors may increase the susceptibility to fatigue. For example, overachievement[12] as well as boredom[41] have been suggested as precipitating factors for fatigue. Thus, in clinical practice, it remains valuable to look at such personal characteristics.

One important point remains to be made. As a proper differential diagnosis of PSF versus post-stroke depression is not always made,[9, 12] this might be another cause for the neglected status of PSF in healthcare. Several reasons can be invoked for this gap. First, there are several assessment issues. In the majority of studies on PSF only subjective questionnaires were used to determine the severity of depression. As a result, clinical depression was almost never assessed according to DSM IV[26] criteria. Thus, there is a positive association of PSF with depressive mood, but not necessarily with a clinically assessed depression. Furthermore, the questionnaires used to assess these depressive symptoms often include fatigue items (e.g. Beck Depression Inventory, Geriatric Depression Scale, Hospital Anxiety and Depression Scale: HADS)[57]. On the other hand, some fatigue questionnaires contain items on motivation that can be influenced by mood (e.g. Short Form-vitality subscale, FSS).[57, 220] Therefore, the associations found between

depressive complaints and PSF might be explained by the overlap inherent in the assessment tools used to measure both concepts. Last, the sequelae of stroke such as cognitive impairment, indifference, unawareness of illness (anosognosia), difficulty with emotional expression (e.g. aprosody), and emotional lability can be mistakenly interpreted as depressive symptoms,[221] especially when using generic questionnaires,[222] leading to artifact associations with fatigue.[9]

Another necessity for the differential diagnosis of depression and fatigue stems from the clear distinction between the two syndromes. Dissociations between patients suffering from PSF and depressed mood have consistently been found.[14, 15, 46, 49, 57, 58, 98, 99] Moreover, in studies excluding clinically depressed patients, prevalence rates of PSF were still high (16%-59%).[45, 66, 118, 223-225] The presented studies corroborate this notion: 88 patients were identified that suffered from severe fatigue but did not meet the DSM-IV criteria for depression. Furthermore, it is known that selective serotonin reuptake inhibitors (SSRIs) have small benefits on mood, but barely affect PSF, as reported in a double blind placebo controlled RCT.[104]

Last but not least, the relationship between PSF and mood is probably bidirectional[9] and complex. Fatigue may precipitate feelings of depression because of its interference with mood, work and leisure activities on the one hand, whereas depressed individuals may experience fatigue as a symptom of their depression,[9, 27] or when they have to put in extra effort to accomplish daily activities. In concordance with our findings, some studies examining the role of physical disease or somatic complaints have shown that the association between fatigue and depressive symptoms diminishes considerably or even disappears when somatic variables are taken into account.[15, 16]

Thus, although fatigue and depression frequently co-occur after stroke, there is no clear evidence for a causal relationship between them. Therefore, anecdotal reports of patients being prescribed SSRIs to treat fatigue lack empirical evidence. Moreover, a recent systematic review of 14 trials involving 1515 patients with stroke did not reveal clear-cut effects of pharmacological interventions on the prevention of depression.[226] Since several adverse side effects of antidepressants have been reported[221] and SSRIs do not improve PSF,[104] caution against their use to treat PSF is warranted.

In sum, it seems that PSF is still neglected by many professionals in stroke rehabilitation. No clinical or demographical characteristics of patients suffering from PSF have been found to affect the support or help that they receive. Furthermore, no clear-cut psychological or social profile of PSF patients has as yet been identified. However, on an individual basis, depressive symptoms and anxiety can aggravate primary fatigue or may be direct causes of secondary fatigue, and should be treated accordingly. A careful differential diagnosis of PSF

versus depression is, however, essential to select the most appropriate treatment. The cognitive coping and the central fatigue hypotheses both offer plausible explanations for underlying mechanisms of PSF, corresponding with the subjective experience of patients. As such, they can be used to design theory-driven therapies.

7.2.2. The experience and assessment of PSF: FSS, CIS20-R and beyond

As previously mentioned, in the absence of valid biological markers, the assessment of PSF is restricted to the self-report of experienced fatigue. Mental effort is difficult to measure without sophisticated tools, such as fMRI. This is probably the reason why objective assessment tools for fatigue in clinical practice have not yet been developed. On the other hand, the subjective experience of fatigue is the main reason why patients seek professional help. Therefore, it is sensible to assess, understand and treat subjective complaints of fatigue in clinical practice. With regard to the assessment of PSF, several considerations are relevant.

First, the experience of fatigue can differ greatly between patients. As found in the internet study, 57% of the participants experienced both physical and mental fatigue, whereas about 20% experienced either physical or mental fatigue. These findings are congruent with those of Barbour and Mead (2012)[41], who reported that some patients described their fatigue solely as “a tiredness in the muscles”, “a general feeling of tiredness”, or “mental tiredness”, whereas others reported that their fatigue was best described by more than one of these characterizations. Furthermore, in two studies with stroke patients completing modified versions of fatigue scales developed for MS, it was suggested that both physical and cognitive fatigue were components of PSF.[224, 227] Hence, a definition of PSF and its derived assessment tools need to incorporate aspects of both physical and mental fatigue. Neither previous studies nor the studies reported in this thesis investigated the emotional aspects of fatigue as a separate entity. Therefore, this remains a subject for further research.

Different fatigue scales assess different components of fatigue.[28, 51] In the presented studies, emphasis was placed on the well-known and commonly used FSS and CIS20-R. These scales assess different constructs, with moderate mutual correlations. This was congruent with the study on psychosocial characteristics, where both instruments correlated with qualitatively distinct variables. Furthermore, in the internet study, the correlations between the FSS7 and visual numerical scales assessing fatigue severity was only moderate (r=.39). This underscores the conclusion that the FSS assesses “the impact of fatigue” on daily functioning, as the developers stated in the original paper.[54] However, in the current literature the FSS is often used as a tool for measuring fatigue severity. To

complicate matters even further, different cut-off scores for PSF have been applied: 4,[35, 46, 57, 58, 65, 66, 80, 83, 117, 118, 123] 5[16, 51, 82] or even 5.2.[91]

A further issue related to the FSS concerns its limited sensitivity to change. Only in a few studies clinical change was detected with the FSS in non-stroke patients, including small samples of patients with MS and Lyme disease described in the original paper.[54, 228] In contrast, in later clinical trials using the FSS in addition to other fatigue measures, significant changes were found with the other assessment tools, but not with the FSS.[224, 228] This is in agreement with the findings of the intervention study reported in chapter 6. Although the FSS-data of the RCT were not reported in this chapter, every patient was assessed at all time-points with this questionnaire. No significant changes on the FSS (or on the FSS7) were found between the different time points (prior to treatment T0: M=5.2 ± .99; after qualification period T1: M=5.3 ± .95; after intervention T2: M=5.0 ± 1.0; at follow-up T3: M=5.0 ± 1.2; p>.05). However, considering the low responsiveness of the FSS,[224, 228, 229] it is questionable whether the conclusion that fatigue impact did not improve after the intervention would be justified, particularly given the finding that many other measures of fatigue and activity improved.

In contrast, the CIS-20R[52, 53] and its CIS-f subscale have a well-established quality of responsiveness in different diseases, such as cancer, chronic fatigue syndrome and arthritis.[52, 229] Moreover, the CIS-20R consists of several subscales that assess different domains, such as the CIS-fatigue and the CIS-concentration subscales. A closer look at item-level, however, reveals a less solid subscale structure, which also bears an inherent risk. For instance, the fatigue severity subscale contains specific 'physical' items. As patients suffering from severe and predominantly mental fatigue may score low on these items, these scores might not reach the detection threshold and, subsequently, the severity of their fatigue may be underestimated. The CIS-concentration seems to consist of items referring to both attentional problems as well as mental fatigability. This needs to be further investigated.

Both the FSS and the CIS20-R include questions about the experience of fatigue during the last week(s) and, thus, do not capture diurnal variations. For this diurnal variation aspect, the Self-Observation-fatigue (SOL-f) scale was used in the treatment study. Patients were asked to complete this scale at four fixed times per day during seven consecutive days. This scale is time consuming and cognitively demanding, which are major drawbacks. However, to gain qualitative insight into individual patterns of fatigability, it is still useful to apply the SOL-f to skilful and compliant patients. So far, however, it has not been validated for stroke patients, nor does it have published and reliable norm scores.

None of the previously mentioned questionnaires has specifically been developed for stroke patients, and the above discussed problems might be related

to this issue. Three recently developed stroke specific tools seem to be promising in this regard. These are the Dutch Multidimensional Fatigue Scale (DMFS),[230] the Fatigue Scale for Motor and Cognitive Functions (FSMC),[231] and the Neurological Fatigue Index for Stroke (NFI-Stroke).[227] The latter two were originally developed for MS patients and were adapted for stroke patients by analysing the validity of the individual items and, subsequently, eliminating the invalid ones. Both the NFI-Stroke as well as the FSMC have a cognitive as well as a physical subscale. A study on the FSMC in stroke patients showed that the cognitive tasks (such as verbal short-term memory, working memory, mental speed and flexibility) were predominantly related to cognitive fatigue.[224] The items of the DMFS have been generated from in-depth interviews with a group of stroke patients. The scale is, thus, specifically tailored to the stroke population.[230] The psychometric properties and usability of the DMFS are currently being investigated.[230] In addition, as outcome tools, the sensitivity to change of all the three above-mentioned scales needs to be investigated.

7.2.3. The treatment of PSF, is it possible to reduce fatigue after stroke?

In chapter 6 the evaluation of the COGRAT treatment has been reported. Since fatigue diminished significantly as measured by two different assessment tools, it was concluded that it is possible to reduce PSF by a comprehensive treatment. In post-hoc analyses (not described in chapter 6) significant, moderate to large time effects (but no interaction effects) were found for the other subscales of the CIS-20R, which further substantiates the efficacy of COGRAT with regard to fatigue (ANOVA on intention-to- treat basis: CIS-concentration $F_{(2,78)}$=12.2, p<.001, η^2=.24; CIS-motivation $F_{(2,78)}$ =20.2,p<.001, η^2=.34; CIS-activity $F_{(2,76)}$=10.8, p<.001, η^2=.22). In contrast, no positive effects were found on cognitive tests of attention (Sustained Attention Test and Attention Network Task) or memory (Rivermead Behavioural Memory Task and California Verbal Learning Task). This latter finding is not surprising, since COGRAT did not focus on the improvement of cognitive functions and the participants were all in the chronic phase of stroke. In this stage (spontaneous) improvements in cognitive functions may no longer be expected. Yet, in line with the cognitive coping hypothesis, it can be expected that patients have become less fatigable, because they learned how to handle the challenges of daily life with less mental effort.

Additional analyses were performed to tease out the effects of medication on PSF. Medication included pharmacological agents for cardiac diseases (51.8%), antihypertensive medication (66.3%), non-steroid anti-inflammatory drugs (NSAIDs) (27.7%), antiepileptic medication (4.8%), antidepressants (14.5%), sleep medication (9.6%), and cholesterol reducing agents (60.2%). These pharmaceuticals were frequently prescribed with a mean number of 2.7 (± 1.5) drugs per patient. This quantity did not differ between patients with a stroke post-onset time of more than 5 years and those with an onset time of

less than 5 years (all p>.05). This suggests a relatively stable distribution of medical co-morbidities over time. Besides, neither the amount of medication used, nor the use of specific drugs predicted treatment outcome.

Furthermore, none of the other variables assessed predicted treatment outcome. Neither demographic variables nor etiology of stroke, stroke post-onset time, cognitive performance or psychological variables predicted levels of fatigue reduction. This finding has considerable clinical implications. It means that COGRAT can be offered with success to a wide range of chronic stroke patients suffering from severe PSF. Nevertheless, several questions remain unanswered. Of all the patients who received the COGRAT intervention, 58% improved substantially, 29% improved slightly (but this improvement did not reach clinically significant levels), and 13% showed no decline on the CIS-f scale. Thus, not all patients benefited equally from the treatment, which is not a new finding. Successful treatments in other populations with fatigue complaints have also yielded mixed results. [232, 233] Further research is needed to understand which variables determine therapeutic success and to find ways to help treatment-resilient patients.

Another related question concerns the content of the cognitive treatment protocol. Several treatment elements such as psycho-education on PSF, sleep hygiene, goal-setting, CBT, and the three behavioral compensation strategies were incorporated. Some therapy ingredients might have been more effective than others, whereas on the other hand the combination of therapeutic elements might have resulted in the observed benefits. It is also possible that for patients suffering from predominantly mental fatigue, the compensation strategies were most helpful, whereas physical fatigue was better treated with GRaded Activity Training (GRAT) and emotional fatigue by CBT. Due to the study design, it was impossible to disentangle the influence of each treatment component. Future research should, therefore, be focused on the specific treatment elements or various combinations of treatment elements as used in the CO(GRAT) protocol.

More patients improved to clinically significant levels after the COGRAT intervention compared to the CO intervention alone, which may imply that the addition of graded activity training is responsible for this differential effect. Although physical endurance has not been found to be associated with PSF,[34] patients indicated that exercise alleviated their fatigue.[41] In addition, graded exercise has been found to effectively alleviate fatigue in other medical conditions associated with fatigue.[71, 126, 181, 234] It is well known that cardiovascular condition in stroke patients is generally poor[117, 235] and that physical deconditioning, caused by a lack of physical exercise, may exacerbate fatigue.[34] In this perspective, graded activity training can be a safe treatment to counteract this deconditioning, thereby reducing fatigue. Because physical exercise has been found to have a

small but helpful effect in the treatment of depression,[236] it has been suggested that it might also have positive effects on the neuroendocrine system and eventually on the regulation of the HPA-axis.[237] Exercise might, therefore, prove to be effective in patients who have been submitted to prolonged psychological distress. Finally, the inclusion of graded activity into general rehabilitation practice seems to have a preventive effect on the recurrence of stroke and on the occurrence of secondary diseases.[184, 185] A wider implementation of programs promoting physical activity after stroke is, thus, recommended.

7.2.4 Study limitations

Despite promising results, the studies reported in this thesis have several limitations. Except for the intervention study (chapter 6), all studies used a cross-sectional design. Therefore, no directions could be established for the observed associations, which would have required the use of a longitudinal study design. Second, in the internet study (chapter 2), it is likely that a bias occurred in favor of individuals suffering from fatigue, actively searching for information. This might have led to overestimation of the observed lack of information and attention with regard to their fatigue. As for the studies on the psychosocial profile of PSF patients (chapter 3) and the evaluation of the (CO)GRAT treatment (chapter 6), patients were specifically selected for participation in a rehabilitation intervention aimed at reducing fatigue, while those with a clinical depression were excluded. Therefore, the results of these studies can only be generalized to patients with relatively good outcome and a clear motivation for treatment. On the other hand, this careful patient selection allowed the investigation of the relationship between psychosocial variables and PSF without confounding by depression or severe cognitive impairment. In all reported studies, stroke patients were included regardless of etiology and stroke post- onset time, which suggests that the results are applicable to multiple types of stroke patients in various phases. This can be considered a major strength, since a more homogeneous inclusion would have substantially reduced the generalizability of the results as well as the feasibility of the study, often-serious problems in clinical trials. Our strategy of patient selection is (post-hoc) corroborated by the results that indicate that stroke location and post-stroke interval were not associated with the outcome of the (CO)GRAT intervention.

Another limitation is related to the use of self-report measures of fatigue, psychological variables, somatic complaints and sleep disturbances. These self-report measures may be biased in several respects; retrospective bias, response bias, social desirability and neurological influences may have limited the validity of the findings. As for depression, although clinical interviews were used to exclude clinically depressed patients, the severity of depressive symptoms was assessed merely by two self-report measures (and not by psychiatric examination). With regard to the assessment of fatigue, unfortunately, there was no golden standard

to validate our results with. The CIS-f scale was used as one of the primary outcome measures in the RCT (chapter 6). This scale emphasizes several physical aspects of fatigue. Therefore, it cannot be excluded that the additional benefit found for GRAT (in terms of number of patients with a clinically relevant improvement on this scale) might have been due to a reduction of these 'physical' aspects of fatigue. In future studies a more differentiated fatigue scale including subscales of mental, physical and emotional fatigue should be used to shed more light on the specificity of treatment effects.

From a design point-of-view, it would have been preferable to also include a sham treatment as a control condition in the intervention study (chapter 6) as well as a treatment condition including GRAT alone. In the absence of a sham condition ('placebo') it is not possible to control for the influence of aspecific (e.g. Hawthorne) effects. The addition of a GRAT arm would have given information about whether and to what extent GRAT alone would also have been effective. However, using a similar RCT design, this would have implicated that at least an additional 80 patients had to be included in the intervention study, which was not feasible within the constraints of this PhD project. Nevertheless, we conducted the first controlled intervention study for post-stroke fatigue, showing that COGRAT is effective, thereby paving the way for future (replication) studies.

A possible source of allocation bias in the RCT was that patients who were allocated to either the CO or COGRAT intervention had significantly different levels of fatigue at baseline, despite randomization. The larger decrement in fatigue found in the COGRAT group might, therefore, be (partly) due to a 'regression-to-the-mean' effect. Controlling for this discrepancy was not possible since the interaction between group and the covariates was significant for all outcome measurements, indicating nonparallel regression. However, both groups showed stable scores on all primary and secondary outcomes during the three-month qualification period prior to randomization, which makes this explanation highly unlikely.

It may be argued that for some the patients included in the RCT the relation of their fatigue with stroke is doubtful, since their strokes had occurred more than 5 to 10 years before.[213] Yet, it has repeatedly been found that PSF shows relatively stable levels of severity, even years after stroke.[15, 45-47, 58, 64, 83, 90] In addition, with the coping hypothesis in mind, it can be understood that patients who never learned how to cope with limited energy levels may experience severe chronic fatigue for many years, even life-long. A different argument underscoring that all patients suffered from PSF, regardless of the time since stroke onset, was that patients with co-morbid diseases were excluded. In addition, as shown in chapter 3, the selected stroke patients had a psychosocial profile comparable to patient groups with other chronic diseases, which makes it unlikely that co-morbidities were responsible for the causation of chronic fatigue.

7.2.5 Clinical recommendations

A main aim of this dissertation was to provide clinicians and with specific guidelines for dealing with patients with PSF. Therefore, recommendations for a stepped care approach will be given here.

Recognition and assessment

Adequate recognition and assessment of PSF is direly needed in healthcare. A first step in this recognition is the acknowledgement that PSF is a highly prevalent condition requiring medical attention.[7] Second, PSF is not the same as depression or sleepiness and it generally does not respond to antidepressants[104] or wakefulness promoting agents.[107] Third, patients' experiences of PSF may vary considerably; some experience it as 'physical', whereas others suffer mainly from 'mental' fatigue. In addition, 'emotional' components of fatigue are important as well. It is, thus, important to interview patients about all these dimensions of fatigue. Because some individuals develop PSF more than 6 months after stroke while others show improvement towards subclinical levels of fatigue within the first year, it is recommended to reassess fatigue approximately every three months in the first year after stroke. Caregivers can aid in the detection, especially when the patient's cognitive skills are inadequate. For patients who are unable to communicate about their fatigue, caregivers or hospital staff may also look at secondary behavioral aspects of fatigue such as falling asleep, squinting, agitation, anger outburst or excessive crying.

Psycho-education and cognitive treatment

After appropriate recognition and assessment, the next step is to further provide patients with information about PSF. Informing patients that PSF is a distinct consequence of stroke is a first element of psycho-education.[211] Patients hereby receive validation from a (medical) professional, which facilitates the acceptance of the condition.[30, 31] Since slow information processing, attentional and memory problems are common in stroke patients, it is recommended to provide the necessary information not only verbally, but also through leaflets or information booklets. Patients and their caregivers can read these materials at their own pace. An example is the booklet "Fatigue" (Zorgwijzer Vermoeidheid)[238] that has been issued in 2010 by the Dutch Brain Foundation (Hersenstichting Nederland). This information, together with information on where to find more advice and help, should be made available to patients shortly after their stroke, since many of them will experience PSF at a certain point in time. The provision of information on the possible treatment of PSF is an important aspect of managing patient expectations and hope.

It has repeatedly been proposed that, in order to help stroke patients to

really understand all relevant aspects of PSF, it is important to design tailored educational programs.[42, 46] Education and treatment programs can be entirely focused on PSF. In designing educational programs for patients with PSF, it is recommended to use professionally coached small group interventions whenever possible. Groups foster mutual support and social learning. They reduce isolation and stimulate recognition of problems by sharing experiences. They also promote reduction of fatigue by reinforcing positive change.[239] Groups should preferably consist of four to five patients. The pilot study of COGRAT conducted by Knoop et al[10] indicated that in larger groups overstimulation in combination with attentional problems hamper optimal participation. It is further important to judge whether patients are able to participate in a group at all, and to form groups that are reasonably homogeneous with respect to age, cognitive and learning abilities. Patients with severe executive problems, verbal disinhibition, and lack of awareness or anger outbursts are better off with individual psycho education.

Alternatively, educational programs can also be part of an integrated rehabilitation program in which other sequelae of stroke are treated as well. Teaching patients how to pause effectively and to intersperse activity with rest moments is an example that can be helpful to manage various symptoms, such as physical disabilities, speech problems, memory deficits, and impulsivity. Depending on stroke severity, the individual need for treatment and the timing of treatment, specific (fatigue) programs can be provided either as primary or as an adjunct treatment. When patients are still in the sub-acute phase of rehabilitation, treatment of fatigue may already be provided by occupational therapists as an adjunct therapy by focusing on how to plan and efficiently perform daily activities. Another option for patients in the sub-acute phase is the treatment module “Stop running, Start planning” (“Niet rennen, maar plannen”)[240]. This includes PSF-related information and several compensation strategies adapted from the COGRAT protocol.

In the chronic phase, patients with PSF can either enter a COGRAT treatment or an adjusted treatment when needed, for instance when they exhibit co-morbid cognitive deficits. So far, cognitive behavioral techniques have been recommended in rehabilitation[156, 241] and have been found to be effective in other patient groups suffering from fatigue.[233, 242] Thus, for patients with severe cognitive impairments, psycho-education and compensation strategies can easily be modified by using a more behavioral and directive approach and by including support from the primary care system. Tips and tricks derived from the compensation strategies can be offered and carried out. In the COGRAT protocol, achievable weekly homework assignments are given. These assignments concern both the pursuit of individual goals as well as the application of compensation strategies. Working on these assignments at home helps to incorporate the new

strategies in daily life and, thus, helps to achieve the patients' goals. It thereby increases the effectiveness and generalizability of the treatment. Thus, principles derived from the cognitive coping hypothesis, goal setting and behavioral therapy can also be applied to the more severely affected patients.

Caring for outpatients

As yet, COGRAT has been implemented in several rehabilitation centers in the Netherlands, but it is not available for all stroke patients. The patients who participated in the study and the majority of the patients who now receive COGRAT are outpatients in the chronic phase after stroke who are referred to a rehabilitation centre specifically for PSF or for general cognitive rehabilitation. Many victims of stroke, especially those with minor cognitive or physical sequelae, are discharged home from the hospital and become 'outpatients' from the very beginning. They are not automatically and closely monitored and thus not always referred for further rehabilitation. Even with minor levels of impairment, many of these patients will face great difficulties in returning to their previous levels of activity and participation. The future development of web-based educational and treatment programs, holds a promise in terms of accessibility and cost-effectiveness for these outpatients. As the study on psychosocial characteristics (chapter 3) showed, even patients with severe PSF do not necessarily have a particularly difficult psychological make-up. Hence, extensive psychotherapeutical support for stroke patients is often superfluous, and thus online support may suffice.

Although web-based programs have not yet been developed for stroke patients, attempts have been made in other neurological patient groups. Recently, a study on the effects of online information and self-management for patients with MS, post-polio syndrome and Parkinson's disease has shown a small, but significant decrease in fatigue impact in the participating patients.[243] Unfortunately, general well-being did not improve, nor did self-efficacy. However, further studies that develop and evaluate similar web-based programs for large groups of patients are expected in the near future. As the present programs have been designed for patients with progressive neurological disorders, specific adaptations for patients with acquired brain injury (e.g. stroke) will have to be made.

In conclusion, I would like to convey a message of genuine hope to patients with stroke. Even though PSF is a chronic and debilitating symptom affecting almost all areas of life, it can be treated with success in many of them. Furthermore, interest in PSF has recently been growing and the number of studies on PSF is increasing. With this development, a better understanding of the etiology and the multifaceted nature of PSF can be expected. Such knowledge will lead to more effective treatments and to more patients that will receive the actual help they need.

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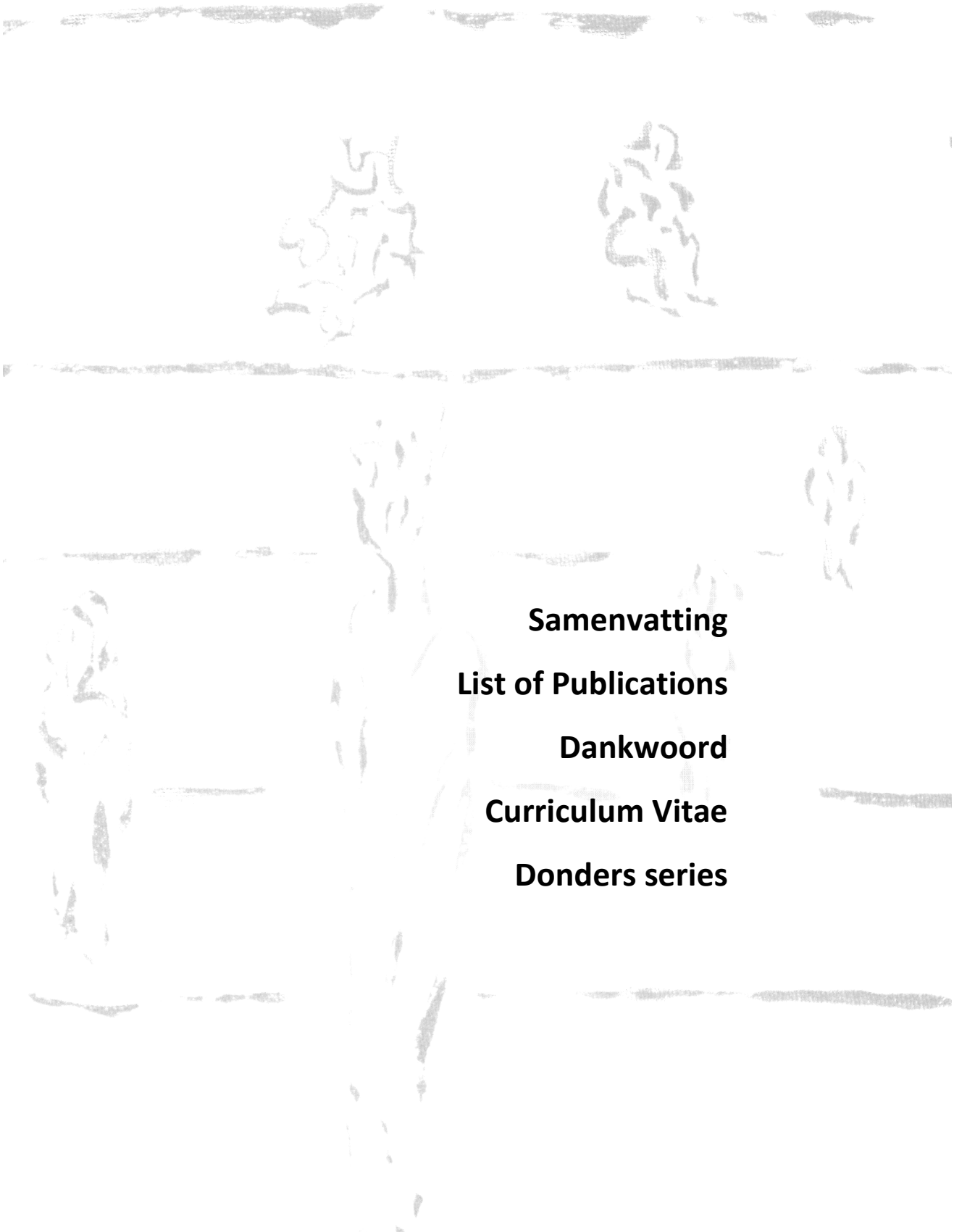

Samenvatting

Ernstige vermoeidheid na een Cerebrovasculair Accident (CVA), oftewel Post-Stroke Fatigue (PSF) is een veel voorkomende, chronische en invaliderende klacht, die door 27% tot 77% van de CVA patiënten wordt ervaren. Dit is zelfs het geval bij patiënten die verder goed herstellen. Het voorkomen van PSF vertoont zelfs jaren na het CVA, geen duidelijke afname . Daarnaast is er een (negatieve) invloed van PSF gevonden op de kwaliteit van leven, de uitkomsten van de revalidatie, de mate van onafhankelijk functioneren, suïcidaliteit en zelfs mortaliteit. Hoewel er in de afgelopen jaren meer aandacht voor vermoeidheid na een CVA is gekomen, wordt het onderwerp door veel onderzoekers en clinici nog steeds onderschat. Dit tekort aan onderkenning wordt versterkt door het ontbreken van een algemeen geaccepteerde en uniforme definitie van PSF en door het gemis aan richtlijnen voor behandeling. Deze knelpunten zorgen ervoor dat PSF een moeilijke en ook weinig aantrekkelijke klacht is om te behandelen. Kennis van de prevalentie, etiologie en associaties met andere stoornissen kan daarom helpen bij een adequate diagnose en een eventuele behandeling van PSF. Deze onderwerpen worden in het eerste deel van dit proefschrift behandeld. Het tweede gedeelte vervolgens gaat in op de behandeling van PSF en de evaluatie hiervan.

Deel 1. Het probleem vermoeidheid na een CVA

In hoofdstuk 1 wordt een overzicht gegeven van de huidige wetenschappelijke literatuur over Post-Stroke Fatigue (PSF), oftewel vermoeidheid na een CVA. Ook al is het duidelijk dat PSF een vaak voorkomende klacht na een CVA is, wordt er nog steeds geen uniforme definitie van gehanteerd. Er zijn op dit moment 17 verschillende definities in omloop. Door het ontbreken van valide biologische markers is het aantal vragenlijsten dat PSF pretendeert te meten zelfs nog groter. Vermoeidheid kan cognitieve, emotionele en/of fysieke aspecten en uitingsvormen hebben. Over het algemeen wordt vermoeidheid gemeten met vragenlijsten die door patiënten zelf worden ingevuld. Deze lijsten lijken verschillende aspecten van vermoeidheid te meten. Deze verscheidenheid bemoeilijkt in ernstige mate de vergelijkbaarheid van onderzoeksresultaten van studies waarin verschillende vragenlijsten gebruikt zijn. Studies gericht op de persoonlijke ervaring van PSF laten zien dat deze vorm van vermoeidheid kwalitatief anders is dan de vermoeidheid die ervaren werd voor het CVA. De vermoeidheid na het CVA wordt met name als langer durend en ernstiger geduid.

Om duidelijkheid te krijgen over de etiologie van PSF, is in veel studies de associatie met verschillende preklinische, klinische, demografische en psychosociale variabelen onderzocht. Van alle premorbide variabelen , is alleen de

preklinische vermoeidheid significant gerelateerd aan PSF. Globale CVA-kenmerken laten geen consequente relaties zien met PSF. Noch de ernst van het CVA, noch het type beroerte, noch de globale lokalisatie zijn significant met PSF gecorreleerd . Niettemin is er enig bewijs voor een hogere prevalentie van PSF na laesies van de basale ganglia. Deze hersengebieden zijn onderdeel van een centraal vermoeidheid netwerk (Chaudhuri & Behan 2000, 2004). Ook zouden volgens recent onderzoeken hormonale dysfuncties zoals een verhoogd cytokine-niveau of een ontregeling van de hypothalamus-hypofyse-bijnier-as een rol kunnen spelen in de ontwikkeling of het in stand houden van PSF. Met betrekking tot klinische variabelen zijn er zwakke associaties gevonden tussen PSF en pijn , terwijl er tegenstrijdige resultaten beschreven zijn omtrent de relatie van PSF met fysieke handicaps en slaapstoornissen . De resultaten van de meeste onderzoeken lijken deels te zijn beïnvloedt door de gebruikte meetinstrumenten.

Wat de psychosociale variabelen betreft zijn depressieve symptomen vrij consistent geassocieerd met PSF, hoewel er ook bewijs voor een dissociatie tussen beide bestaat. Studies over de relatie tussen PSF en andere psychosociale variabelen zijn schaars. In studies waar uitgebreide neuropsychologische testbatterijen zijn gebruikt, zijn er sterke associaties tussen cognitief disfunctioneren en vermoeidheid gevonden. Deze bevindingen ondersteunen de zogenaamde "cognitieve coping-hypothese" van Van Zomeren et al. (1984). Deze hypothese gaat ervan uit dat vermoeidheid vooral veroorzaakt wordt door de extra cognitieve inspanning die patiënten met hersenletsel moeten leveren om te compenseren voor hun informatieverwerkingstekorten om zodoende aan de eisen van het dagelijks leven te voldoen.

In Hoofdstuk 1 van dit proefschrift wordt geconcludeerd dat PSF bestaat uit cognitieve, emotionele en fysieke componenten. Andere aspecten van PSF, zoals etiologie, meetbaarheid en effectieve behandelmethoden zijn echter nog steeds onduidelijk. Daarom werden de volgende onderzoeksvragen in dit proefschrift gesteld .

1: Wordt PSF te weinig gediagnostiseerd in Nederland? Krijgen patiënten voldoende informatie over PSF in de Nederlandse gezondheidszorg en is er een relatie tussen PSF en persoonlijke of klinische variabelen?

Het idee dat in Nederland PSF nog steeds onvoldoende wordt gediagnostiseerd en behandeld kan worden afgeleid uit de bevindingen van hoofdstuk 2. In de studie die in dit hoofdstuk wordt beschreven vulden 538 CVA patiënten een vragenlijst op het internet in. Deze vragenlijst bevatte vragen over de hoeveelheid informatie die zij hadden ontvangen omtrent PSF, de hoeveelheid handvatten om zelf met vermoeidheid om te gaan na het CVA, of ze een behandeling gericht op vermoeidheid hadden gekregen, of ze behoefte hadden aan een dergelijke behandeling, en de aard van hun ervaren vermoeidheid. De

gemiddelde leeftijd van de respondenten was 52 ± 11 jaar. Gemiddeld bevonden zij zich in de chronische fase na het CVA (gemiddeld post-CVA aanvangstijd: 2.7 ± 3.4 jaar). De respondenten waren over het algemeen goed opgeleid en 57% was nog werkzaam. Bijna de helft (48%) van de deelnemers gaf aan met ernstige vermoeidheidsklachten te kampen en 68% gaf aan een grote impact van vermoeidheid op dagelijkse leven te ervaren. Er werden geen associaties tussen PSF en persoonlijk of klinische variabelen gevonden.

Hoewel in deze studie een bias werd verwacht met betrekking tot de (geringe) hoeveelheid informatie die patiënten omtrent PSF hadden ontvangen, waren de resultaten toch verrassend. Zo bleek dat slechts 17% van de respondenten voldoende informatie over PSF had ontvangen en dat alleen 7% was ingelicht over behandelmogelijkheden, terwijl 56% aangaf een aanzienlijke behoefte aan behandeling te hebben. Zoals verwacht was deze behoefte aan behandeling gerelateerd aan de ernst van de vermoeidheid (r = 0,35) als ook aan de impact van vermoeidheid op het dagelijks leven (r = 0,30). Deze bevindingen zijn des te opmerkelijker, omdat de resultaten impliceren dat de cognitieve vaardigheden van de respondenten relatief intact waren na het CVA. De meeste patiënten (81%) ondervonden geen problemen om de vragenlijst binnen 10 minuten te voltooien. Bovendien was het wel of niet werkzaam zijn niet gerelateerd aan vermoeidheid of aan de hoeveelheid informatie die de respondenten over PSF hadden ontvangen. Dit resultaat onderstreept dat de respondenten wel in staat waren om naar informatie te zoeken en deze te begrijpen, maar dat deze informatie niet beschikbaar was.

2. Hebben patiënten met PSF hebben specifieke psychologische of sociale kenmerken? Zo ja, kan kennis van deze kenmerken helpen bij de ontwikkeling van doeltreffende behandelingen?

hoofdstuk 3 worden de psychosociale kenmerken van 88 CVA chronische CVA patiënten met ernstige PSF onderzocht. In deze studie is vermoeidheid gemeten met zowel de Checklist Individual Strength (CIS-20R) subschaal vermoeidheid (CIS-f) als met de Fatigue Severity Scale (FSS). Angst en depressie werden vastgesteld aan de hand van de Hamilton Anxiety and Depression Scale, psychische distress met de Symptom Checklist-90 (SCL-90), copingsstijl met de Coping Inventory for Stressfull Situations (CISS), sociale steun met de Social Support List (SSL) en self-efficacy met de Self Efficacy Scale (SES). Deze psychosociale variabelen werden gecorreleerd met PSF en de gemiddelde scores werden vervolgens vergeleken met die van gezonde controles en patiëntengroepen met andere chronische ziekten.

De FSS en de CIS-f waren niet gecorreleerd met dezelfde psychosociale kenmerken. De FSS was matig gecorreleerd met de subschaal Obsessief Compulsief van de SCL-90 (r = 0,36), hetgeen wijst op een relatie met cognitieve

klachten. De CIS-f was gecorreleerd et de subschalen Somatische klachten (r = 0,53) en Depressie (r = 0,35) van de SCL-90. Deze laatste relatie verdween na een multiple regressieanalyse, waaruit bleek dat alleen de lichamelijke klachten gerelateerd waren aan de CIS-f scores. Geen andere correlaties met vermoeidheid werden gevonden. Bovendien was PSF niet gerelateerd aan persoonlijkheidsproblematiek. In de vergelijking met gezonde controles kwam naar voren dat patiënten met PSF meer last hadden van psychische klachten (SCL-90 en de HADS) en dat zij relatief laag scoorden op het gebruik van probleemgerichte coping stijlen. Er werden echter nauwelijks verschillen gevonden wanneer de scores van patiënten met PSF vergeleken werden met de normatieve gegevens van andere patiëntengroepen met chronische aandoeningen.

In hun geheel genomen, weerleggen deze bevindingen de resultaten van eerdere studies die concludeerden dat emotie georiënteerde coping de belangrijkste determinant van PSF is, en dat persoonlijkheid een significante rol in PSF speelt. Bovendien tonen de resultaten aan dat psychologische factoren vermoeidheid na een CVA niet volledig kunnen verklaren.

3. Wat zijn de uitkomsten van psychometrisch onderzoek naar twee vermoeidheidsvragenlijsten: de ééndimensionale Fatigue Severity Scale (FSS) in vergelijking met de meerdimensionale Checklist Individual Strenght (CIS20-R)? In hoeverre meten beide veelgebruikte vermoeidheidsschalen hetzelfde construct?

In hoofdstuk 4 werden de psychometrische eigenschappen en de onderliggende constructen van de CIS20-R vermoeidheids-subschaal (CIS-f) en de FSS onderzocht. De FSS is de meest gebruikte vragenlijst in onderzoek naar PSF, terwijl de CIS-20R (en vooral de CIS-f subschaal) de geprefereerde lijst is in studies die uitgevoerd zijn in de Benelux. Beide lijsten werden afgenomen bij 196 CVA-patiënten en 112 leeftijds-gematchte controles.

De resultaten lieten zien dat beide schalen een hoge interne consistentie hadden (Cronbach's α: FSS = 0,893; CIS-f = 0,938), maar dat de convergente validiteit van beide schalen matig was (r = .52). Bovendien reduceerden de eerste twee items van de FSS de interne consistentie aanzienlijk en kon met deze items geen onderscheid gemaakt worden tussen CVA-patiënten en de gezonde controles. Met behulp van Principal Axis Factoring analyses op alle items bleek dat 6 van de 8 items van de CIS-f hoog laadden op de factor: "subjectieve gevoelens van zwakte en vermoeidheid", terwijl de twee resterende items laadden op "fysieke conditie". Acht van de 9 items van de FSS laadden op een andere factor die "impact van vermoeidheid op dagelijkse leven" genoemd werd.

Deze resultaten laten zien dat de CIS-f en de FSS verschillende aspecten van vermoeidheid meten. In overeenstemming met eerdere psychometrische studies over de FSS, werd geconcludeerd dat de eerste twee items van de

oorspronkelijke FSS moeten worden overgeslagen bij de afname in de CVA-populatie . Zodoende houdt men een FSS7 over waarmee de impact van vermoeidheid op het dagelijks functioneren in kaart gebracht kan worden. In tegenstelling tot wat de naam van de FSS (Fatigue Severity Scale) suggereert , meet de FSS niet de ernst van vermoeidheid. Met betrekking tot de CIS-f werd geconcludeerd dat met deze subschaal niet alleen de fysieke dimensie van vermoeidheid gemeten wordt, maar ook de ernst van een meer algemene subjectieve ervaring van vermoeidheid.

Deel 2. De behandeling van vermoeidheid na een CVA

4. Welke onderdelen moeten deel uitmaken van een behandelprotocol voor PSF, rekening houdend met de emotionele, cognitieve en fysieke aspecten van vermoeidheid?

Op basis van de positieve resultaten van een pilot-studie ter evaluatie van de PSF-behandelmodule "Omgaan met beperkte belastbaarheid " in de Sint Maartenskliniek in Nijmegen, is het protocol van deze behandeling als uitgangspunt genomen voor de huidige studie. Dit behandelprotocol is vervolgens aangepast naar aanleiding van de ervaringen (feedback) van patiënten en therapeuten. De belangrijkste aanpassingen waren de structurele integratie van cognitieve gedragstherapie (CGT) in het protocol, een verkleining van de behandel-groepsgrootte naar vier patiënten en de toevoeging van een Graded Activity protocol. Dit laatste was gebaseerd op de aanbevelingen voor Stroke Survivors van de American Heart Association. Het volledige behandelprotocol, genaamd COGRAT (Cognitieve en Graded Activity Training) wordt gepresenteerd in hoofdstuk 5.

In het COGRAT behandelprotocol werd de cognitieve coping hypothese als uitgangspunt genomen. Het primaire doel van de COGRAT behandeling was om patiënten in het algemeen te leren hun energie spaarzamer te gebruiken en ze doelmatigere laten omgaan met hun beperkte cognitieve belastbaarheid . Om dit te bereiken werden de patiënten gevraagd om hun activiteiten en hun vermoeidheid per uur registreren gedurende twee weken. Uit deze registraties kon vervolgens het persoonlijk activiteiten- en vermoeidheidspatroon worden afgeleid. Op basis van deze informatie werden drie compensatiestrategieën aangeboden: afwisseling, planning en ontspanning. Eerst werd de patiënten geleerd hoe ze hun activiteiten en de intensiteit hiervan met periodes van rust of ontspanning konden afwisselen om zo vermoeidheid te voorkomen. Ten tweede, leerden ze hoe ze activiteiten beter konden plannen, rekening houdend met de extra tijd die nodig is om de taken te volbrengen en de tijd die nodig is om te herstellen van vermoeidheid. Ten slotte werden de patiënten gecoacht in het zoeken naar nieuwe manieren om te ontspannen. Dit was van belang omdat veel

activiteiten die voor het CVA ontspannend waren, na het CVA veel energie opslorpten.

Om deze gedragsveranderingen en de daarmee gepaarde gaande gedachten beter te leren hanteren, , werden principes uit de Cognitieve Gedragstherapie (CGT) systematisch toegepast. Het doel van de CGT was om 'blokkerende gedachten' (die de uitvoering van de compensatiestrategieën konden belemmeren) te vervangen door 'helpende gedachten'. Verder werd CGT gebruikt om beter om te gaan met gevoelens van vermoeidheid en de bijbehorende psychische klachten. Door het uitvoeren van CGT-huiswerkopdrachten werd patiënten geleerd om rationele en adaptieve gedachten te formuleren om zo beter te kunnen omgaan met de negatieve emoties die samengaan met vermoeidheid. Naast deze vermoeidheids-specifieke behandelstrategieën waren ook meer algemene revalidatie behandelprincipes zoals psycho-educatie, het stellen van persoonlijke doelen en het uitvoeren van huiswerkopdrachten een substantieel onderdeel van de cognitieve behandeling.

De cognitieve behandeling werd één keer per week gedurende twee uur gegeven. Graded activity training liep hier synchroon mee en werd twee keer per week gedurende twee uur gegeven. De behandeling duurde 12 weken. Tijdens de graded activity training volgden de patiënten een trainingsschema gebaseerd op specifieke percentages van de eigen maximale hartslag en maximale spierkracht. De training bestond uit het lopen op een loopband met toenemende inclinatie, geprotocolleerde spierversterkende oefeningen (met gewichten), rompspieroefeningen en wandeloefeningen die als huiswerk werden opgegeven.

5. Is de uitgebreide COGRAT behandeling effectief in het reduceren van PSF in de chronische fase na een CVA?

Hoofdstuk 6 beschrijft de evaluatie van de COGRAT behandeling in vergelijking met alleen een cognitieve behandeling (CO) door middel van een gerandomiseerde gecontroleerde trial (RCT). Deze RCT werd uitgevoerd in acht revalidatiecentra in Nederland. Patiënten werden geselecteerd op basis van de volgende criteria: ernstige vermoeidheid (CIS-f> 40), in staat om 10 meter zelfstandig te lopen, geen ernstige cognitieve stoornissen, geen co-morbide depressie, en geen ernstige hart-of longziekte. Volgens deze criteria, kwamen 88 van 231 patiënten in aanmerking en 83 namen ten slotte deel aan de studie. De primaire uitkomstmaten hadden betrekking op vermoeidheid (CIS-f en Zelfobservatie List-moeheid / SOL-f) terwijl de secundaire uitkomstmaten gericht waren op depressie, angst, functionele gezondheid, pijn, slaapstoornissen en uithoudingsvermogen. Gemeten werd op vier tijdstippen: (1) bij de start van de studie, (2) na een drie maanden durende kwalificatie-periode zonder behandeling (3) na voltooiing van de behandeling en (4) na 6 maanden als follow-up. Randomisatie en toewijzing aan de CO óf de COGRAT behandeling vond plaats na

het tweede meetmoment. De kwalificatie periode van drie maanden werd gebruikt om eventuele effecten van eerdere behandelingen op de studie te voorkomen, en om te zien of patiënten stabiele niveaus van vermoeidheid vertoonden.

De resultaten van deze studie toonden aan dat de CO behandeling op zichzelf al effectief was om vermoeidheid significant te doen afnemen. Echter , de gecombineerde COGRAT behandeling zorgde bij meer patiënten voor een klinisch significante daling van de ervaren ernst van de vermoeidheid dan alleen de CO behandeling (58% vs 24%). Aangezien alle patiënten zich in de chronische fase na het CVA bevonden (gemiddeld: 3,9 jaar post-onset, ± 3.9 jaar) en leden aan ernstige vermoeidheid bij de start van de studie, zonder enige daling in de kwalificatie periode, werd geconcludeerd dat PSF aanzienlijk verlicht kan worden met de cognitieve behandeling. Deze dient bij voorkeur in combinatie met graded activity training te worden gegeven. Verbeteringen van beide behandelingen op secundaire uitkomstmaten werden gevonden voor depressieve symptomen, functionele gezondheid (functional health) en slaapstoornissen. Geen significante veranderingen werden gevonden ten aanzien van angst of pijn. Het fysieke uithoudingsvermogen verbeterde alleen na de COGRAT behandeling.

In Hoofdstuk 7 van dit proefschrift werden allereerst redenen aangedragen voor het onvoldoende herkennen van PSF in Nederland en daarbuiten. Er wordt gesteld dat het ontbreken van een algemeen geaccepteerd definitie van PSF en van een duidelijk oorzakelijk model voor deze aandoening, de achterliggende oorzaak voor dit gebrek aan erkenning en herkenning vormen. De central fatigue hypothese van Chaudhuri en Behan en de cognitieve copinghypothese van van Zomeren bieden een goede aanzet om beide problemen op te lossen.. PSF wordt dan enerzijds duidelijker gekarakteriseerd en afgebakend (central fatigue hypothese) en anderzijds wordt het werkingsmechanisme ontrafeld door PSF afhankelijk te maken van de manier waarop mensen met een hersenbeschadiging cognitieve taken uitvoeren (cognitieve copinghypothese). Studies uit verschillende onderzoeksdomeinen (cardiovasculaire inspannings-fysiologie, imaging-onderzoek en neuropsychologisch onderzoek) ondersteunen deze laatste hypothese. Hoewel er in het huidige onderzoek geen duidelijk eigen psychosociaal- en persoonlijkheidsprofiel van patiënten met PSF is gevonden, spelen psychosociale factoren en stress op individueel niveau waarschijnlijk ook een rol bij de instandhouding van de klachten. Daarnaast blijft van belang om het onderscheid tussen PSF en depressie na een CVA te maken en de behandeling hier op aan te passen.

De gepresenteerde COGRAT behandeling is tot nu toe de eerste therapie die effectief is gebleken en de vermoeidheidsklachten bij PSF significant reduceert. Toch kon niet bij alle patiënten een significante reductie van

vermoeidheid gerealiseerd worden. Toekomstige studies zouden hierbij in kunnen gaan op de individuele verschillen van patiënten en daarnaast de effectiviteit van de verschillende onderdelen van de COGRAT-therapie, zoals de cognitief gedragstherapeutische interventies, het stellen van doelen, de compensatie strategieën en de graded activity afzonderlijk kunnen onderzoeken. Hierbij is het wellicht van belang om in de meetinstrumenten van vermoeidheid een onderscheid te maken tussen de fysieke, de cognitieve als ook de emotionele aspecten van vermoeidheid. Vermoeidheid wordt immers door verschillende patiënten verschillend ervaren.

Vervolgens werden adviezen voor de praktijk gegeven met betrekking tot het geven van psycho-educatie over vermoeidheid en behandelmogelijkheden. Steeds meer informatie en behandelprogramma's zijn voorhanden, zoals de zorgwijzer vermoeidheid van de Hersenstichting Nederland en het ziekenhuisprogramma voor cognitieve revalidatie "Niet rennen maar plannen". Ook is het COGRAT-protocol momenteel geïmplementeerd in meerdere revalidatiecentra.

Tot slot van deze dissertatie wil ik graag een hoopvolle boodschap overbrengen aan CVA-patiënten. Ook al PSF is een chronische en invaliderende klacht die bijna alle terreinen van het leven beïnvloedt, de resultaten van dit proefschrift laten zien dat deze aandoening bij veel slachtoffers met een CVA met succes kan worden behandeld. Bovendien groeit de belangstelling voor PSF en neemt het aantal studies toe. Deze ontwikkelingen leiden waarschijnlijk tot een beter inzicht in het ontstaan van PSF en het veelzijdige karakter ervan. Deze kennis kan leiden tot meer effectieve behandelingen en daardoor zullen meer patiënten de doelgerichte hulp die ze vragen en nodig hebben, ontvangen.

List of Publications

Chronological listing of publications

Zedlitz A. M. E. E, Van Eijk M, Kessels R. P. C, Geurts A. C. H, Fasotti L. Poststroke fatigue is still a neglected issue: Findings from an internet-based study on the need for information and treatment in The Netherlands. *ISRN Stroke*. 2012;2012:629589.

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van Mierlo M, Zedlitz A, van Eijk M, Geurts A, Fasotti L Measurement of post-stroke fatigue CIS-20r & FSS reviewed. Proceedings of VRA Annual Congres, *Revalidata,* 2010. *157*, p13.

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Curriculum Vitae

Aglaia Zedlitz werd geboren op 17 december 1975 te Nijmegen, alwaar zij na een jaar in de VS in 1995haar VWO-diploma aan het Canisius College Mater Dei behaalde. Daarna ging zij na een jaar Scheikunde, in 1996 Psychologie studeren aan de Universiteit Utrecht. In 2001 behaalde zij hier haar doctoraal in de Klinische Psychologie. Zowel in haar afstudeeronderzoek als in haar vrijwilligerswerk bij de depressiestichting, hadden patiënten met angst-stemmingsstoornissen haar interesse. Na haar afstuderen reisde ze en werkte zij enkele jaren bij een bank en bij een vakbond. In 2004 startte zij met de master Neuropsychologie aan de Universiteit Utrecht dat zij in 2006 Cum Laude voltooide. In 2007 startte zij met het door ZonMw gesubsidieerde onderzoek naar de effectiviteit van behandelingen in de cognitieve revalidatie, waarvan het huidige proefschrift het resultaat is. Naast dit onderzoek vervulde zij verscheidene bestuursfuncties, zoals in het afdelingsbestuur van D66 Utrecht, het promovendi-overleg in Nijmegen, en de sectie Neuropsychologie van het NIP. In het laatstgenoemde bestuur is zij momenteel nog penningmeester. Sinds 2011 werkt zij parttime als psycholoog in de tweedelijnsinstelling G-kracht Psychomedisch Centrum te Amsterdam. In 2012 begon zij daarnaast aan haar functie als Universitair Docent Klinische Neuropsychologie aan de Universiteit in Leiden. Aglaia Zedlitz woont in Delft samen met haar man, Michiel van Vreeswijk, en hun twee katten: Freud en Jung.

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