

Cognitive and Graded Activity Training Can Alleviate Persistent Fatigue After Stroke : A Randomized, Controlled Trial

Aglaia M.E.E. Zedlitz, Toni C.M. Rietveld, Alexander C. Geurts and Luciano Fasotti

Stroke. 2012;43:1046-1051; originally published online February 2, 2012;
doi: 10.1161/STROKEAHA.111.632117

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/content/43/4/1046>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>

Cognitive and Graded Activity Training Can Alleviate Persistent Fatigue After Stroke

A Randomized, Controlled Trial

Aglaia M.E.E. Zedlitz, MSc; Toni C.M. Rietveld, PhD; Alexander C. Geurts, MD, PhD; Luciano Fasotti, PhD

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 centers. Eighty-three stroke patients (>4 months after 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-minute walk test) were collected at baseline (before and after qualification period) and after treatment (immediate and 6-month follow-up).

Results—The qualification period showed stable outcome measures. Both treatments showed significant beneficial effects on fatigue (CIS-f: $\eta_p^2=0.48$, $P<0.001$) 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% versus 24%) and on physical endurance ($\eta_p^2=0.20$, $P<0.001$).

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. (*Stroke*. 2012;43:1046-1051.)

Key Words: fatigue ■ stroke ■ rehabilitation ■ outcome

See related article, p 933.

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.^{1,2} Although the definition of poststroke fatigue (PSF) is still subject of debate,^{1,2} 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.”^{1–4} Prevalence rates are as high as 38–73% without spontaneous amelioration in the chronic phase.¹ Moreover, research on its natural history shows that PSF often does not diminish even years after stroke.^{4–7} The etiology of PSF appears 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 recur-

rent stroke yielding a greater risk of fatigue.^{1,4,8,9} 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,¹ and no effective pharmacological or nonpharmacological treatment for PSF is yet available.²

Evidence from other patient populations with chronic fatigue suggests that tailored cognitive behavioral therapy, exercise therapy,^{10,11} and teaching energy conservation strategies¹² 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.¹³ A

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

Received July 10, 2011; accepted November 8, 2011.

From the Donders Centre for Cognition, Radboud University Nijmegen (A.M.E.E.Z., L.F.), Sint Maartenskliniek Research, Development, and Education (A.M.E.E.Z., L.F.), the Department of Linguistics, Radboud University Nijmegen (T.C.M.R.), and Nijmegen Centre for Evidence Based Practice, Radboud University Nijmegen Medical Centre, Department of Rehabilitation (A.C.G.), Nijmegen, The Netherlands.

Correspondence to Aglaia M.E.E. Zedlitz, MSc, Donders Centre for Cognition, Radboud University Nijmegen, Spinozabuilding, Mont 3, B02.09, PO Box 9104, Nijmegen, The Netherlands, 6500. E-mail a.zedlitz@donders.ru.nl

© 2012 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.111.632117

Graded Activity Training (GRAT) was offered alongside the cognitive treatment. GRAT consisted of walking on a treadmill, strength training, and physical fitness home work assignments. A full description of these interventions has been published previously.¹³

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. Because 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,¹⁴ 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 multicenter, 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 3 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 before random assignment, and that a stable baseline of the outcome measures can potentially be established.¹⁵ Immediately after the qualification period, the outcome measures were administered again (T1).

Thereafter, when 8 patients were available at a center, random assignment 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 1 intervention group by means of a sealed envelope. Directly after treatment another assessment took place (T2); 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 Helsinki¹⁶ 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 >4 months before recruitment, (2) reported severe fatigue (Checklist Individual Strength-subscale Fatigue score ≥ 40),^{7,17} (3) were between ages 18–70 years, and (4) were able to walk independently. Patients were excluded if they had severe cognitive deficits (Behavioral Inattention Test ≤ 129 , Rivermead Behavioral Memory Test-screening score < 8 , Behavioral Assessment of the Dysexecutive Syndrome less than borderline, Token Task > 12)¹⁸ or severe comorbidity, such as cardiac disease, pulmonary disease, or depression (Hospital Anxiety and Depression Scale-depression subscale score > 10 ,¹⁹ or based on a clinical DSM-IV interview²⁰ if the Hospital Anxiety and Depression Scale (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 after onset of stroke, single versus recurrent stroke, Motricity Index²¹) 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.¹³ In addition, a GRAT protocol was designed including walking on a treadmill, strength training, and home work 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.^{13,22} GRAT was given in groups of maximally 4 patients as well. The CO group received weekly 2-hour sessions of cognitive therapy for 12 weeks. In addition to group CO, the COGRAT group received 24, 2-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 (A.Z.). 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)¹⁷ and a fatigue self-observation list (SOL-f)²³ were used to obtain information on patient's fatigue. Both tools are well validated and are widely used in the Benelux countries.^{9,23–25} The CIS-f contains 8 questions on fatigue severity regarding the 2 weeks preceding the assessment. The CIS-f has good reliability, is sensitive to change,^{3,17} and has been validated for the stroke population.^{7,9} 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.^{7,23} With the validated SOL-f, patients recorded their fatigue severity on a 5-point scale (0–4) 4 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.^{23–25}

Secondary Outcomes

Depression and anxiety were assessed with the HADS.¹⁹ 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).²⁶ Subscale sum scores are categorized as normal (0–7), mild (8–10), moderate (11–14), or severe (15–21).²⁷

Functional health status was assessed with the well-validated Stroke-Adapted Sickness Impact Profile 30 (SA-SIP 30).²⁸ This tool has 30 items, and scores are calculated as a percentage of maximum dysfunction, ranging from 0–100%. 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).^{24,25} An SOL was also used to record the quality of sleep. Patients indicated whether they had slept well or recorded which of 3 sleep disturbances had occurred that night (difficulty falling asleep, restless sleep, early awakening). The amount of sleep disturbances was totaled for each day (0–3). Scores were then expressed as the average amount of sleep disturbances per night (SOL-Sleep D; range, 0–3).^{24,25}

The 6-minute walk test (6MWT) is a validated tool to assess physical endurance.²⁹ The total walking distance in meters during 6 minutes was recorded.

Furthermore, after treatment (T2), patients were given a Visual Analog 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"

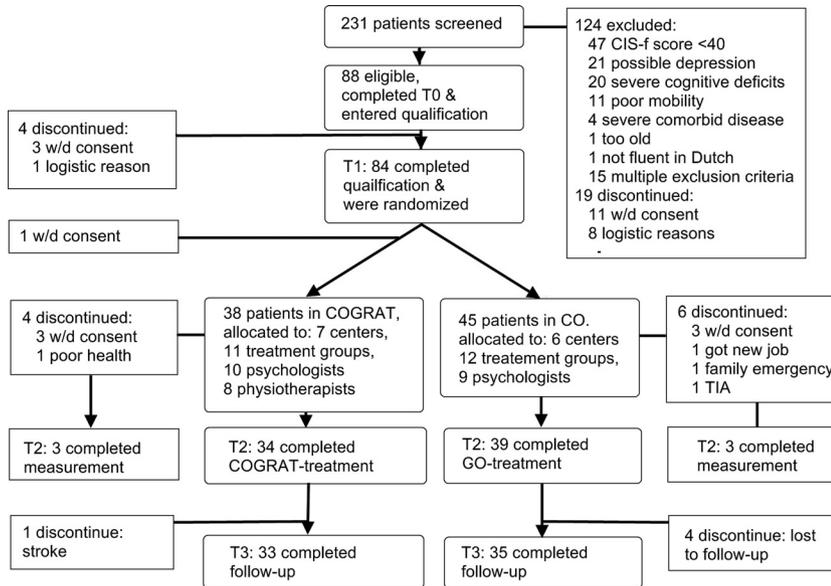


Figure 1. Consort diagram. CIS-f indicates Checklist Individual Strength–subscales Fatigue; TIA, transient ischemic attack.

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 <35 . This score is situated within 2 standard deviations of CIS-f scores in healthy control subjects.^{23,25,30} At an individual level, a clinically important reduction of fatigue was set at a reliable change index (RCI) >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.^{23,30}

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 0.10 and an α level of 0.05.^{23,30} Data analyses were performed using SPSS (version 18.0). Holm correction was used to control for multiple outcomes.³¹

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 nonparallel 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 0–1.

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 nonsignificant (RCI <1.96).³⁰ We used the 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 dropout, 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, hemorrhagic, 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 nonparticipation were a CIS-f score <40 ($n=47$) and symptoms of depression ($n=21$). Due to insufficient numbers of eligible patients at the different centers, individual random assignment 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.

Mean post-onset time of stroke in participants was 3.9 years (SD, 3.9). For 5 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 $P>0.05$).

Primary and Secondary Outcomes

Before the start of the interventions, after the 3 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 $P<0.001$; SOL-f $P=0.007$). Effect sizes were substantial for CIS-f ($\eta_p^2=0.48$) and less for SOL-f ($\eta_p^2=0.12$). 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 Patients (n=83)

	CO Mean (SD)	COGRAT Mean (SD)
n	45	38
Age, y	54.8 (9.1)	55.6 (8.8)
Men, %	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, y	4.4 (4.2)	3.3 (3.9)
<1 y after stroke, %	8.9%	13.2%
1–2 y after stroke, %	26.7%	34.2%
2–5 y after stroke, %	40.0%	34.2%
5–10 y after stroke, %	15.6%	15.8%
>10 y after stroke, %	8.9%	2.6%
Range	0.8–22.2	0.4–23.0
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 and mixed)	4	3
Prior rehabilitation	75.6%	76.3%
Mean No. of prior 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

CO indicates cognitive treatment; COGRAT, cognitive and graded activity training; MI, Motricity Index; 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 ($P < 0.001$, $\eta_p^2 = 0.20$). Figure 3 indicates that after treatment and at follow-up, physical endurance had improved more in the COGRAT group than in the CO group.

Clinically Important Change

At follow-up, only the mean CIS-f score of the COGRAT group had improved to < 35 . In contrast, the mean CIS-f score of the CO group was still (albeit marginally) higher than this cutoff 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 ($P = 0.002$) (Table 3).

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 $> 98\%$ 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 of 12) or completed homework assignments (nearly always). The median number of GRAT sessions followed in the COGRAT group was 23 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 $P > 0.05$). Separate trend analyses of the outcome measures leaving out patients with SAH yielded the same statistically significant main and interaction effects, except for a nonsignificant effect of time on SOL-f ($F_{(70)} = 3.98$, $P = 0.023$) (nonsignificant after Holm correction for multiple outcomes).

Discussion

The results of this multicenter, 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 2 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 with 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 70 m.²⁹ At follow-up, however, this improvement had decreased to approximately 40 m. 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 multicenter design, the 3-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 dropouts remained within acceptable limits.³² Moreover, 4 of the 10 patients who 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

Table 2. Outcome Measurements (n=83)

Outcome Variables	Mean (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	<0.001†	.48	0.06	>0.1	2.16	0.121
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	0.007†	.12	1.39	>0.1	1.39	0.256
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	0.002†	.14	2.25	>0.1	0.12	0.884
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	0.035	.08	0.19	>0.1	0.04	0.963
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	0.002†	.14	0.00	>0.1	3.25	0.044
SOL-sleep D	0.71 (0.64)	0.58 (0.56)	0.57 (0.56)	0.71 (0.49)	0.60 (0.58)	0.49 (0.51)	5.25	0.007†	.12	0.03	>0.1	0.67	0.516
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	0.765	.01	0.41	>0.1	0.17	0.841
6MWT	438 (123)	444 (112)	441 (123)	437 (107)	504 (94)	481 (92)	14.43	<0.001†	.27	1.98	>0.1	9.72	<0.001†

CO indicates 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.

*df values are omitted to improve legibility.

†Significant with Holm correction for multiple outcomes: $P < 0.008$ for time and $P < 0.043$ for interaction effect.

addition, post-onset times in our study varied considerably, with 5 patients having had a stroke >10 years before enrollment. Because we did not assess the full medical history of comorbidities, 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.⁴⁻⁷ Because no significant changes occurred in any of the outcome measures during the qualification period, the beneficial effects observed after treatment are probably attributable to the intervention.

Two sources of heterogeneity in our study sample may be considered limitations: stroke etiology and previous treatment. Because 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.^{1,33} Although more patients with SAH were allocated to the CO than to the COGRAT group (7 versus 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 probably due to a loss of power, since all other effects remained unaltered. The etiologic 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

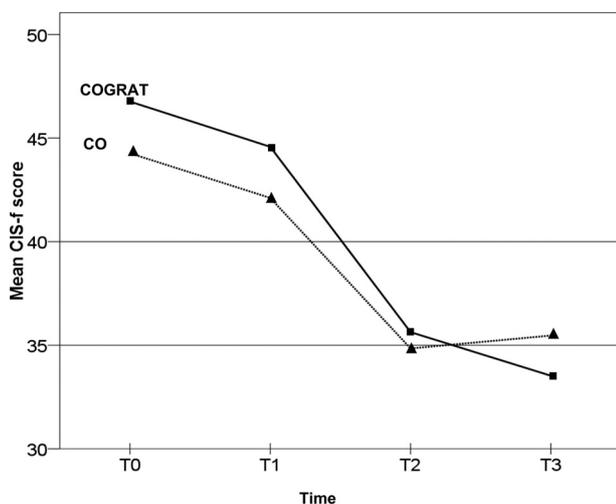


Figure 2. Checklist Individual Strength-subscale Fatigue (CIS-f) scores at the 4 time points for the cognitive therapy (CO) and CO with graded activity training (COGRAT) groups (n=83).

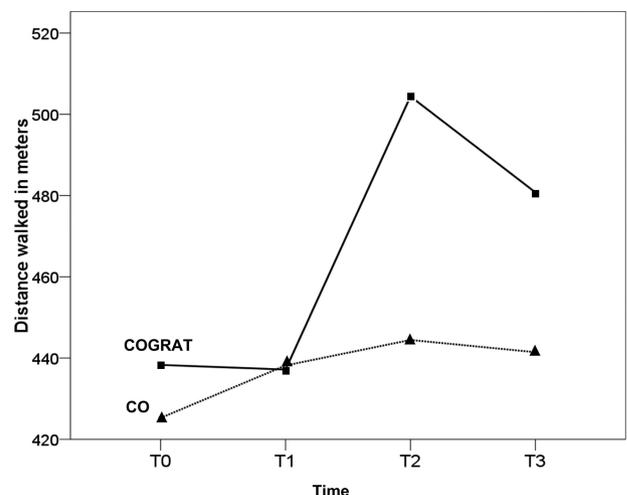


Figure 3. Six-minute walk test: Distance walked in meters at the 4 time points for the cognitive therapy (CO) and CO with graded activity training (COGRAT) groups (data of 1 patient are missing on all 4 occasions; n=82).

Table 3. Clinically Relevant Improvement (n=83)

	CO, n (%)	COGRAT, n (%)
Improvement	11 (24.4%)	22 (57.9%)
No improvement	34 (75.6%)	16 (42.1%)

CO indicates cognitive treatment; COGRAT, cognitive and graded activity training.

Clinically relevant improvement (see text for definition).

Likelihood ratio: $\chi^2=9.63$, $P=0.002$; Contingency coefficient=0.322.

determine post hoc 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 3-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. Because 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.

Acknowledgments

We express our profound appreciation to all therapists and evaluators across the 8 participating COGRAT facilities for their diligence and commitment to excellence during this clinical trial.

Sources of Funding

This study was funded by a Dutch Health Research and Development (ZonMw) grant 14350053.

Disclosures

None.

References

- Lerdal A, Bakken L, Kouwenhoven S, Pedersen G, Kirkevold M, Finset A, et al. Poststroke fatigue: a review. *J Pain Symptom Manage*. 2009;38:928–949.
- McGeough E, Pollock A, Smith LN, Dennis M, Sharpe M, Lewis S, et al. Interventions for post-stroke fatigue. *Cochrane Database Syst Rev*. 2009;CD007030.
- Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res*. 2004;56:157–170.
- Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Fatigue at long-term follow-up in young adults with cerebral infarction. *Cerebrovasc Dis*. 2005;20:245–250.
- Christensen D, Johnsen SP, Watt T, Harder I, Kirkevold M, Andersen G. Dimensions of post-stroke fatigue: a two-year follow-up study. *Cerebrovasc Dis*. 2008;26:134–141.
- Schepers V, Visser-Meily A, Ketelaar M, Lindeman E. Post-stroke fatigue: course and its relation to personal and stroke-related factors. *Arch Phys Med Rehabil*. 2006;87:184–188.
- van der Werf SP, van den Broek HL, Anten HW, Bleijenberg G. Experience of severe fatigue long after stroke and its relation to depressive symptoms and disease characteristics. *Eur Neurol*. 2001;45:28–33.
- Tang WK, Chen YK, Mok V, Chu WCW, Ungvari GS, Ahuja AT, et al. Acute basal ganglia infarcts in poststroke fatigue: an MRI study. *J Neurol*. 2009;257:178–182.
- Snaphaan L, van der Werf S, de Leeuw FE. Time course and risk factors of post-stroke fatigue: a prospective cohort study. *Eur J Neurol*. 2011;18:611–617.
- Gonzalez H, Olsson T, Borg K. Management of postpolio syndrome. *Lancet Neurol*. 2010;9:634–642.
- Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. *Clinical Oncol*. 2010;22:208–221.
- Mathiowetz V, Matuska K, Murphey M. Efficacy of an energy conservation course for patients with multiple sclerosis. *Arch Phys Med Rehabil*. 2001;82:449.
- Zedlitz AMEE, Fasotti L, Geurts ACH. Post-stroke fatigue, a treatment protocol that is being evaluated. *Clin Rehabil*. 2011;25:487–500.
- Saunders D, Greig C, Mead G, Young A. Physical fitness training for stroke patients. *Cochrane Database Syst Rev*. 2009;CD003316.
- Knipschild P, Leffers P, Feinstein AR. The qualification period. *J Clin Epidemiol*. 1991;44:461–464.
- World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *JAMA*. 2000;284:3043–3045.
- Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res*. 1994;38:383–392.
- Lezak MD. *Neuropsychological Assessment*. Oxford, NY: Oxford University Press; 2004.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361–370.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(Suppl 20):22–57.
- Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. *J Neurol Neurosurg Psychiatry*. 1990;53:576–579.
- Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update. *Circulation*. 2007;115:2675–2682.
- Vercoulen JH, Hommes OR, Swanink CM, Jongen PJ, Fennis JF, Galama JM, et al. The measurement of fatigue in patients with multiple sclerosis: a multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. *Arch Neurol*. 1996;53:642–649.
- Servaes P, Prins J, Verhagen S, Bleijenberg G. Fatigue after breast cancer and in chronic fatigue syndrome: similarities and differences. *J Psychosom Res*. 2002;52:453–459.
- Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet*. 2001;357:841–847.
- Sagen U, Vik TG, Moum T, Morland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: comparison of the Hospital Anxiety and Depression Scale and the Montgomery and Asberg Depression Rating Scale. *J Psychosom Res*. 2009;67:325–332.
- Whelan-Goodinson R, Ponsford J, Schonberger M. Validity of the hospital anxiety and depression scale to assess depression and anxiety following traumatic brain injury as compared with the structured clinical interview for DSM-IV. *J Affect Dis*. 2009;114:94–102.
- van Straten A, de Haan RJ, Limburg M, Schuling J, Bossuyt PM, van den Bos GA. A stroke-adapted 30-item version of the sickness impact profile to assess quality of life (sa-sip30). *Stroke*. 1997;28:2155–2161.
- ATS statement: Guidelines for the six-minute walk test. ATS committee on proficiency standards for clinical pulmonary function laboratories. *Am J Respir Crit Care Med*. 2002;166:111–117.
- Knoop H, van der Meer JW, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. *Br J Psychiatry*. 2008;193:340–341.
- Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal Stat Society*. 1995;Series B, 57:289–300.
- Tansy CM, Matté AL, Needham D, Herridge MS. Review of retention strategies in longitudinal studies and application to follow-up of ICU survivors. *Intensive Care Med*. 2007;33:2051–2057.
- Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. *Stroke*. 2010;41:e519–e536.