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Cognitive Rehabilitation in Patients With Gliomas: A Randomized, Controlled Trial

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ABSTRACT

Purpose
Patients with gliomas often experience cognitive deficits, including problems with attention and memory. This randomized, controlled trial evaluated the effects of a multifaceted cognitive rehabilitation program (CRP) on cognitive functioning and selected quality-of-life domains in patients with gliomas.

Patients and Methods
One hundred forty adult patients with low-grade and anaplastic gliomas, favorable prognostic factors, and both subjective cognitive symptoms and objective cognitive deficits were recruited from 11 hospitals in the Netherlands. Patients were randomly assigned to an intervention group or to a waiting-list control group. The intervention incorporated both computer-based attention retraining and compensatory skills training of attention, memory, and executive functioning. Participants completed a battery of neuropsychological (NP) tests and self-report questionnaires on cognitive functioning, fatigue, mental health–related quality of life, and community integration at baseline, after completion of the CRP, and at 6-month follow-up.

Results
At the immediate post-treatment evaluation, statistically significant intervention effects were observed for measures of subjective cognitive functioning and its perceived burden but not for the objective NP outcomes or for any of the other self-report measures. At the 6-month follow-up, the CRP group performed significantly better than the control group on NP tests of attention and verbal memory and reported less mental fatigue. Group differences in other subjective outcomes were not significant at 6 months.

Conclusion
The CRP has a salutary effect on short-term cognitive complaints and on longer-term cognitive performance and mental fatigue. Additional research is needed to identify which elements of the intervention are most effective.

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INTRODUCTION

Gliomas, the most common type of primary brain tumors, and their treatment can cause deficits in various cognitive domains, including attention, memory, and executive functioning.[1-3] Although these impairments, in general, are not severe in nature,[2,4,5] they can have a significant impact on patients' daily lives.[6] Moreover, subjective cognitive symptoms are among the most common neurologic problems reported by patients with brain tumors.[7,8]

Pharmacologic interventions have not proven effective yet in the treatment of cognitive deficits in patients with gliomas.[9] Cognitive rehabilitation interventions represent an alternative treatment approach. Only one small, retrospective study has investigated cognitive rehabilitation in patients with primary brain tumors.[10] Although the results were positive, they were not based on statistical testing. Cognitive rehabilitation efforts have proven effective in other patient populations, including in those patients with traumatic brain injury,[11] stroke,[11] and Alzheimer's disease.[12]

This randomized, controlled trial investigated the effectiveness of a multifaceted cognitive rehabilitation program (CRP) on objective and subjective measures of cognitive functioning in patients with gliomas whose diseases were in remission. The primary hypothesis was that patients who underwent the CRP would perform significantly better on objective neuropsychological (NP) tests of attention, memory, and executive functioning and would

report significantly fewer cognitive symptoms than patients in a waiting-list control group. It was also hypothesized that the CRP would have a significant, positive effect on self-reported mental fatigue, mental health–related quality of life (QOL), and community integration.

PATIENTS AND METHODS

Study Sample and Design

Eligible patients were identified via pathology databases or direct referral from 11 Dutch hospitals, including 10 of the 18 Dutch neurosurgical centers. Medical inclusion criteria were as follows: histologically proven or presumed (on the basis of clinical and magnetic resonance imaging features), diffuse, low-grade (ie, WHO grade 2) gliomas (ie, astrocytomas, oligodendrogliomas, or oligoastrocytomas) and age between 18 and 70 years; or anaplastic gliomas, age younger than 50 years, and good performance status (ie, Karnofsky performance score $>$ 70). Patients had to be clinically stable (ie, without any evidence of disease progression) for a minimum of 6 months before study entry, and they could not be receiving antitumor treatment during that period. Exclusion criteria included the following: any additional serious neurologic or psychiatric disorder; inability to undergo the NP assessments (NPAs) or CRP because of premorbid IQ score less than 85; visual, motor, language, or other severe cognitive problems; lack of basic proficiency in Dutch; or participation in a concurrent study with NP testing and/or health-related QOL assessments. Patients with progressive disease during the course of the study were not automatically excluded from additional participation; this decision was left up to the individual patient.

Medically eligible patients were invited by their physicians to undergo screening for cognitive eligibility (Fig 1). They were screened first via a telephone interview for the presence of subjective cognitive symptoms. Those who reported at least one cognitive symptom from the Medical Outcomes Study (MOS) Cognitive Functioning Scale (CFS)[13] (Table 1) and who indicated interest in participating in a CRP were referred for objective NP testing. Patients who scored at least one standard deviation less than the mean of a healthy comparison group (N = 294)[35] on at least four of 20 objective NP test variables were considered eligible. By employing both subjective and objective cognitive eligibility criteria, it was possible to identify patients who would both be motivated to participate and who would potentially benefit from the CRP.

Patients were assigned to the intervention group or to a waiting-list control group by means of the minimization method,[36] which balanced on age, sex, education, tumor grade, hemisphere, radiotherapy, neurosurgery, disease duration, and institution.

To evaluate the effect of the CRP, a battery of NP tests and self-report questionnaires was administered at baseline, directly after cognitive rehabilitation (or an equivalent time point for the control group), and at the 6-month follow-up. Participants were offered the choice of undergoing the NPAs and the CRP sessions in their home or at their hospital. The trial was approved by the institutional review boards of all participating hospitals, and all patients provided written, informed consent.

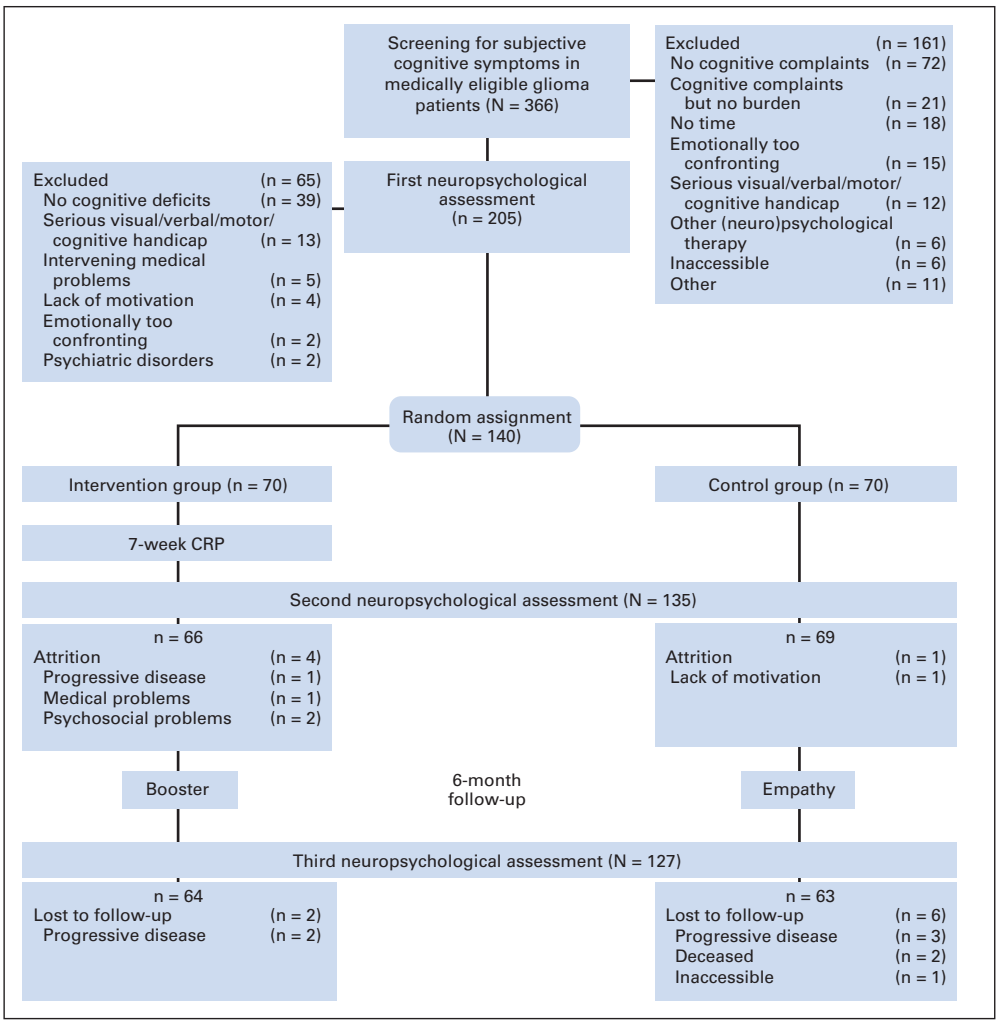

Fig 1. Flow of participants through the trial (enrollment and attrition). CRP, cognitive rehabilitation program.

Table 1. Objective and Subjective Outcome Measures

Test Name	Subscore or Subtest	Parameter Measured
	Objective measures	
Screening tests		
DART (Dutch Adult Reading Test)*[14]		Premorbid intelligence
DMT (Drie-Minuten-Toets) [Three-Minute-Test][15]		Reading abilities
SCWT (Stroop Color-Word Test)*[16,17]	Subtests: Card I, card II, card III, interference	Attention, information processing speed, mental control
LDST (Letter Digit Substitution Test)*[18]	Subtests: Writing, reading, motor	Attention, information processing speed, psychomotor speed
MST (Memory Scanning Test)*[19]	Subscores: Slope, intercept	Speed of memory processes
VVLT (Visual Verbal Learning Test), direct and delayed recall*[20]	Subscores: Trial 1, max, delta, total, delayed recall, recognition	Verbal learning and memory
CST (Concept Shifting Test)*[21]	Subtests: CST-A, CST-B, CST-C, CST-motor	Attention, executive functioning, psychomotor speed
CF (Category Fluency) animals, from the GIT*[22]	Subscore: Number correct	Speed and flexibility of verbal thought process and application of strategies
Neuropsychological tests for the evaluation of intervention effects		
Attention		
SCWT*[16,17]	Subtest: Card III (time in seconds)‡	Attentional inhibition of a dominant response
DS (Digit Span) from the WAIS-R[23]	Forward (span: 0-8)†	Immediate verbal recall
	Backward (span: 0-7)†	Working memory
LDST*[18]	90 Sec writing (number correct: 0-125)†	Psychomotor speed and speed of information processing
MST*[19]	Slope (time score)‡	Time needed for memory scanning
	Intercept (time score)‡	Time to complete nonmemory stages
TEA (Test of Everyday Attention)[24]	El-Dis (Elevator counting with distraction; number correct: 0-10)†	Auditory selective attention and working memory
Verbal memory		
VVLT, direct and delayed recall*[20]	Trial 1 (number correct: 0-15)†	Immediate verbal span
	Delta (number correct: 0-15)‡	Verbal learning effect
	Delayed recall (number correct: 0-15)†	Verbal memory after an interval
Executive functions		
CST*[21]	Subtest: CST-C (time in seconds)‡	Alternating attention
LF (Letter Fluency)[25]	Score: Number correct (0-∞)†	Speed and flexibility of verbal thought process
CF animals* and professions, from the GIT[22]	Score: Number correct (0-∞)†	Speed and flexibility of verbal thought process and application of strategies
BADS (Behavioural Assessment of the Dysexecutive Syndrome)[26,27]	Subtest: Zoo map (profile score: 0-4)†	Planning and priority setting
TEA (Test of Everyday Attention)[24]	El-Rev (Elevator counting with reversal; number correct: 0-10)†	Auditory working memory
	Tel+Count (Telephone search while counting; decrement in speed due to 2nd task)†	Divided attention
	Subjective measures	
Cognitive symptoms		
CFS (Cognitive Functioning Scale) from the MOS[13]	Total score (6-36)†	Frequency of cognitive complaints
Burden (study-specific measure)	Total (3-18)† of three questions on the impact of cognitive complaints on daily life, worry about cognitive complaints, being troubled by the cognitive complaints	Burden of CFS complaints
CFQ (Cognitive Failure Questionnaire)[28,29]	Total score (0-100)‡	Cognitive failures in daily life
SF-36 (Short-Form 36) from the MOS[30,31]	Mental component summary score (Mean = 50: SD = 10)†	Mental health–related quality of life
MFI (Multidimensional Fatigue Inventory)[32]	Mental fatigue, reduced activity, reduced motivation (4-20)‡	Mental aspects of fatigue
CIQ (Community Integration Questionnaire)[33]	Home integration (0-10), social integration (0-12), productivity (0-7)†	Integration in community
Additional subjective measures		
Motivation	Study-specific measure administered for screening purposes	Motivation to participate in the CRP
Evaluation	Study-specific evaluation form administered after completion of the CRP	Patients' evaluation of the CRP

Screening tests used available normative data (from a sample of 294 individuals comparable to study sample based on age, sex and education.[35] Neuropsychological tests were specifically selected for evaluation of possible intervention effects. Subjective measures were self-report questionnaires. Not all screening variables were used as evaluation variables, as some of the screening measures were considered as less relevant for the evaluation of the intervention effect and some other variables did not meet the assumptions for doubly multivariate repeated measures analyses of covariance. Not all tests for evaluation of intervention effects were used as screening measures because of a lack of normative data.

Abbreviations: GIT; Groningen Intelligence Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised; MOS, Medical Outcomes Study; CRP, cognitive rehabilitation program.

*Klein.[34]

†Higher scores indicate better performance.

‡Higher scores indicate worse performance. Score or scale ranges are in parentheses; ∞ indicates score has no upper limit.

CRP

The CRP consisted of six weekly, individual sessions of 2 hours each. The intervention, carried out by one of seven neuropsychologists, incorporated both cognitive retraining and compensation training (Table 2). For the retraining component, a computer program (C-Car[37]) was developed, which consisted of a series of hierarchically graded tasks designed to strengthen various aspects of attention on the basis of patient needs. The program focused on attention, because attention deficits are frequently experienced by patients with gliomas,[38,39] and rehabilitation of attention deficits also may have a salutary effect on other cognitive domains.[40-43] The compensation training component consisted of six psychoeducation sessions that addressed attention, memory, and executive function. These sessions included both didactic and practical elements aimed at helping patients compensate for impaired cognitive functions.

Additional weekly homework assignments consisted of computer-based attention retraining exercises and of logs kept about experiences with applying compensatory strategies in daily life. Approximately 3 months after completion of the CRP, participants had a telephone-based booster session, during which key aspects of the compensation training were re-emphasized.

Control Condition

The waiting-list control group received usual care (ie, regular medical follow-up; no cognitive interventions). Contact with the research staff was at similar intervals as the intervention group, except for the CRP sessions. Control-group patients also received a telephone-based empathy session, during which attention was paid to possible cognitive problems but without explicit advice as to how to deal with them. At completion of the study, participants in the control group were offered the opportunity to undergo the CRP.

Study Measures

Sociodemographic data, including age, sex, and education, were obtained via personal interview. Clinical variables, including tumor characteristics, treatment history, and antiepileptic drug use, were obtained from the medical records.

An extensive battery of NP tests (Table 1) was administered to objectively assess attention, verbal memory, and executive function. Also included were two tests to identify patients with a premorbid IQ less than 85 and/or serious reading problems.

Two self-report questionnaires (Table 1) were used to assess subjective cognitive symptoms and functioning: the MOS CFS,[13] supplemented by three additional questions on perceived symptom burden (ie, burden) and two questions on motivation to participate in the CRP; and the Cognitive Failure Questionnaire (CFQ), which assessed cognitive problems in daily life.[28,29] Other self-report measures included the three mental subscales of the Multidimensional Fatigue Inventory (MFI),[32] the mental component summary score (MCS) of the Short-Form 36 (SF-36) Health Survey,[30,31] and the three subscales of the Community Integration Questionnaire (CIQ).[33] After completion of the CRP, patients in the intervention group were queried about their experiences with the program. The NP assessors were blinded to group allocation.

Sample Size Calculations and Statistical Methods

With α set at .05, power at .80, and a minimal Cohen's effect size for between-group differences (d) in the primary outcomes of 0.50, a minimum of 64 patients per group was required.[44] Independent t tests, χ^2 tests, and Mann-Whitney tests were used to compare group baseline characteristics and to select possible covariates. For the primary statistical analysis, a hierarchical approach

Table 2. Description of the Cognitive Rehabilitation Program

Overall description
Six weekly, individual sessions of approximately 2 hours, plus several hours of homework, provided by a neuropsychologist. Both compensatory strategies (for attention, memory, and executive functioning) and (computer-based attention) retraining
Compensation training
Six integrated psychoeducational lessons addressing attention, memory, and executive function ("planning"), with both didactic and practical/experiential elements. Text chapter was read in advance of the session, the content was discussed in that specific session, and homework was completed afterward and discussed at the start of the next session
Session 1: Cognitive problems; methods of cognitive rehabilitation; compensation: factors influencing cognitive functioning (homework example: keeping a daily log of cognitive problems encountered in daily life)
Session 2: The cognitive functions attention, memory and executive functioning and their interrelationships; compensation techniques: general conditions, strategies and external devices to improve functioning; relaxation exercises (homework examples: finding strategies for cognitive problems noted in daily log; finding personal situations for application of the general conditions, strategies and devices in daily life)
Session 3: Attention and its relevance; strategies for selective, sustained attention, alternating attention, and divided attention; psychological factors of influence (homework example: matching strategies to personal situations, eg, for preventing external distraction)
Session 4: Planning and regulation; designing a plan; strategies for planning an activity; strategies for planning multiple activities (homework examples: application of the 'Seven-Steps-of-Planning-Scheme', planning a busy day)
Session 5: Memory and its functioning; conditions, strategies and external devices (homework example: keeping a log of memory problems and the application of memory strategies to them)
Session 6: Summary of the five former sessions: general overview of the compensation training, re-emphasis of specific conditions, strategies and devices to improve functioning (no homework)
Retraining
For the retraining component, a computer program, 'C-Car' (Concentration Car[16]), was developed by the research team in close collaboration with NeuroCognitief Centrum Nederland
Training of four aspects of attention:
Sustained (prolongation of exercises)
Selective (addition of distraction)
Alternating (alternation between exercises)
Divided (performing multiple tasks simultaneously)
Attractive "game-like" platform (driving an old-timer car and processing information from road signs in changing landscapes)
Exercises in both the visual and the auditory modality; verbal and nonverbal exercises
Tailored to the needs of the individual patient by hierarchical grading of tasks: As soon as the patient has mastered preliminary attentional skills, higher level skills are trained
Real-time feedback to the patient
Automatic registration of a number of outcome variables
Primarily consisting of homework: Exercising ("whenever, wherever") by using a notebook computer

Table 3. Patient Demographics and Disease Characteristics

Characteristic	Intervention Group	Control Group	No. of Patients: Intervention Group	No. of Patients: Control Group	*P*
Available for evaluation			70	70	
Age in years*					.303
Mean	42.0	43.8			
Standard deviation	9.4	10.5			
Sex†					.864
Male			41	40	
Female			29	30	
Education†					.898
Low			12	10	
Medium			26	27	
High			32	33	
Disease duration in years‡					.697
Median	5.2	6.1			
Range	38.1	28.3			
Tumor grade†					.820
Low grade (2)			58	59	
Anaplastic (3)			12	11	
Tumor classification†					.953
Astrocytoma			32	35	
Oligodendroglioma			24	21	
Oligoastrocytoma			10	10	
Presumed glioma			4	4	
Hemisphere†					1.000
Left			39	39	
Right			29	29	
Bilateral			2	2	
Surgery†					.931
No			4	4	
Biopsy			21	19	
Resection			45	47	
Cranial irradiation†					1.000
No			27	27	
Yes			43	43	
Chemotherapy†					.785
No			62	63	
Yes			8	7	
Years since last tumor treatment‡					.495
Median	2.6	3.1			
Range	20.6	14.1			
No. of epileptic seizures in the past year‡					.760
Median	2.0	2.0			
Range	2,500	780			
Antiepileptic drugs†					.494
No			10	13	
Yes			60	57	
No. of test scores ≥ 1 SD below the norm group mean*					.732
Mean	7	7			
SD	13	15			
Progressive disease at NPA2 (N = 135)†					.178
No			59	56	
Yes			7	13	
Progressive disease at NPA3 (N = 127)†§					.007
No			57	44	
Yes			7	19	

The following factors were used for stratification in minimization: patient age, sex, and education; disease duration; tumor grade; hemisphere; surgery; cranial irradiation; and institution (not shown).

Abbreviations: SD, standard deviation; NPA2/3, second/third neuropsychological assessment.

*Independent-samples *t* test.

†Pearson's χ^2 test.

‡Mann-Whitney test.

§Total number of patients in the intervention group with progressive disease at NPA3 = 7 (7 with PD at NPA2 − 2 who subsequently discontinued study participation (see Fig 1) + 2 diagnosed with PD between NPA2 and NPA3). Total number of patients in the control group with progressive disease at NPA3 = 19 (13 with PD at NPA2-3 who subsequently discontinued study participation (Fig 1) + 9 diagnosed with PD between NPA2 and NPA3).

Table 4. Immediate and Longer Term Effects of Cognitive Rehabilitation on Neuropsychological Measures in Patients With Gliomas

	NPA1 N = 140						NPA2 N = 135				Immediate Effects				NPA3 N = 127				Longer Term Effects		
	Intervention Group			Control Group			Intervention Group		Control Group		*P*				Intervention Group		Control Group		*P*		Effect
Outcome Measure	Mean	SD	Z ≤ −1	Mean	SD	Z ≤ −1	Mean	SD	Mean	SD	Step 1	Step 2	Step 3	Effect Size *d*	Mean	SD	Mean	SD	Step 2	Step 3	Size *d*
Attention																					
Step 1											.028										
Step 2												.463							.004		
SCWT card III	110.94	41.28	44%	119.97	53.92	54%	103.93	37.40	103.29	31.20			—		103.16	32.61	110.62	27.20		.041	0.23
DS																					
Forward	5.23	1.08	*	5.14	0.98	*	5.52	1.46	5.52	1.21			—		5.53	1.19	5.17	0.99		.004	0.43
Backward	4.49	1.09	*	4.29	0.95	*	4.64	1.36	4.30	1.13			—		4.74	1.23	4.18	1.02		.001	0.55
LDST 90 sec writing	43.23	8.74	66%	42.19	9.04	64%	48.49	7.66	47.05	6.39			—		49.38	8.02	47.12	6.69		.010	0.26
MST																					
Slope	16.05	10.49	24%	14.67	7.54	24%	13.61	6.73	13.86	5.61			—		13.82	7.33	15.72	6.12		.095	
Intercept	28.83	8.43	53%	30.67	9.75	54%	27.76	9.25	27.91	7.72			—		28.09	8.24	28.15	6.87		.692	
TEA El-Dis	7.32	2.75	*	7.26	2.69	*	8.33	2.39	8.08	1.99			—		8.32	2.67	7.79	2.23		.078	
Verbal memory																					
Step 1											.015										
Step 2												.323	—						.009		
VVLT																					
Trial 1	5.77	2.29	13%	5.61	1.66	11%	7.68	2.55	7.46	2.10			—		8.82	2.78	7.86	2.29		.003	0.48
Delayed recall	9.17	3.19	27%	8.94	2.95	34%	11.34	3.14	10.87	2.58			—		12.08	3.32	10.79	2.74		.002	0.43
Delta	6.20	2.21	34%	5.94	1.70	39%	5.80	2.78	5.38	2.29			—		4.61	2.62	5.00	2.16		.226	
Executive functions step 1											.218	—						—			
CST-C	37.13	15.50	34%	39.41	17.30	41%	30.52	17.17	33.22	13.52			—		35.91	19.83	35.63	16.26		—	
LF	19.41	8.37	*	18.91	8.51	*	21.29	7.29	21.69	5.98			—		20.59	8.87	20.77	7.27		—	
CF	35.79	7.86	43%	37.31	9.41	33%	37.88	9.48	37.56	7.78			—		38.61	8.55	36.12	7.01		—	
BADS Zoo map	2.21	1.24	*	2.17	1.30	*	2.46	1.57	2.34	1.29			—		2.76	1.57	2.46	1.29		—	
TEA El-Rev	4.64	3.01	*	3.74	2.78	*	5.68	3.10	5.78	2.54			—		6.34	3.28	5.35	2.70		—	
TEA Tel+Count	1.87	2.76	*	3.79	7.79	*	1.52	3.28	1.40	2.69			—		1.19	2.49	1.30	2.04		—	

For first neuropsychological assessment (NPA1), raw unadjusted means are shown; for NPA2 and NPA3, means are corrected for covariates. Dashes indicate that models at steps 2 and 3 were not performed because of a statistically nonsignificant result in the prior step.

Abbreviations: Z ≤ −1, percentage of patients out of 70 with score of at least 1 SD below the norm group mean; SD, standard deviation; SCWT, Stroop Color-Word Test; DS, Digit Span; LDST, Letter Digit Substitution Test; MST, Memory Scanning Test; TEA, Test of Everyday Attention; El-Dis, Elevator Counting with Distraction; VVLT, Visual Verbal Learning Test; CST, Concept Shifting Test; LF, Letter Fluency; CF, Category Fluency; BADS, Behavioural Assessment of the Dysexecutive Syndrome; El-Rev, Elevator Counting With Reversal; Tel+Count, Telephone Search While Counting.

*No norm group data available.

was used to minimize the possibility of type I errors as a result of multiple testing. First (ie, step 1), six doubly multivariate, repeated-measures analyses of covariance (ANCOVAs)[45] were conducted on conceptually related objective and subjective measures to investigate group differences over time. The NP tests were clustered into attention, memory, and executive functioning domains (Table 1). The CFS, burden questionnaire, and CFQ were analyzed together, as were the three MFI subscales and the three CIQ subscales. The SF-36 MCS was analyzed separately by using repeated measures ANCOVA.

In step 2, those sets of outcomes that yielded statistically significant between-group differences on the basis of the doubly multivariate, repeated-measures ANCOVAs were submitted to additional statistical testing using multivariate analyses of covariance (MANCOVAs) to determine if observed group differences were present at immediate postintervention and/or at the 6-month follow-up.

In step 3, in those grouped variables for which the simple MANCOVAs yielded significant results at immediate postintervention and/or at 6-month follow-up, a series of ANCOVAs was carried out separately for the individual outcome measures.

In all analyses, relevant baseline values (eg, baseline memory scores when memory test variables were the dependent variables) and possible confounders (eg, disease progression) were included as covariates. The magnitude of statistically significant group differences as analyzed by the ANCOVAs was calculated according to the formula for generalized eta-squared[46] and was converted to Cohen's *d* statistic.[44] According to Cohen's guidelines,[44] an effect size of 0.20 was considered small, 0.50 was medium, and 0.80 was large.

Additionally, group differences in the proportion of patients that no longer met our criteria for cognitive impairment at both follow-up assessments were analyzed with χ^2 tests. Finally, a subgroup analysis was performed, which excluded patients who experienced disease progression during the course of the study, and a sensitivity analysis was carried out to determine whether the timing of disease progression had an effect on immediate or long-term outcomes.

For all statistical tests, SPSS 15.0.1 (SPSS Inc, Chicago, IL) was used, and *P* less than .05 was considered statistically significant.

RESULTS

Patient Recruitment

Patients were enrolled from November 2004 until December 2006. After various levels of screening (Fig 1), 140 eligible patients were randomly assigned to the intervention group or to the waiting-list control group. During the course of the study, 13 patients (six in the intervention group; seven in the control group) were lost to follow-up, primarily as a result of progressive disease.

Table 5. Immediate and Longer Term Effects of Cognitive Rehabilitation on Subjective Measures in Patients With Gliomas

					Immediate Effects						Longer Term Effects		
	NPA1 (N = 140)		NPA2 (N = 135)		*P*				NPA3 (N = 127)		*P*		
Outcome Measure	Intervention Group	Control Group	Intervention Group	Control Group	Step 1	Step 2	Step 3	Effect Size *d*	Intervention Group	Control Group	Step 2	Step 3	Effect Size *d*
Cognitive symptoms													
Step 1					.003								
Step 2						.001					.311		
CFS total							.000	0.48				—	
Mean	21.01	22.07	25.75	23.34					24.44	23.78			
SD	4.24	4.63	4.50	3.77					6.21	5.20			
Burden total							.009	0.38				—	
Mean	9.81	10.76	11.98	10.68					11.96	11.47			
SD	2.85	3.15	3.49	2.93					4.21	3.52			
CFQ total							.014	0.31				—	
Mean	47.99	45.99	38.33	43.60					37.58	41.32			
SD	10.31	14.22	12.56	10.52					14.07	11.78			
SF-36 step 1					.165	—							
MCS							—				—		
Mean	42.03*	46.35	46.94	44.21					45.14	43.63			
SD	10.34	9.72	10.68	9.15					12.37	10.60			
MFI													
Step 1					.049								
Step 2						.370					.044		
Mental fatigue												.026	0.41
Mean	15.33*	13.87	11.51	11.44					11.04	11.73			
SD	3.09	4.02	2.42	1.97					2.55	2.08			
Reduced activity												.816	
Mean	12.93*	10.57	12.73	12.18					12.20	12.11			
SD	4.44	4.64	2.25	1.83					2.28	1.86			
Reduced motivation												.063	
Mean	10.94	9.18	11.70	11.88					11.41	12.07			
SD	3.74*	3.67	3.02	2.46					2.65	2.16			
CIQ step 1					0.980	—					—		
Home integration							—					—	
Mean	5.79	5.85	5.97	6.02					5.68	5.75			
SD	2.75	2.77	1.82	1.51					2.05	1.70			
Social integration							—					—	
Mean	8.63	8.63	9.05	8.78					8.65	8.43			
SD	2.42	2.17	2.02	1.68					2.43	2.01			
Productivity							—					—	
Mean	4.03	4.00	4.23	4.21					3.70	3.71			
SD	1.83	1.90	1.25	1.04					1.63	1.35			

For first neuropsychological assessment (NPA1), raw unadjusted means are shown; for NPA2 and NPA3, means are corrected for covariates. Dashes indicate that models at steps 2 and 3 were not performed because of a statistically nonsignificant result in the prior step.

Abbreviations: NPA, neuropsychological assessment; CFS, Cognitive Functioning Scale; SD, standard deviation; CFQ, Cognitive Failure Questionnaire; SF-36, Medical Outcomes Study Short-Form 36; Mental CS, Mental Component Summary of the Mental Outcomes Study SF-36; MFI, Multidimensional Fatigue Inventory; CIQ, Community Integration Questionnaire.

*Statistically significant group difference at baseline $\alpha = .05$.

Sociodemographic and Clinical Characteristics

No statistically significant differences were observed between groups in sociodemographic or baseline clinical characteristics (Table 3). However, at the third assessment, the incidence of progressive disease was significantly higher in the control group (Table 3). As disease progression at this third assessment was related significantly to two of the outcomes (MFI reduced motivation [$P = .030$] and CIQ total score [$P = .008$], we employed it as a time-varying covariate in all step-1 analyses. For steps 2 and 3, we employed progression at the second NPA (NPA2) as a covariate for the short-term interval (NPA2 − NPA1) analyses, and progression at the third NPA (NPA3) for the long-term interval (NPA3 − NPA1) analyses.

Baseline NP and Subjective Measures

There were no statistically significant between-group differences in baseline NP test scores (Table 4). However, the intervention group scored significantly worse at baseline on the MFI scales and on the SF-36 MCS (Table 5). As stated in the Patients and Methods section, all baseline scores on the NP tests and subjective measures that were

directly related to the dependent variables were also included as covariates in the analyses.

Overall Effects

Significant group differences over time were observed for objective NP measures of attention ($P = .028$) and verbal memory ($P = .015$; Table 4; Fig 2). Differences in measures of executive functioning were not statistically significant.

For the subjective measures (Table 5; Fig 2), a significant group difference over time was found for the combined analysis of the CFS total score, burden, and CFQ total score ($P = .003$) and for mental aspects of fatigue ($P = .049$). There were no statistically significant group differences over time for the remaining self-report measures.

As these initial analyses had a gatekeeper function, additional statistical testing was carried out only for test scores of attention and verbal memory (Table 4) and for the self-reported measures of cognitive functioning and mental fatigue (Table 5).

Short-Term NP Outcomes

Immediately post-treatment, there were no statistically significant group differences in attention or verbal memory scores. Both study arms showed similar improvement in most of the attention and memory tests (Fig 2), and the percentage of patients that no longer met criteria for cognitive impairment did not differ between groups (28% *v* 30% in the intervention and control group, respectively; $P = .801$).

Long-Term NP Outcomes

At the 6-month follow-up, a statistically significant group difference was found for the combined attention tests ($P = .004$). Four of the seven individual attention tests yielded significant

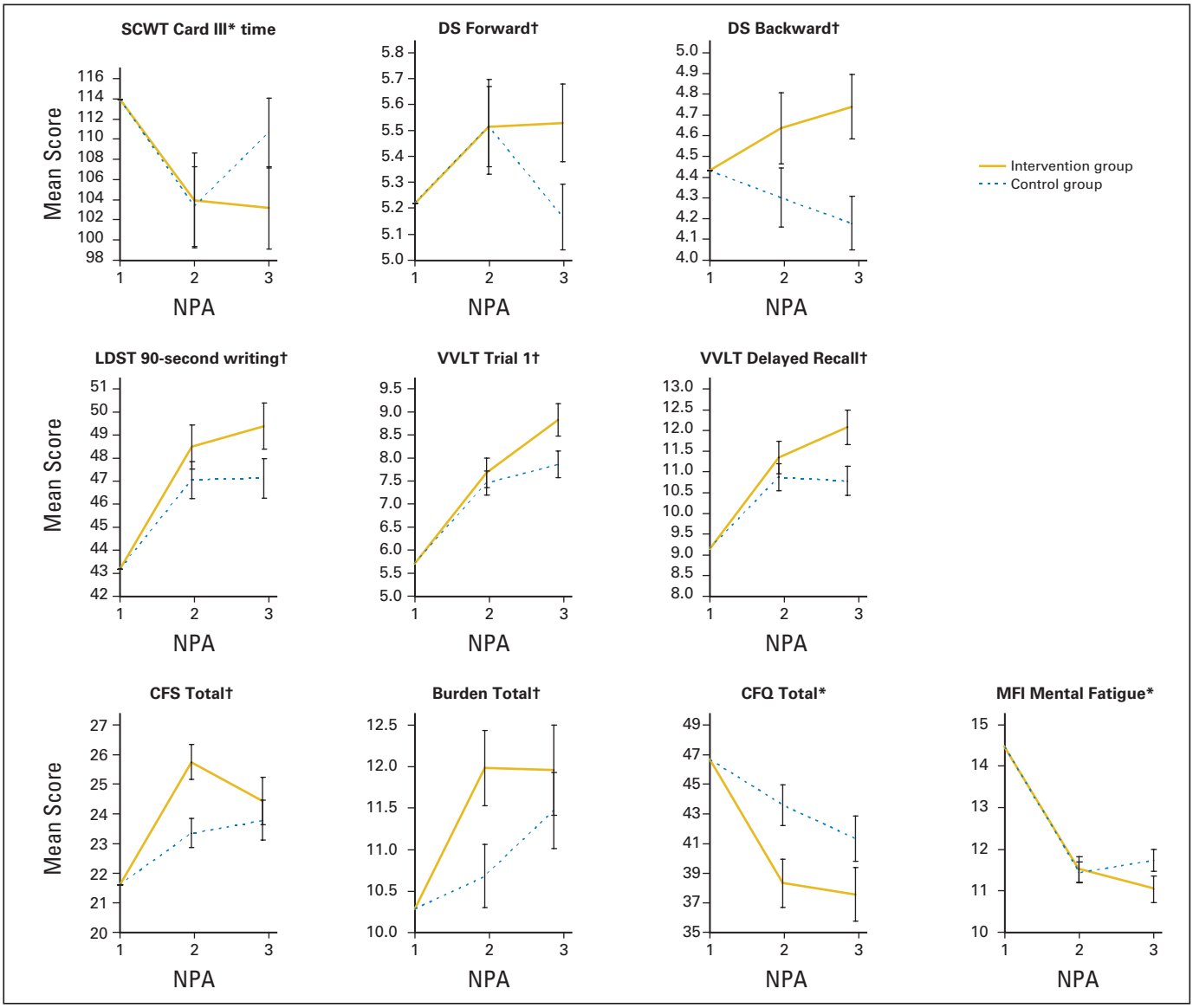

Fig 2. Corrected means and standard errors (bars) of significant objective and subjective intervention effects (N = 127). SCWT, Stroop Color-Word Test; DS, Digit Span; LDST, Letter-Digit Substitution Test; VVLT, Visual Verbal Learning Test; CFS, Cognitive Functioning Scale; CFQ, Cognitive Failure Questionnaire; MFI, Multidimensional Fatigue Inventory. (*)Higher scores indicate better performance. (†)Higher scores indicate worse performance.

group differences that favored the CRP group, and effect sizes ranged from 0.23 to 0.55.

Similarly, significant group differences were observed for the combined tests of verbal memory ($P = .009$), and two of the three individual variables yielded significant results that favored the CRP group (effect sizes, 0.48 and 0.43).

The percentage of patients who no longer met criteria for cognitive impairment at the 6-month assessment was 39% in the intervention group versus 21% in the control group ($P = .027$).

Short-Term Subjective Outcomes

Immediately post-treatment, statistically significant differences that favored the intervention group were found in self-reported cognitive functioning (CFS, burden, and CFQ; $P = .001$), and effect sizes ranged from 0.31 to 0.48. There were no significant, short-term group differences in mental fatigue scores.

Long-Term Subjective Outcomes

At the 6-month follow-up, there were no longer statistically significant group differences in self-reported cognitive functioning. The pattern of results (Fig 2) suggests that the CRP group largely maintained its gains in self-reported cognitive functioning, whereas the control group exhibited continued gains over time. Statistically significant group differences that favored the intervention group were observed for the MFI scales ($P = .044$), in particular for mental fatigue (effect size, 0.41).

Subgroup and Sensitivity Analyses

As the number of patients whose disease progressed during the study differed between the groups, a subgroup analysis was performed in which patients with progressive disease (n = 26) were excluded. The results indicated significant intervention effects for verbal memory ($P = .048$) and subjective cognitive functioning ($P = .008$). Group differences in attention and mental fatigue were no longer statistically significant. However, it should be noted that these analyses had substantially less statistical power because of the reduced sample size (n = 101 *v* n = 127 in the primary analysis).

A sensitivity analysis was performed (N = 127), in which it was assumed that progression occurred either at NPA2 or at NPA3. The *P* values for these (ie, step 2) MANCOVAs per domain were all in the same range (data not shown). This indicated that the timing of disease progression did not affect immediate or long-term outcomes.

Patient Evaluations of CRP

Eighty percent of the patients in the CRP group reported that the content of the program largely/completely addressed their cognitive problems, 87% used the learned compensation strategies regularly/often in daily life, and 79% indicated a decrease in the impact of cognitive problems on daily functioning.

DISCUSSION

In this trial we observed significant improvement in self-reported cognitive functioning at the immediate postintervention assessment, but not at the 6-month follow-up. Conversely, although no significant group differences in NP test scores were observed at the immediate postintervention, clear differences in attention and verbal memory were found at the 6-month follow-up. The magnitude of the observed effects was moderate. Consistent with these results, the percentage of patients who no longer met criteria for cognitive impairment was similar for both groups at the immediate post-treatment, but the percentage was significantly higher in the CRP group at the 6-month follow-up. Significant intervention effects were also found for long-term mental fatigue scores. The CRP did not have a significant effect on self-reported mental health–related QOL or community integration.

The absence of a significant group effect for the objective NP measures immediately after the intervention may reflect the fact that both study arms exhibited improved objective cognitive performance (ie, attention and memory) in the short term. A practice effect (ie, improved test performance as a result of repeated NP test completion), or regression to the mean, may have initially overwhelmed any intervention effect. At the 6-month assessment, the CRP group exhibited continued improvement in objective cognitive performance, whereas the control group did not. This delayed salutary intervention effect on cognitive performance may indicate that patients require a longer period of time to integrate learned strategies into their daily routine.[47-49]

The positive effects observed on mental fatigue may reflect a direct effect of the intervention (ie, learned time management strategies) or an indirect effect that results from improved cognitive functioning.

The fact that significant group differences were observed in self-reported cognitive functioning in the short term but not in the long term should be interpreted in light of the pattern of change over time. The CRP group reported a significant improvement in self-reported cognitive functioning early on, and this was largely maintained through to the 6-month follow-up. The control group exhibited a smaller, more gradual improvement in self-reported cognitive functioning over time, which might reflect a combination of regression to the mean,[50] response shift,[51] and natural recovery (eg,[52,53]).

The discrepancy observed between objective and subjective cognitive measures is consistent with results of earlier studies among patients with cancer and with other neurologic disorders.[54,55] In general, self-reported cognitive functioning tends to correlate more highly with self-reported measures of distress and with well-being than with objective NP tests.[56-58]

Several possible limitations of the study should be noted. First, the study included a relatively large number of outcome measures. This was necessary, given the complex nature of the phenomena under investigation and the current state-of-the-art of NPA. To minimize the possibility of type I errors, we employed a hierarchical approach to the statistical analysis.

Second, the study results can only be generalized to glioma patients who both report having cognitive symptoms and score below a predetermined cutoff on objective NP tests. They may not apply to patients who have significant cognitive impairment on the basis of objective test results, but who do not report cognitive symptoms. Also, the results may apply only to patients with relatively mild deficits, similar to the group studied, who have sufficient cognitive resources and motivation to follow the rehabilitation program. Finally, the study could not tease out the relative effectiveness of cognitive retraining versus the use of compensatory strategies.

In conclusion, this first, randomized, controlled trial of cognitive rehabilitation in patients with gliomas provides initial evidence of a

salutary effect on short-term cognitive complaints and on longer-term cognitive performance and mental fatigue. Future trials are needed to more clearly identify the most effective elements in such a program, to determine how to achieve a sustained, positive effect on cognitive problems in daily life, and to determine the value of such a CRP when used with other patient populations with NP deficits.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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