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A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept

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Abstract

Background. Patients with glioma often suffer from cognitive deficits. Physical exercise has been effective in ameliorating cognitive deficits in older adults and neurological patients. This pilot randomized controlled trial (RCT) explored the possible impact of an exercise intervention, designed to improve cognitive functioning in glioma patients, regarding cognitive test performance and patient-reported outcomes (PROs).

Methods. Thirty-four clinically stable patients with World Health Organization grades II/III glioma were randomized to a home-based remotely coached exercise group or an active control group. Patients exercised 3 times per week for 20–45 minutes, with moderate to vigorous intensity, during 6 months. At baseline and immediate follow-up, cognitive performance and PROs were assessed with neuropsychological tests and questionnaires, respectively. Linear regression analyses were used to estimate effect sizes of potential between-group differences in cognitive performance and PROs at 6 months.

Results. The exercise group ($n = 21$) had small- to medium-sized better follow-up scores than the control group ($n = 11$) on several measures of attention and information processing speed, verbal memory, and executive function, whereas the control group showed a slightly better score on a measure of sustained selective attention. The exercise group also demonstrated small- to medium-sized better outcomes on measures of self-reported cognitive symptoms, fatigue, sleep, mood, and mental health–related quality of life.

Conclusions. This small exploratory RCT in glioma patients provides a proof of concept with respect to improvement of cognitive functioning and PROs after aerobic exercise, and warrants larger exercise trials in brain tumor patients.

Key Points

1. Proof of concept: Exercise may improve cognitive function in glioma patients.
2. Exercise may benefit patient-reported outcomes in glioma patients.
3. Larger trials of exercise for cognitive improvement in glioma patients are warranted.

Importance of the Study

Few efforts have been undertaken to ameliorate the cognitive impairment in glioma patients despite patients' relatively young age and rather favorable prognosis. Physical exercise has been effective in ameliorating cognitive deficits in older individuals and neurological patients and in improving quality of life of cancer patients. Therefore, exercise is a promising intervention that may address multiple brain cancer symptoms, including cognitive impairment. We conducted a small RCT of a 6-month home-based remotely coached aerobic exercise program that specifically aimed for amelioration of cognitive deficits in glioma patients. In a previous feasibility evaluation in the sample of motivated patients, adherence and patient satisfaction were good. Although statistical testing was limited by small groups, the current study provides a proof of concept regarding physical fitness, cognitive test performance and cognitive symptoms, fatigue, sleep, mood, and quality of life. This study provides practical suggestions for future larger exercise trials in brain tumor patients.

After initial medical treatment, many patients with lower-grade glioma at first glance seem to live free from neurological symptoms for years until the disease progresses. However, they may suffer from deficits in various cognitive domains, including attention, memory, executive functioning, and language, which primarily result from the tumor and its treatment.[1,2] Although in most cases the cognitive deficits, as determined by neuropsychological tests, are mild or moderate, they can substantially impact patients' lives. In particular during the progression-free period, these relatively young patients experience the effects of their cognitive impairment when they attempt to resume normal family, work, and social activities. Only few studies have evaluated interventions aimed at amelioration of cognitive impairment in patients with brain tumors. These have included behavioral interventions, such as cognitive rehabilitation, and pharmacological approaches.[3]

Research has indicated that physical exercise can be effective in delaying or ameliorating cognitive decline, in particular in healthy individuals and those suffering from dementia, but also in other patients with neurological disorders and, as most recently described, in patients with breast cancer.[4–7] Several neuroplastic mechanisms have been reported to be involved in exercise-related improvement (or maintenance) of brain/cognitive function.[4,8,9] These include enhancement of angiogenesis, synaptogenesis and neurogenesis, upregulation of neurotrophic factors, such as brain-derived neurotrophic factor, and anti-inflammatory effects.[4,8,9]

Very recently, researchers have begun to explore exercise interventions in single-arm studies with small samples of patients with brain tumors. These studies have demonstrated safety and feasibility and have provided indications of improvements on measures of well-being.[10–12] Interestingly, a recent crossover study on exercise for the improvement of neural recovery in 28 pediatric survivors of brain tumors demonstrated exercise-related increase of white matter integrity and hippocampal volume, and associated improvements in reaction time.[13]

Recently, we published the first findings on feasibility and intermediate outcomes in a small pilot randomized controlled trial (RCT) of an exercise intervention specifically aimed at the improvement (or maintenance) of cognitive functions in patients with lower-grade glioma. The 6-month, home-based intervention, including 3 aerobic exercise sessions per week with distant monitoring by a physical therapist, was found to be feasible in a group of motivated patients.[14] Patients adhered, on average, to 79% of the prescribed training sessions, and their experiences were positive. At 6 months follow-up, the exercise group showed larger improvements in aerobic fitness (volume of peak oxygen uptake [VO_2 peak][1]: +158.9 mL/min; 95% CI: −44.8 to 362.5) compared with the control group.

The study also included a battery of neuropsychological tests and patient-reported outcome (PRO) measures. Here, we evaluate indications of effects of the program at the group and individual level on cognitive performance scores of attention, memory, and executive function and at the group level on PROs (cognitive symptoms, fatigue, sleep, mood, and quality of life).

Patients and Methods

Study Design

The study was designed as a pilot RCT, in which 60 patients would be allocated in a 2:1 ratio to a 6 months of exercise intervention or a waiting-list control group. Treatment allocation was done by a computer program (ALEA[15]), using a minimization procedure[16] that balanced groups on age (<40, 40–50, >50), education (lower, higher), World Health Organization (WHO) tumor grade (II, III), disease duration (<5, ≥5 y), relative VO_2 classification (recreational physical activity, sedentary[17]) and performance on the letter-digit substitution task (≤43, >43[18]). Assessments of cardiorespiratory fitness, cognitive performance, and PROs were conducted before randomization and after 6 months. As the objective of this small exploratory study was not to test hypotheses, we evaluated effect sizes for group level comparisons.

Approval was obtained from the medical ethics committee Brabant, Netherlands (file NL44024.008.13). The trial was registered with www.clinicaltrials.gov: NCT02303938. All patients provided written informed consent.

[1] VO_2 peak was determined as the highest value of oxygen uptake achieved during a maximal incremental cycle ergometer test, and reflects the current aerobic capacity.

Participants

Patients were recruited from September 2013 until December 2014 from 3 Dutch hospitals: Elisabeth-TweeSteden Hospital Tilburg, Haaglanden Medical Center The Hague, and Erasmus Medical Center Rotterdam. Based on historical patient census data from these centers, we anticipated being able to recruit 60 patients into the study in the time available.

Adult patients were eligible for participation if they had: (i) histologically proven or presumed WHO grade II glioma or (ii) anaplastic (grade III) glioma and were clinically stable for a minimum of 6 months prior to study entry as determined by MRI. Other inclusion criteria were: a self-reported low or moderate level of physical activity (ie, less than 20 minutes of vigorous exercise on fewer than 3 days per week), access to the internet, basic fluency in the Dutch language, interest to participate in the physical exercise program, and a VO_2 peak, as assessed with maximal cardiopulmonary exercise testing (CPET), within the range of sedentary or recreationally active reference groups.[17]

Exclusion criteria were: anti-tumor treatment (ie, surgery, radiotherapy, chemotherapy, corticosteroids) within 6 months prior to study entry, use of beta-blockers, psychiatric or severe cognitive problems that would preclude program participation, and presence of comorbid conditions that contraindicate exercise without face-to face supervision as assessed with the Physical Activity Readiness Questionnaire (PAR-Q)[19] or as judged by the sports physician based on CPET.

Procedures

For a detailed description of study procedures, see Gehring et al.[14] Briefly, patients who were medically eligible received a study information letter from their physician and a reply card to indicate permission to be approached by the study team. Interested patients received a phone call to explain study procedures and to screen for physical activity level and safety of the exercise. Interested and eligible patients provided informed consent, underwent neuropsychological assessment (NPA) at their homes, and received questionnaires on PROs to be completed and returned by mail. Subsequently, patients were invited to undergo CPET at one of the 4 sports medical centers involved in the study.

Patients who were eligible according to all criteria were randomized and informed about their allocation by phone. After 6 months, NPA, PRO assessments, and CPETs were repeated. Neither patients nor assessors were blinded to group allocation, except for the sports physicians performing the CPETs. The decision to halt participation in case of progressive disease was left up to the patient and the treating physician.

Physical Exercise Intervention

The home-based, remotely coached intervention comprised 3 aerobic training sessions per week for a period of 6 months. Based on their baseline level of cardiorespiratory fitness and exercise tolerance, patients received an individual home-based exercise prescription regarding intensity (60–85% of their maximum heart rate) and duration (20 to 45 minutes) of the training sessions from the physical therapist. Exercise duration and intensity were progressed over the months. Patients could choose one or more activities of their own preference (eg, running, cycling, swimming) as long as they could meet the exercise prescription. During the activities, participants wore a training watch with heart rate monitor and Global Positioning System. This watch provided immediate feedback about heart rate and, if applicable, speed and distance, and could be connected to an online platform recording the activities. The physiotherapist could access these data and thereby guide the patients remotely on a weekly basis.

Waiting-List Control Condition

Patients in the active control group received a motivational brochure in the first week after randomization and at 3 months in which they were advised to maintain an active lifestyle in accordance with the Dutch public health guidelines.[20] They also received bimonthly phone calls during which general questions about their health were asked. This minimum intervention was intended to provide some control for attention effects. After completion of all study assessments, patients in the control group were offered a training watch and a general exercise prescription.

Outcome Measures

We obtained data on patients' age, sex, and level of education via interview and retrieved clinical information from medical records. We assessed cognitive performance of both study groups at the patients' homes at baseline (NPA1) and after 6 months (NPA2) with a battery of neuropsychological tests of attention, memory, and executive function (see Table 1). Subsequently, patients in both groups completed several PRO questionnaires on cognitive symptoms, fatigue, sleep, mood, and health-related and aspects of brain cancer–related quality of life (see Table 1).

Statistical Methods

Summary statistics for baseline characteristics with respect to sociodemographic and clinical variables, cognitive performance, and PROs were calculated for the 2 groups. In order to facilitate comparisons of the magnitude of group change over time across outcome measures, we standardized all NPA and PRO scores by subtracting the total group baseline mean score from each patient's individual score and dividing this by the total group baseline standard deviation. For this, we used "trimmed" means and standard deviations, by recalculating the baseline mean and standard deviations, leaving out raw scores equating Z scores > |3.29|.[39] When needed, we recoded scores so that, for all measures, higher Z scores indicate better outcomes. We present changes in Z scores from baseline to follow-up for both groups in bar charts.

No *a priori* level of statistical significance for between-group differences in outcome was set, as the objective of this exploratory pilot study with many outcome measures was

Table 1 NPA and PRO measures at baseline and follow-up

Cognitive Performance Measures			
Test	Abbreviation	Scores Used for Analysis (Score or Scale Range)	Domain Measured
Attention			
Stroop Color-Word Test[21–23]	SCWT-Int	Interference—ratio of the additional time needed for Card III relative to Card I (time) and II (time)	Attentional inhibition of a dominant response
Letter Digit Substitution Test[18]	LDST-Read	90 Sec Reading (number correct: 0–125)	Information processing speed
	LDST-Write	90 Sec Writing (number correct: 0–125)	Psychomotor and information processing speed
WAIS-R Digit span[24,25]	DS-Forw	Forward (span: 0–8)	Attention span
	DS-Backw	Backward (span: 0–7)	Working memory
Test of Everyday Attention[26]	ElevCount-Distr	Elevator counting with Distraction (number correct: 0–10)	Auditory selective attention and working memory
	TelSearch	Telephone Search task (time per target: 0–∞)	Sustained selective attention
	TelSearch-Count	Telephone Search while Counting (decrement in speed due to 2nd task)	Divided attention
Memory			
Visual Verbal Learning Test[27]	VVLT-T1	Trial 1 (number correct: 0–15)	Immediate verbal recall
	VVLT-Tot	Total (number correct: 0–75)	Verbal learning
	VVLT-DelRec	Delayed Recall (number correct: 0–15)	Delayed verbal memory
WMS-III Verbal Paired Associates[24]	VPA-DiRecA	Direct Recall List A (number correct: 0–8)	Immediate verbal association memory
	VPA-TotRec	Total Recall (number correct: 0–32)	Verbal association learning
	VPA-DelRec	Delayed Recall (number correct: 0–8)	Delayed verbal association memory
Executive function			
Concept Shifting Test[28,29]	CST-Shift	Additional time needed for CST-C above CST-A and CST-B	Alternating attention/shifting
GIT Letter Fluency[25]	GIT-LF	LF (number correct: 0-∞)	Speed and flexibility of verbal thought process
GIT Category Fluency[30]	GIT-CF	CF (number correct: 0-∞)	Speed and flexibility of verbal thought process and application of strategies
Test of Everyday Attention[26]	ElevCount-Rev	Elevator counting with Reversal (number correct: 0–10)	Auditory working memory/ shifting
Patient-reported outcome measures			
Questionnaire			
Subjective cognitive functioning			
MOS Cognitive Functioning Scale[31]	CFS total	Total score (6–30)	Subjective cognitive function
Cognitive Failure Questionnaire[32,33]	CFQ total	Total score (0–100)	Subjective cognitive failures in daily life
Subjective fatigue and sleep			
Multidimensional Fatigue Inventory[34]	MFI-GF	General Fatigue (4–20)	General fatigue
	MVI-PF	Physical Fatigue (4–20)	Physical fatigue
	MVI-RA	Reduced Activity (4–20)	Reduced activity
	MVI-RM	Reduced Motivation (4–20)	Reduced motivation
	MVI-MF	Mental Fatigue (4–20)	Mental fatigue
Pittsburgh Sleep Quality Index[35]	PSQI total	Total score (0–21)	Quality of sleep

Table 1 Continued

Patient-reported outcome measures			
Questionnaire	Abbreviation	Scores Used for Analysis (Score or Scale Range)	Domain Measured
Mood			
Profile of Mood States[36]	POMS total	Total score (22–120)	Mood
Quality of life			
Brain-cancer specific HRQL questionnaire[37]	QLQ-BN20 FU	Future Uncertainty (0–12)	Brain-cancer specific future uncertainty
	QLQ-BN20 VD	Visual Disorder (0–9)	Brain-cancer specific visual disorder
	QLQ-BN20 MD	Motor Dysfunction (0–9)	Brain-cancer specific motor dysfunction
	QLQ-BN20 CD	Communication Deficit (0–9)	Brain-cancer specific communication deficit
MOS Short-Form 36[38]	SF-36 PCS	Physical Component Scale (0–100)	Mental health–related quality of life
	SF-36 MCS	Mental Component Scale (0–100)	Physical health–related quality of life

∞: no upper limit.
Abbreviations: GIT, Groningen Intelligence Test. HRQL, health-related quality of life. MOS, Medical Outcomes Study. WAIS-R, Wechsler Adult Intelligence Scale–Revised. WMS-III, Wechsler Memory Scale III.

not to test a prespecified hypothesis. Instead, we present 95% confidence intervals (CIs) around estimates to indicate their precision and effect sizes for all group level comparisons. SPSS v24.0.0.0 was used for all group level comparisons.

Analyses of between-group differences in cognitive performance and PROs

As the primary approach to assessing potential intervention effects, we used linear regression analyses for all NPA and PRO scores at 6 months, including baseline scores as covariates. When an extreme baseline or follow-up Z score ($Z > |3.29|$) resulted in violation of an assumption, the outlier score was replaced by the less extreme value of $|3.29|$.[39] If the subsequent model met its assumptions, this value was used in the group level analyses.

Due to the standardization of scores, the beta coefficients of the regression analyses (ie, the between-group differences in outcome) are equal to Glass's delta effect sizes. Effect sizes ≥0.2 were considered small, between 0.50 and 0.79 medium, and ≥0.8 large. Results are reported in the text when effect sizes were ≥0.2.

Analyses of individual reliable cognitive change

Reliable change indices (RCIs) for all individual patients were calculated for changes in all NPA raw scores. A regression-based RCI[40] was employed, which takes common methodological confounds resulting from repeated neuropsychological testing into account, such as practice effects and imperfect test-retest reliabilities. We used neuropsychological data from the non-intervention control group from our previous RCT on cognitive rehabilitation to determine practice effects and test-retest reliabilities[41,42] for the interval from baseline to about 8 months follow-up. This non-intervention control group included 63 cross-sectionally recruited low-grade and anaplastic glioma patients. Extreme individual scores of patients from the current study were not replaced by alternative values in the calculations of their RCIs.

Individual change was defined by RCI values exceeding ±1.645 (corresponding with a 90% CI). The numbers of patients with reliably improved, declined, or nonchanged performance were compared between groups for each NPA variable. Standardized residuals were calculated, whereby values exceeding ±1.5 were used as cutoff for disproportionate distributions.

Results

Patient Recruitment and Retention

Thirty-four of 136 invited patients (25%) were recruited and allocated to the exercise ($N = 23$) or the control ($N = 11$) group. Fig. 1 displays detailed information on recruitment and retention. A more detailed description of reasons for non-participation can be found in Gehring et al.[14]

Two patients dropped out of the exercise group. There was no attrition in the control group before NPA2. In addition, one exercise group patient did not return self-report questionnaires. All control group patients returned completed questionnaires.

Baseline Characteristics

The patients in the intervention group ($n = 21$) and control group ($n = 11$) with complete NPA1 and NPA2 data were comparable with respect to baseline sociodemographic,

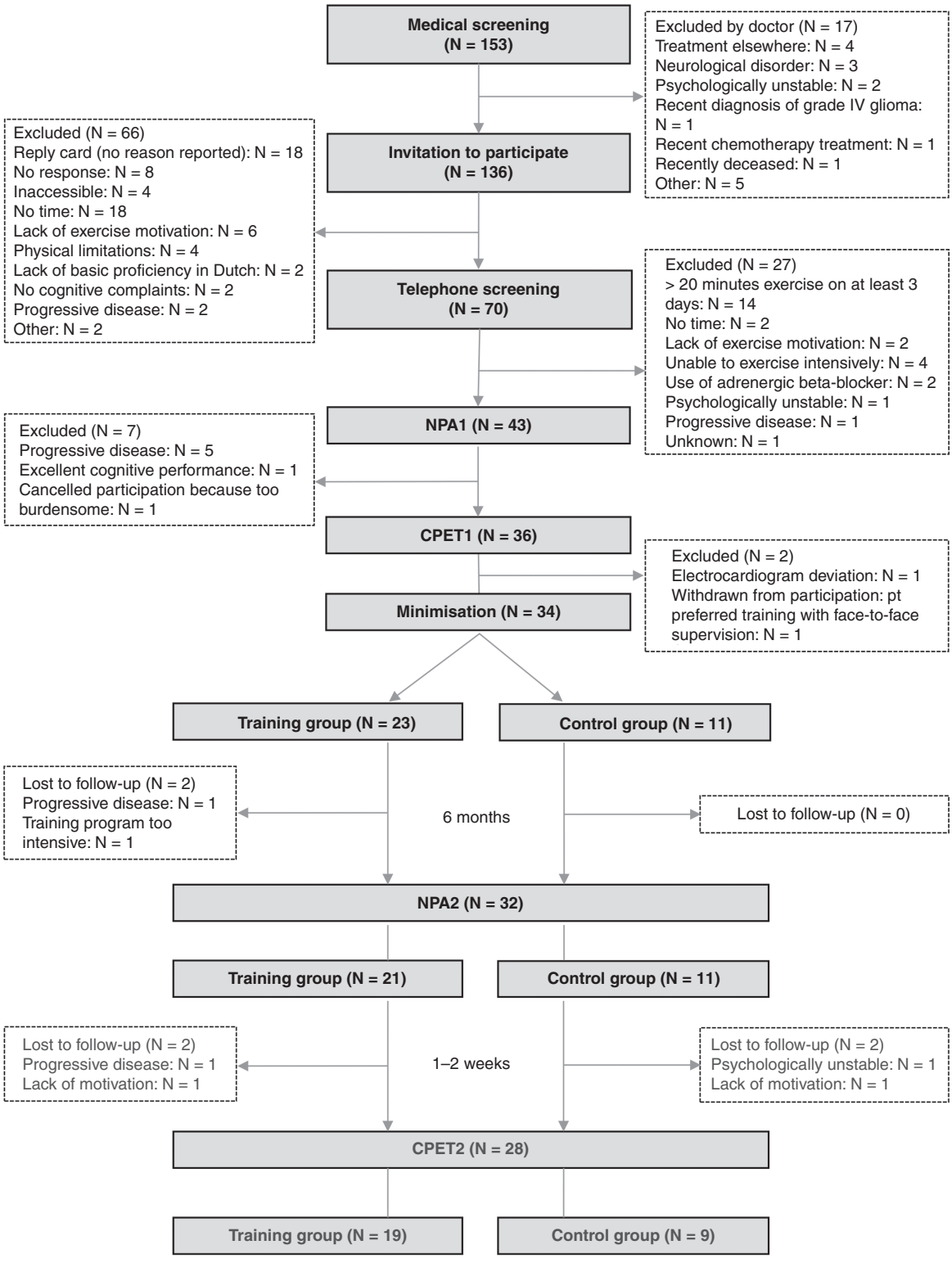

Fig. 1 Flow of participants through the trial.

clinical, and physical fitness characteristics (Table 2). As the exercise group dropouts included one patient with a grade II and one with a grade III astrocytoma, there was a slightly higher proportion of grade II astrocytoma in the final intervention group. For a small majority of cognitive tests, performance at baseline was somewhat better for the exercise group, while baseline PRO scores were somewhat better for the control group (Supplementary Table 1).

Table 2 Baseline characteristics of participants with complete NPA1 and NPA2 data

Characteristic	Exercise Group ($N = 21$)	Control Group ($N = 11$)
Age, y		
mean (SD)	49.2 (8.9)	48.0 (11.9)
Female, *n* (%)	12 (57)	6 (55)
Education, *n* (%)		
low	2 (10)	0 (0)
middle	9 (43)	6 (55)
high	10 (47)	5 (46)
WHO tumor grade, *n* (%)		
II	15 (71)	6 (55)
III	6 (29)	5 (46)
Tumor histology, *n* (%)		
astrocytoma	6 (29)	5 (46)
oligodendroglioma	12 (57)	5 (46)
oligoastrocytoma	3 (14)	1 (9)
Disease duration, y	7.6 (5.0)	8.5 (8.6)
mean (SD)		
Left hemisphere, *n* (%)	10 (48)	4 (36)
Surgery, *n* (%)		
biopsy	2 (10)	1 (9)
resection	19 (90)	9 (82)
Chemotherapy, *n* (%)	8 (38)	4 (36)
Radiotherapy, *n* (%)	12 (57)	5 (46)
Epilepsy, *n* (%)	15 (71)	8 (73)
Anti-epileptic drugs, *n* (%)	12 (57)	6 (55)
VO_2 peak classification,[17] *n* (%)		
recreational (versus sedentary)	4 (19)	1 (9)
LDST-Write,[18] number correct, mean (SD)	43.4 (11.9)	43.4 (10.0)

Results of Analyses of Between-Group Differences in Cognitive Performance

One patient in the control group had an extremely low Z score for baseline TelSearch and another patient in this group for follow-up CST-Shift, resulting in violation of the regression assumptions. These scores were replaced by –3.29, which resolved the issue.

Fig. 2 displays within-group Z score changes in bar charts. Mean or median baseline and follow-up standardized scores, within-group changes therein, and 95% CIs can be found in Supplementary Table 1. Table 3 shows that, for attention, the exercise group had higher follow-up scores than the control group on measures of attentional inhibition (SCWT-Int), of attention span (DS-Forw) and of auditory selective attention and working memory (ElevCount-Distr), both with a medium effect size. In addition, the exercise group performed slightly better than the control group on a measure of information processing speed (LDST-Read). However, we also observed a small benefit for the control group on a measure of sustained selective attention (TelSearch). For memory, there was a small difference in favor of the exercise group for immediate verbal recall (VVLT-T1). Finally, the exercise group had higher follow-up scores on 2 measures of executive function: auditory working memory (ElevCount-Rev) and alternating attention (CST-Shift), with small effect sizes.

Individual Change in Cognitive Performance Over Time

For a measure of auditory selective attention and working memory (ElevCount-Distr) and for a measure of attentional inhibition (SCWT-Int), disproportionally more patients with reliably declined scores (RCIs < –1.645) were found in the control group than in the exercise group (see Supplementary Table 2). However, for the measure of sustained selective attention [TelSearch], fewer patients declined in the control group (including one patient with the extremely low baseline score) than in the exercise group.

Five (24%) participants in the exercise group versus 2 (18%) in the control group showed a reliable improvement on 2 or more cognitive measures (see Table 4). A reliable decline on 2 or more measures was observed for 4 (19%) exercise group participants, versus 3 (27%) control group participants.

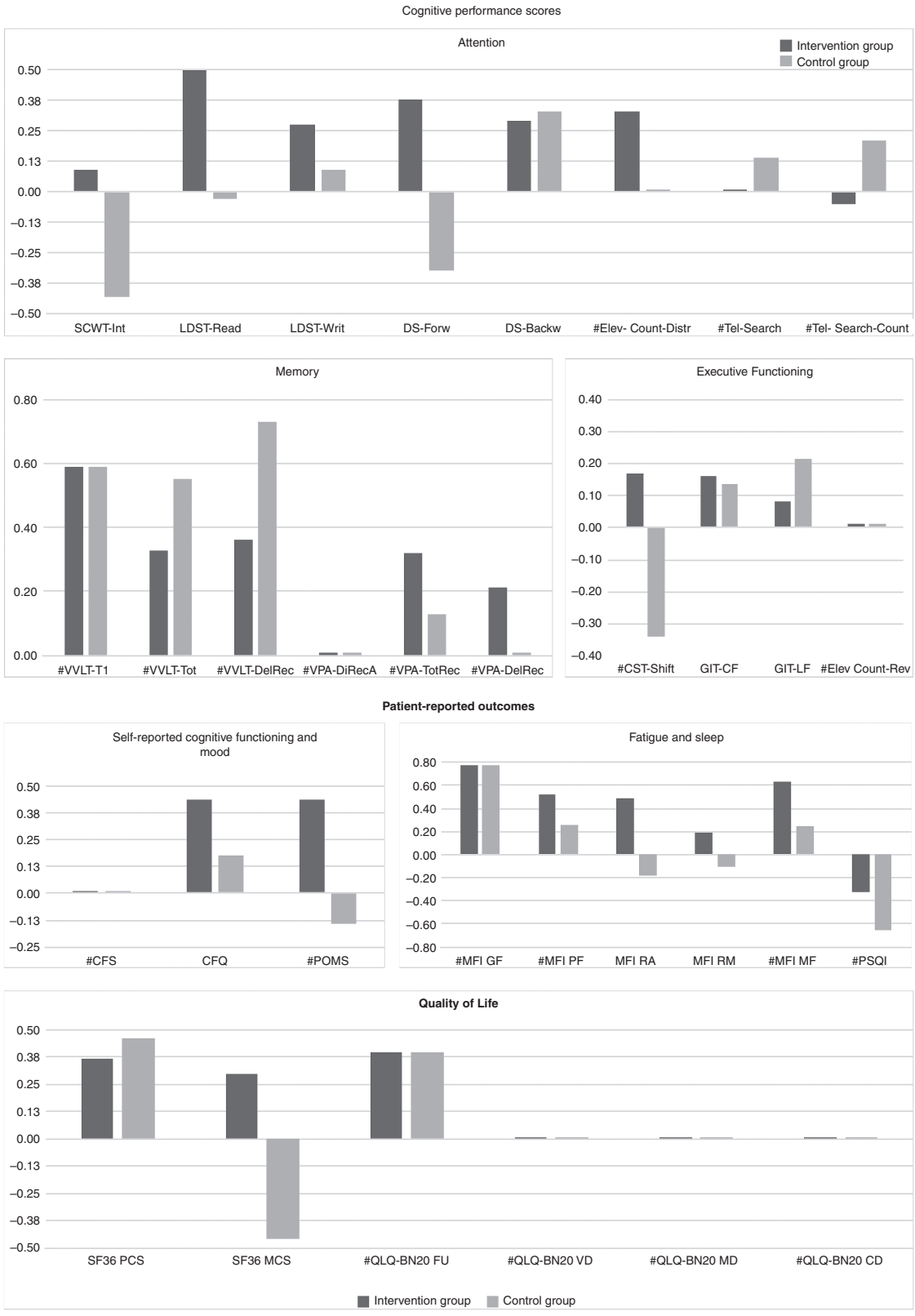

Fig. 2 Within-group mean/#median changes in Z scores for NPA and PRO measures. For all measures, positive changes indicate improvement in outcomes.

Table 3 Between-group effects on NPA and PRO measures

Cognitive Performance Measures	B [95% CI] Exercise Group $n = 21$ Control Group $n = 11$	Patient-Reported Outcomes	B [95% CI] Exercise Group $n = 20$ Control Group $n = 11$
Attention		**Self-reported cognitive functioning**	
SCWT-Int	+0.52 [0.05;0.99]	CFS total	+0.20 [−0.45;0.86]
LDST-Read	+0.47 [−0.16;1.10]	CFQ total	+0.04 [−0.52;0.60]
LDST-Write	+0.18 [−0.20;0.56]	**Fatigue and sleep**	
DS-Forw	+0.57 [−0.01;1.14]	MFI–GF	+0.14 [−0.43;0.71]
DS-Backw	−0.04 [−0.89;0.81]	MFI–PF	+0.52 [−0.23;1.27]
ElevCount-Distr	+0.51 [0.03;0.98]	MFI–RA	+0.63 [−0.17;1.43]
TelSearch	−0.47 [−1.43;0.49]	MFI–RM	+0.19 [−0.51;0.89]
TelSearch-Count	−0.13 [−0.81;0.55]	MFI–MF	0.00 [−0.57;0.56]
Memory		PSQI total	+0.34 [−0.23;0.91]
VVLT-T1	+0.29 [−0.56;1.13]	**Mood**	
VVLT-Tot	+0.16 [−0.42;0.74]	POMS total	+0.50 [0.04;0.96]
VVLT-DelRec	+0.11 [−0.49;0.71]	**Quality of life**	
VPA-DiRecA	−0.02 [−1.13;1.10]		
VPA-TotRec	+0.13 [−0.35;0.62]	SF36 PCS	−0.18 [−0.86;0.49]
VPA-DelRec	+0.14 [−0.20;0.48]	SF36 MCS	+0.63 [−0.16;1.41]
Executive function		QLQ–BN20 FU	+0.08 [−0.52; 0.68]
CST-Shift	+0.35 [−0.30;0.99]	QLQ–BN20 VD	+0.19 [−0.27; 0.66]
GIT-LF	−0.13 [−0.61;0.35]	QLQ–BN20 MD	+0.14 [−0.30; 0.59]
GIT-CF	+0.07 [−0.45;0.59]	QLQ–BN20 CD	−0.01 [−0.46; 0.45]
ElevCount-Rev	+0.25 [−0.23;0.73]		

Abbreviations: B, regression coefficient. CI, confidence interval.

Table 4 Numbers of tests with reliably improved and reliably declined individuals in each group

		Reliable Improvement		Reliable Decline	
		Exercise Group	Control Group	Exercise Group	Control Group
Number of test variables (standardized residuals)	0	9 (−0.3)	6 (0.4)	12 (0.7)	3 (−0.9)
	1	7 (0.2)	3 (−0.2)	5 (−0.6)	5 (0.8)
	2	1 (−0.7)	2 (1.0)	4 (0.0)	2 (0.0)
	3	2 (0.6)	0 (−0.8)	0 (−0.8)	1 (1.1)
	4	1 (0.4)	0 (−0.6)	–	–
	5	1 (0.4)	0 (−0.6)	–	–
Total *n* patients		21	11	21	11

Results of Analyses of Between-Group Differences in PROs

Fig. 2 displays within-group changes of Z scores in bar charts. Mean or median baseline and follow-up standardized scores, within-group changes therein, and 95% CIs are shown in Supplementary Table 1.

Post-intervention, the exercise group had higher outcomes than the control group on 1 of 2 measures of self-reported cognitive functioning (CFS total), with a small effect size (Table 3). We also observed a small benefit for sleep (PSQI total) and less fatigue with respect to 2 scales (Physical fatigue and Reduced activity) of medium effect size, for the exercise group. Finally, patients reported better mood (POMS total) and mental health–related quality of life (SF36 MCS) in the exercise group versus the control group, both with a medium effect size. We observed no between-group differences for the brain cancer specific health-related quality of life scales (QLQ BN-20 FU, VD, MD, and CD).

Discussion

We conducted a pilot RCT of a 6-month, home-based, remotely coached aerobic exercise program intended to ameliorate cognitive impairment in patients with stable grades II and III glioma. Thirty-four patients were randomized to the exercise group or to the control group. In our first report on the feasibility of this program,[14] we concluded that recruitment was challenging and time-consuming but that adherence, safety, and patient satisfaction were good. In addition, physical fitness, as measured with maximum exercise testing, improved in the exercise group but not in the control group.

Here, we evaluated indications of effects of the program on cognitive test performance and PROs. Although, at the group level, the results suggested trends toward better cognitive performance after exercise, at the individual level these changes did not always reach our rather stringent cutoffs for reliable change. Despite this, trends supporting further exploration of exercise interventions in patients with glioma are clearly present.

In this sample, for most cognitive measures, between-group differences at follow-up, after correction for baseline cognitive performance, favored the exercise group. Patients in the exercise group had higher scores than those in the control group on a measure of attentional inhibition, of attention span, and of auditory selective attention and working memory, each with a medium effect size. In addition, small differences in favor of the exercise group were observed for a measure of information processing speed and of immediate verbal recall, and for 2 measures of executive function: auditory working memory and alternating attention/shifting. However, we also observed a small benefit for the control group on a measure of sustained selective attention.

The cognitive benefits of exercise were mostly observed for measures with a clear component of information processing speed and working memory, functions that are important for everyday mental operations, such as calculating, reasoning, and decision making. These findings are consistent with the literature on cognitive effects of exercise in other patient populations, in which effects on global or multiple domains of cognitive function have been reported most frequently.[43,44] However, in studies that evaluated effects on separate cognitive domains, benefits for attention and executive function are most often reported.[9,43]

The individual-level findings (somewhat more patients who declined on a measure of attentional inhibition and of auditory selective attention and working memory, and fewer patients who declined on a measure of sustained selective attention [or vigilance] in the control group compared with the intervention group) were consistent with the group-level findings for these measures. One explanation for the observed benefit for the control group on sustained selective attention may be that exercise reduces participants' arousal levels, resulting in lower vigilance, as has been reported in a previous small trial in patients with insomnia.[45] It may also be an effect of the advice to maintain an active lifestyle, or it could be a chance finding.

Overall, at the individual level, only a few patients appeared to improve reliably over time, although improvements occurred slightly more frequently in the exercise group. At the same time, individual cognitive decline occurred rather frequently in both groups. The criteria for individual reliable change were based on a control group of patients who were somewhat younger and for whom data from a third assessment were used,[41] and therefore practice effects in that previous group may have been larger. In that case, the number of improved and declined individuals in the current sample may have been underestimated.

With respect to the PROs, analyses suggested consistent between-group differences in favor of the exercise group. At 6 months, these patients reported less physical fatigue and less reduced activity, and better mood and mental health–related quality of life, all of medium effect size. In addition, we observed small effects for sleep and self-reported cognitive functioning. No substantial differences were observed for general fatigue, mental fatigue, and reduced motivation or for brain cancer specific and physical health–related quality of life.

We would emphasize that, due to the small sample size in this exploratory trial, the results are tentative and suggestive only. As this was one of the first studies in this area, we included many outcome measures to estimate potential effects for the multitude of symptoms that patients with brain tumors face. The combination of many outcome measures and small groups—in which we observed some extreme values—increases the likelihood of chance findings related to sample idiosyncrasies. After 2 dropouts, the proportion of patients with grade III glioma in the exercise group was somewhat smaller (29%) than in the control group (46%) at the 6-month timepoint. Therefore, neuropsychological improvements over time in the intervention group could have been affected, in part, by the slightly higher proportion of grade II patients.

The sample we were able to include was smaller than we had anticipated. This was due to a combination of stringent selection criteria and low uptake (25% of eligible patients).[14] During recruitment, many eligible patients reported a lack of time or motivation to participate in the trial and/or training program. Consequently, the sample consisted of a motivated group of patients for whom an intensive exercise program may be particularly feasible. This suggests that the intervention, in its current form, may be of interest and benefit to a relatively small subset of the target population.

A strength of the study was the careful consideration of the exercise parameters, based on previous research in other populations indicating that the cognitive benefits of exercise, and the underlying biological mechanisms in terms of enhanced angiogenesis, upregulation of neurotrophins, and increased neurogenesis, may be more strongly related to aerobic training versus other types of exercise, such as resistance training (only).[9,44] Given this rationale, we considered cardiorespiratory fitness as an intermediate endpoint to determine feasibility of an exercise program specifically designed to improve cognitive function. The setup of our exercise program (ie, 3 aerobic training sessions of 20 to 45 minutes at 60–85% of the maximum heart rate per week during 6 months) resulted in increased cardiorespiratory fitness and suggested cognitive

improvements, which is consistent with the conceptual working mechanism of our exercise intervention. A drawback of this rather intensive exercise regimen, however, is that during the study's recruitment phase it may have been perceived as too intimidating for less motivated patients. Among the motivated group of participants we included, 17 reported a willingness to continue to exercise, of whom 9 indicated the intention to decrease the frequency to 1 or 2 training sessions per week. It is unclear whether a lower-frequency regimen would yield or maintain acceptable effects on physical and cognitive measures and/or PROs.

To conclude, 6 months of home-based, remotely coached exercise is feasible in terms of adherence, safety, and patient satisfaction in a select group of motivated stable glioma patients, and exercise may improve their cardiorespiratory fitness.[14] Small to medium effects were also observed for several cognitive performance measures of attention, memory, and executive function and for self-reported cognitive functioning, fatigue, sleep, mood, and quality of life.

Although the performance of this trial required much effort and did not demonstrate clear cognitive effects of exercise for individual patients, we believe that conducting follow-up research would be worth the effort. Patients with brain tumors are known to have considerably reduced physical fitness.[46] Recently, Cormie and colleagues provided a strong theoretical rationale, based on evidence from other cancer and chronic disease populations, for the potential beneficial effects of exercise on the physical, cognitive, and psychological symptoms related to brain cancer and its treatment.[12] In addition, exercise may be beneficial in terms of reducing seizure susceptibility.[47] If exercise aids in the management of multiple brain cancer symptoms, this may be a relatively inexpensive intervention.[12] Appropriately designed, well-executed RCTs are needed to demonstrate whether (home-based, remotely coached) exercise interventions are (cost) effective in reducing a range of symptoms and functional limitations, with very few adverse effects, in patients with brain cancer.

These studies especially need larger samples to obtain sufficient power to perform formal hypothesis tests, and to detect small to medium effects on physical and cognitive measures and PROs. However, recruitment of large samples will be a challenge. Therefore, sufficient time should be allocated, and involvement of a relatively large number of study centers may be necessary. Studies offering a program with a lower frequency of exercise sessions per week might have a higher uptake. During such a program, the frequency could be increased for patients who are able and willing to meet the exercise recommendation for cancer survivors.[48] Although brain tumor patients generally report a preference for home-based exercise,[49,50] 4 patients in our sample indicated preferring face-to-face or group training.[14] Offering patients the choice of home-based training, face-to-face supervision, and/or group training in a physical therapy center may further increase uptake. Furthermore, combining physical training with (simultaneous) cognitive training with gaming elements may be more attractive for patients to attend to, and at the same time have stronger cognitive effects.[8] The larger samples that may be obtained in these ways may facilitate determining which specific patients would benefit most from exercise interventions. In addition, dose-response relationships should be examined to determine a minimal effective dose. Including a long-term follow-up assessment could provide information on the maintenance of exercise behavior and the benefits of exercise. Furthermore, future studies could include inflammatory markers or measures of neurotrophic factors such as brain-derived neurotrophic factor to determine biological mechanisms of the potential relationship between exercise and cognitive function in patients with brain tumors.

Supplementary Material

Supplementary data are available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

Keywords

brain neoplasms | cognitive function | exercise | glioma | patient reported outcome measures

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