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Effects of two types of exercise training on psychological well-being, sleep and physical fitness in patients with high-grade glioma (WHO III and IV)

Larina Eisenhut[a,b,c,1], Dena Sadeghi-Bahmani[d,1], Attill Seamann[a], Laurin Staub[b], Serge Brand[b,c,e,f,g,2], Dominik Cordier[a,2,*]

[a] University of Basel, Department of Neurosurgery, Basel, Switzerland
[b] University of Basel, Department of Sport, Exercise and Health, Division of Sport Science and Psychosocial Health, Basel, Switzerland
[c] Center for Affective, Stress and Sleep Disorders (ZASS), Psychiatric University Hospital Basel, 4002, Basel, Switzerland
[d] Department of Psychology, Stanford University, Stanford, CA, USA
[e] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, 67146, Iran
[f] Substance Abuse Prevention Research Center, Health, Institute, Kermanshah University of Medical Sciences, Kermanshah, 67146, Iran
[g] School of Medicine, Tehran University of Medical Sciences, Tehran, 25529, Iran

A R T I C L E I N F O

Keywords:
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Radiochemotherapy
Exercising
Active control condition
Depression
Fatigue

A B S T R A C T

Background: There is evidence that regular exercise training has the potential to improve psychological well-being among cancer survivors. However, limited findings are available for individuals with high-grade glioma (HGG; WHO grade III and IV) after neurosurgery and undergoing radiochemotherapy. Given this, endurance and strengths training were employed to investigate their impact on symptoms of depression, feelings of stress and anxiety, fatigue, insomnia, and physical fitness, compared to an active control condition.
Methods: A total of 29 patients (M = 52.07, SD = 12.45, 55.2% women) participated in this randomized controlled trial (RCT). After neurosurgical treatment and during adjuvant radiotherapy and chemotherapy or combined radiochemotherapy, patients were randomly assigned to the following conditions: Endurance training (n = 10); strengths training (n = 11); active control condition (n = 8). At baseline, three weeks and six weeks later at the end of the study physical fitness was objectively measured with a 6-min walk test (6MWT) and a handgrip test. Participants completed a series of questionnaires covering sociodemographic information, symptoms of depression, stress, anxiety, fatigue, and insomnia. Further, experts rated participants' severity of symptoms of depression.
Results: Over time and compared to the strengths and active control condition, self-rated symptoms of depression, state and trait anxiety, stress and insomnia decreased in the endurance condition. Over time and compared to the endurance and active control condition, no changes on symptoms of depression, anxiety, stress, or insomnia were observed in the strengths condition. Over time and compared to the endurance and strengths condition, symptoms of depression (self-ratings), stress, insomnia and fatigue decreased in the active control condition. Fatigue increased in both exercising conditions. Over time and irrespective from the study condition, physical fitness did neither improve nor decrease.
Conclusions: The pattern of results suggests that endurance training and an active control condition improved dimensions of depression, stress, and anxiety, while mere strengths training appeared to neither improve, nor decrease dimensions of psychological functioning. Further, exercise interventions did not change physical fitness, but increased fatigue. Overall, endurance training and an active control condition appeared to favorably impact on psychological well-being among patients with high-grade glioma after neurosurgery and undergoing radiochemotherapy.

* Corresponding author. University Hospital of Basel, Department of Neurosurgery, Basel, Switzerland.
E-mail address: dominik.cordier@usb.ch (D. Cordier).
[1] Shared the first authorship and contributed equally to the manuscript.
[2] Shared last authorship.

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1. Introduction

Gliomas are characterized by high morbidity and mortality due to their localization and often invasive growth (Weller et al., 2015). The global incidence of gliomas in adults in the United States is 6.8/100,000 (Molinaro et al., 2019). However, the rate of newly diagnosed gliomas varies widely by histologic type, age at diagnosis, gender, ethnicity, and geographic location (Ostrom et al., 2015). In their statistical review, Ostrom et al. (2014b) captured all diagnosed primary tumors of the brain and central nervous system in the United States from 2007 to 2011, and 33.7% of all tumors captured were high-grade tumors/gliomas (HGG). Results showed that among HGG, glioblastoma was the most common tumor (45.6%). High-grade gliomas occurred clustered in the fifth to seventh decades of life, but can be observed in all age groups, including children. The incidence of HGG increases with age, peaking after the age of 65 years (Nayak and Reardon, 2017; Ostrom et al., 2018). The usual treatment for HGG includes neurosurgical resection of the tumor and postoperative combined radiochemotherapy (Nayak and Reardon, 2017). Modern glioma surgery aims at achieving maximal tumor resection to improve symptom management, progression-free survival, and overall survival (D'Amico et al., 2017). Subsequent to surgical resection, combined radiochemotherapy is prescribed in most cases. Depending from the genetic sub-classification of the glioma and from patient-specific factors such as age and clinical condition, postoperative treatment sometimes consists of radiotherapy or chemotherapy only (Cordier et al., 2019). Unlike many other malignancies, the prognosis of individuals with glioma has improved only slightly in recent decades. Gliomas remain incurable (Bleeker et al., 2012). Therefore, the median survival time of individuals with gliomas is short: The survival rate after five years is less than 30% (Levin et al., 2016), and the time lapse of 12–16 months post-diagnosis is considered to be the peak incidence of mortality (Smoll et al., 2013), with a slow decline after that (Wang et al., 2015). However, age, tumor biomarkers, and extent of tumor resection influence survival time (Brown et al., 2016; Ostrom et al., 2014a). In addition to various side effects, glioma treatment often causes psychological and physical reactions, which are an additional major burden for the patients. In general, coping with this such side effects and symptoms may unfavorably impact on psychological well-being among individuals with cancer (Andersen et al., 2006).

There is increasing evidence that individuals with cancer benefit from adjuvant exercise training. Exercise interventions improve physical and psychological well-being both before and after cancer-specific therapy (Courneya et al., 2003a; Craft et al., 2012; Mock et al., 2001; Segal et al., 2001, 2003), such as depression (Courneya et al., 2003a; Mock et al., 2001; Segal et al., 2003), anxiety (Courneya, 2003; Courneya et al., 2003a, 2003b; Segar et al., 1998) and endurance and strength (Courneya et al., 2003b; Mock et al., 2001; Nieman et al., 1995; Schmitz et al., 2019; Segal et al., 2003). Exercise interventions can reduce treatment-associated symptoms and side effects such as paresthesia, fatigue, or infections (Andersen et al., 2006; Cormie et al., 2018a, 2018b; Hayes et al., 2019; Schmitz et al., 2019; Spence et al., 2020)). Further, exercise interventions proved to be safe and effective for cancer survivors (Ballard-Barbash et al., 2012; Courneya, 2003; Courneya and Friedenreich, 2011). Further, home-based aerobic and resistance exercise interventions appeared to be feasible (Batalik et al., 2021). Importantly, radiochemotherapy increased fatigue among individuals with cancer, in general (de Dreu et al., 2020), and in individuals with brain tumor cancer, in specific (de Dreu et al., 2020; Valko et al., 2015). To counter fatigue in palliative care a recent systematic review and meta-analysis showed that compared to non-exercise interventions, exercise interventions improved cancer-related fatigue (Kessels et al., 2018).

As regards individuals with HGG, research on the impact of exercise interventions on psychological functioning and physical fitness is scarce (Cormie et al., 2015); three case studies, two feasibility studies, and two interventional studies were identified: A structured, 12-weeks resistance and aerobic exercise program (two sessions the week for 60min) and self-managed aerobic sessions improved distress and depression, and reduced morbidity among two females with HGG, and after resection and during radiochemotherapy (Levin et al., 2016). After resection and during radiochemotherapy, a 54-years old male with HGG attended all physical activity sessions (1–2/week) over six weeks; compared to baseline, aerobe power (+24%), muscle strength (+38%), standing balance (+71%), walking ability (+9%), and global health status improved (Hansen et al., 2019). A 33-years old male (after resection and during radiochemotherapy) showed that even high-paced (four weekly training sessions over a time lapse of 87 weeks) physical activity interventions had no adverse side-effects. The individual participated at two marathons at a pace of 5 km-min, and gained in fitness despite intensive therapies and tumor progression (Troschel et al., 2019). In their feasibility study (N = 24; glioma grades I to IV) Hansen et al. (2018) showed that compared to an unsupervised individual training, therapeutically supervised aerobic training three times the week over a time lapse of six weeks was associated with lower drop-out rates, high adherence and high patient satisfaction. A further feasibility study (N = 34; stable grades II and III gliomas) showed that compared to a control condition, a six-months lasting exercise intervention (three times/week for 20–45min) improved cardiorespiratory fitness and BMI (Gehring et al., 2018) and cognitive function (Gehring et al., 2020). Adherence rate was 79%.

Overall, research on the favorable impact of exercising interventions on cancer survivors is growing, though this is much less the case for individuals with HGG after resection and during radiochemotherapy. Further, exercising interventions appeared feasible and without adverse effects. Given this background, and given that regular exercising has the potential to improve dimensions of mental health, the overall aim of the present study was investigate in a randomized clinical trial with an active control condition, if and to what extent two exercising interventions (endurance training; strenghts etraining) improved dimensions of physical and mental health.

As regards the type of exercising Levin et al. (2016) employed both resistance and aerobic exercise training, though without investigating, if one intervention was superior to the other. Next, findings from neurological disorders showed that regular physical activity may favorably impact on fatigue (Heine et al., 2015; Razazian et al., 2016, 2020; Rooney et al., 2019; Sadeghi Bahmani et al., 2019a; Safari et al., 2017). For cancer, five meta-analyses and systematic reviews are available. Kessels et al. (2018) showed that compared to non-exercising conditions, exercising improved cancer-related fatigue. Wagoner et al. (2021) reported that compared to non-exercise conditions, community-based exercise programs improved cancer-related fatigue, though effect sizes were small. Among women with breast cancer, Juvet et al. (2017) showed a slight decrease in fatigue in the exercising conditions, compared to non-exercising conditions. Cramp and Byron-Daniel (2012) showed in their Cochrane-based systematic review that exercise interventions impacted favorably on fatigue, when exercising was delivered during or post-adjuvant cancer therapy. Further, aerobic exercise significantly reduced fatigue, but resistance training and alternative forms of exercise failed to reach significance.

Last, there is sufficient evidence that regular physical activity favorably impacted on subjective sleep quality (Chennaoui et al., 2015; Kalak et al., 2012; Kredlow et al., 2015), and that a restoring sleep is associated with a broad range of favorable mental health outcomes (Cirelli and Tononi, 2008; Tempesta et al., 2018). In contrast, such data are not available for individuals with HGG after resection and during radiochemotherapy. With this background, the decision was to introduce subjective sleep as a further outcome variable.

Given this background, the following four hypotheses and one exploratory research question were formulated. First, following previous research on individuals with cancer types other than HGG (Hansen et al., 2018, 2019, 2020; Levin et al., 2016; Troschel et al., 2019), we expected improvements in psychological functioning (depression, anxiety, stress) after a strengths and endurance training, compared to an active control condition. Second, again following previous research on individuals with cancer types other than HGG (Hansen et al., 2018, 2019, 2020; Levin et al., 2016; Troschel et al., 2019), we expected improvements in physical performance, compared to an active control condition. Third, following previous research on the association between physical activity and sleep among clinical and non-clinical samples (Chennaoui et al., 2015; Kalak et al., 2012; Kredlow et al., 2015), we expected higher subjective sleep after a strengths and endurance training, compared to an active control condition. Fourth, following previous research on individuals with neurological issues and cancer other than HGG (Cramp and Byron-Daniel, 2012; Heine et al., 2015; Juvet et al., 2017; Kessels et al., 2018; Razazian et al., 2016, 2020; Rooney et al., 2019; Sadeghi Bahmani et al., 2019a; Safari et al., 2017; Wagoner et al., 2021), we expected improvements in fatigue in the exercising conditions, compared to the active control condition. We took as exploratory the research question, if strengths or endurance training had a higher impact on psychological well-being, fatigue and insomnia, or if both interventions showed an equal impact.

We hold that the present study had the potential to expand upon previous studies on three ways. First, exercising interventions (strengths; endurance) were compared to an active control condition; in doing so, possible effects due to the mere social interaction with professional hospital members could be controlled for. Second, we introduced subjective sleep quality, which is crucial for psychological and physical wellbeing. Third, we compared two types of exercising.

2. Method

2.1. Study procedure

Individuals with HGG after resection and during radiochemotherapy were approached to participate at this interventional and randomized clinical trial. All individuals were informed about the study aims and the confidential and anonymous data handling. Thereafter, they signed the written informed consent. Participants were randomly assigned to an endurance training, strengths training, or to the active control condition. At baseline, and after three and six weeks (study end), participants completed a series of questionnaires covering sociodemographic information, psychological functioning, fatigue and insomnia (see below). Further, their physical performance was objectively assessed at the same time points (see below). The ethics committee (Ethikkommission Nordwest- und Zentralschweiz EKNZ: 2018-01314) approved the study, which was performed in accordance with the current and seventh edition (World Medical Association, 2013) of the declaration of Helsinki. The study was registered at ClinicalTrials.gov: Protocol Record 2018-01314; NCT03775369.

2.2. Participants

We recruited patients of the Neurosurgical Clinic of the Basel University Hospital (USB; Basel, Switzerland). Inclusion criteria were: 1. Age between 18 and 75 years; 2. High-grade glioma (grading criteria, WHO III and IV) after neurosurgical tumor resection or biopsy; 3. Undergoing postoperative chemotherapy, or radiotherapy, or both at the same time; 4. Willing and able to follow the study intervention, and to comply with the study conditions; 5. Signed written informed consent. Exclusion criteria were: 1. Severe psychiatric issues (psychosis, suicidal behavior, substance abuse disorder), as ascertained by a trained and experienced clinical psychologist and based on the structured clinical interview (First, 2015) for psychiatric disorders (American Psychiatric Association, 2013); 2. Severe and somatic comorbidities (severe cardiovascular disease, severe diabetes, impairments of the musculoskeletal system); severe cardiopulmonary issues and musculoskeletal issues hampering physical activity interventions, as ascertained by a trained and experienced physician. 3 Withdrawal from the study, either due to patient withdrawal, or due to unfavorable somatic or mental issues leading to unsuitability for further participation in the study.

2.3. Sample size calculation and randomization

As mentioned elsewhere (Cordier et al., 2019), two sources helped us to define the sample size. First, Julious (2005) reported a group size of n = 12 as rule of thumb for pilot studies; second, we performed a power analysis with G*Power (Faul et al., 2007) and with the following assumptions: Cohen's f for ANOVAs with repeated measures: 0.25; alpha: 0.05; power: 0.80; number of groups: 3; number of timepoints: 3; calculated sample size: N = 36. To counterbalance drop-outs, the sample size was set at N = 45. Randomization was performed using an online software from the website Randomization.com (http://www.randomization.com). The online generator randomized each subject to a single treatment using a method of randomly permuted blocks, with random block sizes for sex. Based on the generated list, a third party not involved in the study prepared 45 sealed envelopes, which were placed in an opaque and sealed ballot box and mixed again before selection. Next, the third party draw an envelope from the ballot box and assigned study participants to one of the three groups (Cordier et al., 2019).

2.4. Study design

After neurosurgical removal of the glioma, patients underwent chemotherapy, radiation therapy, or a combined therapy. In parallel, they were informed about the study content and the study objectives. Prior to enrollment, all potential participants were screened for sociodemographic data (e.g. age, gender, living status, etc.) and glioma-related information (e.g. WHO grade, type of surgical removal, biomarkers). At baseline, at week three and week six (end of the study) cardiovascular fitness (6MWT), grip strength (handgrip strength test) and psychological well-being were assessed (see details below). The flow chart is reported in Fig. 1 and provides the following number of patients: Patients approached (n = 45); patients randomized (n = 29); patients at the end of the study (n = 27). Reasons for non-participations were: Lack of motivation: n = 5; side-effects of post-surgery cancer treatment: n = 11. Further, one patient in the endurance and one patient in the strengths condition did not complete the study. Accordingly, drop-out rate was 6.89%; adherence rate was 93.16%.

2.5. Measures

2.5.1. Sociodemographic and glioma related information

Participants reported their age, civil status, and highest level of education. Glioma-related information, such as WHO grade, type of surgical removal, biomarkers of glioma, MGMT status (status of O6-methylguanine-DNA methyltransferase), IDH-type (isocitrate dehydrogenase) and treatments were obtained from medical records.

2.5.2. Psychological well-being

Psychological well-being included depressive symptoms, feelings of anxiety and stress.

2.5.2.1. Depression

2.5.2.1.1. Depressive symptoms were assessed via experts' and self-ratings. For expert rating, the Hamilton Depression Rating Scale (HDRS) was used (Hamilton, 1960). The HDRS consists of 17 basic items to assess the severity of depressive symptoms and of four additional items for more detailed description. The intensity of symptoms is assessed using three- to five-point ordinal scales (0–2 and 0–4). A total score is obtained from the first 17 items; this number is used to determine the severity of depression. A higher total score is associated with more severe depressive symptoms. The HDRS is administered by a professional

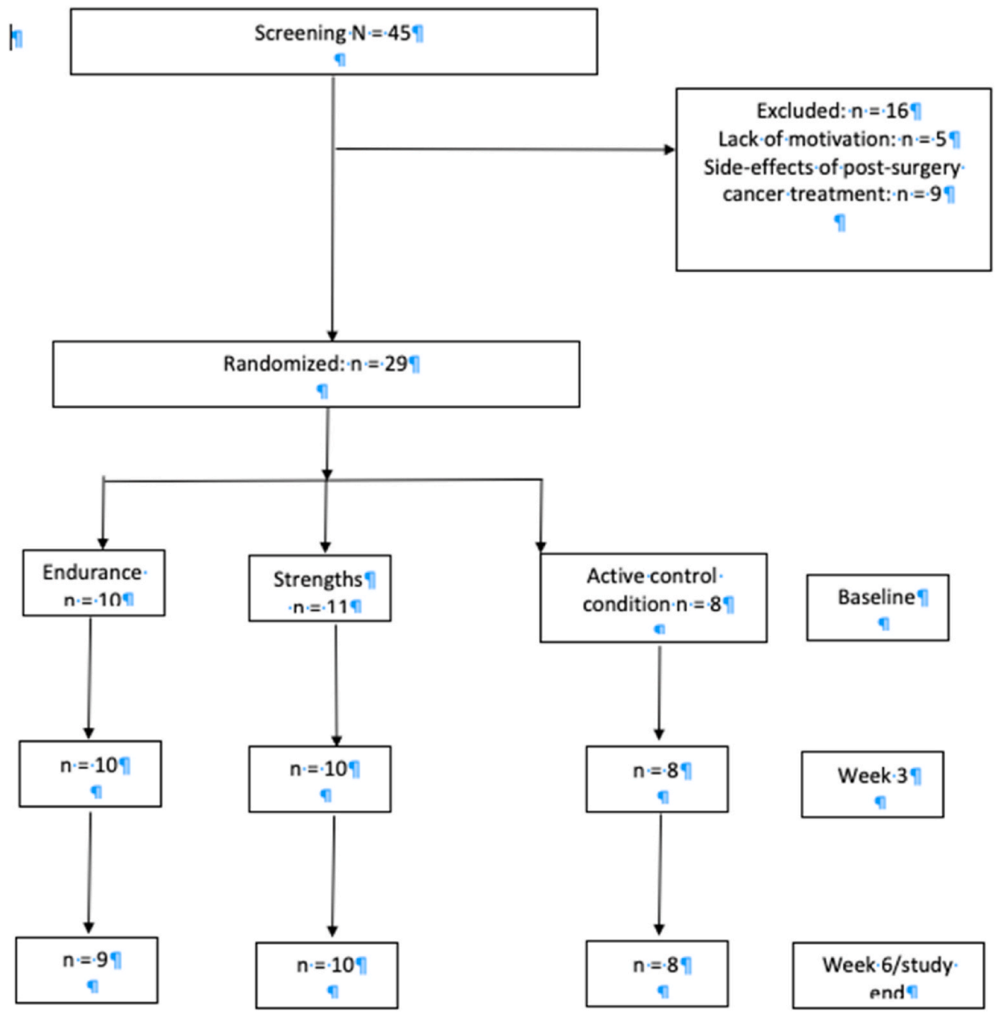

Fig. 1. Flow chart of patients approached, screened, randomized and assessed during the study.

with participants at all three measurement time points. The expert responsible for this rating was blind as regards participants' assignement to the study condition.

To self-report the severity of depressive symptoms, the Beck Depression Inventory (BDI) is used. The BDI is a widely used self-report inventory for measuring the severity of depression in adolescents and adults. The questionnaire consists of 21 items with typical features of depression such as depressed mood, loss of appetite, thoughts, and similar (Beck et al., 1961). For each item, a four-point Likert scale ranging from 0 to 3 points is available for selection. A higher total score corresponds to increased severity of depressive symptoms.

2.5.2.2. Anxiety. The State-Trait Anxiety Inventory (STAI) is used to assess the state and trait anxiety (Spielberger et al., 1983). The questionnaire self-assesses the presence and severity of current anxiety symptoms and the general tendency towards anxiety. The questionnaire consists of two subscales. The first subscale (State) measures current anxiety. The second subscale (Trait) measures the characteristics of anxiety in general. For statistical analysis, the two subscales are considered separately. The original version of the STAI consists of 40 items with 20 items per subscale. Responses are given on an 8-point rating scale. A higher total score reflects higher levels of anxiety.

2.5.2.3. Perceived stress. Subjectively perceived stress levels are assessed using the Perceived Stress Scale (PSS)(Cohen et al., 1983). The items of the questionnaire capture how unpredictable, uncontrollable. The questionnaire consists of 10 items from which the total stress experienced during the previous month can be determined (Cohen et al., 1983). Responses are given on a five-point rating scale, with higher scores reflecting greater perceived stress.

2.5.2.4. Insomnia. Insomnia as a proxy of subjective sleep complaints was assessed using the Insomnia Severity Index (ISI) (Bastien et al., 2001). The ISI is a self-report questionnaire designed to assess subjective perceptions of sleep complaints. The questionnaire consists of a total of 7 items. The first 4 items relate to difficulty falling asleep and staying asleep, early awakenings, and sleep quality. The remaining items relate to wakefulness and impairment of daily functioning due to sleep complaints. The various items are assigned to scores on a five-point Likert scale (0 = not at all, 5 = very much). The addition of all items gives the total score, which ranges from 0 to 35. A high score indicates a higher risk for insomnia.

2.5.2.5. Fatigue. The Fatigue Severity Scale (FSS) is used for subjective assessment of fatigue. It is one of the most widely used inventories for measuring fatigue in people with chronic diseases (Krupp et al., 1989). The scale makes it possible to determine whether fatigue symptoms are present or not. It measures how much fatigue affects motivation, physical functioning, getting chores done, family, and social life. The questionnaire consists of 8 questions. Each of the eight items is assigned a value on the seven-point Likert scale (1 = "strongly disagree" to 7 = "strongly agree"). The mean of the total score is calculated to evaluate the questionnaire. A higher score corresponds to greater fatigue.

2.5.3. Physical fitness

Physical fitness is determined using the 6-min walk test (6MWT) and handgrip strength test. We used the 6MWT as a measure of cardiorespiratory fitness (Solway et al., 2001). The 6MWT is a submaximal exercise test, which was developed specifically for patients with chronic diseases (Schmidt et al., 2013). Pulse and oxygen saturation are measured at the start, after 6min and after 8min. In addition, subjects were asked about their well-being before and after the test, and possible breaks are noted. For data analysis, we compared the number of completed lengths.

Upper body strength is determined by the Grip Strength Test. To determine the maximum isometric grip force a mechanical hand dynamometer (Jamar Handgrip Dynamometer; dealer: Rehaforum MEDICAL GmbH; Elmshorn, Germany) is used. The Grip Strength Test is considered a valid measurement tool for upper body strength (Hamilton et al., 1992). Participants have three trials per hand. All six trials and the mean value of the left and right hand are recorded. For the statistical analysis, the mean of all six trials was computed.

2.6. Interventions

The present interventions were exercising interventions (Kalb et al., 2020) understood as a form of physical activity with the following characteristics: 1. It is performed repeatedly over an extended period of time (here: six weeks, two times/week); 2. There is a specific external objective to achieve (here; improved physical and mental health).

2.6.1. Endurance training

Endurance training consisted of two sessions per week for six consecutive weeks. Sessions were either in small supervised groups of 2–4 participants or in individual supervision. After a 5-min warm-up, patients exercised for 25–35 min on a treadmill or bicycle at a speed of 11–14 points on the Borg scale (0 = rest, 20 = maximum speed). Participants were allowed to choose their own pace and vary during the workout. Participants were encouraged to maintain the pace for as long as possible, but were allowed to take breaks if necessary. Following the workout, a 5-min cool down was performed, light exercises to help the body transition into the rest phase. The workout lasted a total of 35–45 min.

2.6.2. Strength training

Strength training also consisted of two sessions per week for six consecutive weeks. The sessions also took place either in small supervised groups of 2–4 participants or in individual supervision. A 5-min warm-up was followed by a structured and standardized workout to strengthen all major muscle groups such as weight lifting and resistance exercises at with appropriated devices. 3–5 series of 10–15 repetitions each were performed at 11–15 points on the Borg scale. Intervals between each series lasted 1–3 min. The workout was followed by a 5-min cool-down period to help the body transition into the rest phase. The workout lasted a total of 35–45 min.

2.6.3. Active control condition

Identically to the two groups mentioned above, patients in the active control group met twice a week in supervised groups for 30–45 min for six consecutive weeks. In contrast to the endurance and strength training condition, participants in the control group did not perform any physical activity. The active control intervention was not a psychotherapy with the aim of a cognitive-emotional improvement (Wampold et al., 1997). Coping strategies were not suggested by a psychologist as usual, tough participants were encouraged to make suggestions themselves and to share experiences from their daily lives. Thus, the active control condition was not a *bona fide* intervention in the psychotherapeutic sense, but rather an exchange of practical advice for everyday life (Cordier et al., 2019; Jasbi et al., 2018; Norouzi et al., 2020; Sadeghi Bahmani et al., 2019b, 2020c, 2020d).

2.7. Statistical analysis

Statistical analyses were performed with intent-to-treat (ITT), with the last observation carried forward (LOCF). First, we compared the sociodemographic and glioma-related information between the three groups with a series of χ^2-tests. To examine whether and to what extent the three study conditions (endurance training, strength training, and active control condition) affected the outcome variables over time, a series of mixed ANOVAs for repeated measures was performed. Factors were Time (baseline, week 3, week 6), Group (endurance group, strength group, control group), the Time-by-Group-interaction. Dependent variables were: depressive symptoms, anxiety, stress, insomnia, fatigue, cardiorespiratory fitness, and grip strength). For experts' ratings of depression, baseline values differed between the three study conditions; given this, baseline scores were introduced as co-variate.

The nominal level of significance was set at alpha <0.05. Effect sizes for F-statistics were reported as partial eta squared (ηp^2), with 0.019 = trivial effect size [T]; $0.020 < \eta p^2 < 0.059$ = small effect size [S], $0.06 < \eta p^2 < 0.139$ = medium effect size, [M], and $\eta p^2 \geq 0.14$ = large effect size [L]. Following the examples from previous studies (Sadeghi Bahmani et al., 2019, 2020), Cohen's d effect sizes were reported for the pre-post change within the three groups. Effect sizes for t-tests were reported as Cohen's d (Cohen, 1988) with the following ranges: d = 0.0–0.19: trivial effect sizes; d = 0.20–0.49: small effect sizes; d = 0.50–0.79: medium effect sizes; d ≥ 0.80: large effect sizes. All calculations were performed with SPSS® 28.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Sociodemographic and glioma-related information

Participants in the three groups did not statistically differ regarding to age, living status, and educational level (F- and all χ^2 -tests < 1.00, p > .05). Further, no statistically significant differences were observed for diagnosis (WHO grade III or IV), clinical symptoms, surgical removal of glioma, MGMT status, IDH type, 1p19q status, type of treatment after surgical removal (F- and all χ^2 -tests < 1.00, p > .05).

3.2. Symptoms of depression (experts' ratings; self-rating), stress, anxiety, fatigue, insomnia, and physical fitness (6min walking; handgrip test) over time and between the three study conditions

Tables 2 and 3 provide the overview of descriptive and inferential statistical indices. Accordingly, statistical indices are not repeated in the text again.

Symptoms of depression, as rated by experts, decreased over time (large effect size), but more so in the active control condition (large effect size of interaction), compared to the endurance and strengths training. Group differences were medium.

Self-rated symptoms of depression decreased over time (medium effect size), but more so in the endurance training (medium effect size of interaction), compared to the strength training and active control condition.

Perceived stress decreased over time (large effect size), but more so in the endurance training and active control condition (large effect size of interaction), compared to the strengths condition.

State anxiety decreased over time (large effect size), but more so in the endurance training, compared to the strengths training and active control condition (large effect size of interaction).

Trait anxiety did not change over time (small effect size); trait anxiety decreased in the endurance training, increased in the strengths training, and remained unchanged in the active control condition (large

Table 1
Sociodemographic and glioma-related data of participants, separately for the three groups.

	Endurance training (n = 10)	Strength training (n = 11)	Active control (n = 8)
Sociodemographic data			
Age M (SD)	49.1 (13.14)	54.6 (13.45)	53.0 (10.78)
Glioma-related data			
Diagnosis			
WHO grade III	2	4	1
WHO grade IV	8	7	7
Surgical intervention			
No intervention	0	0	1
Biopsy	1	1	2
Partial resection	3	3	1
Total resection	6	7	4
MGMT status			
Non-methylated	8	6	7
Methylated	2	5	1
IDH-type			
Wild-type	7	8	7
Mutated	3	3	1
Treatment			
Combined therapy	10	10	7
Radiotherapy only	0	1	1

Notes: MGMT status = status of O6-methylguanine-DNA methyltransferase; IDH-type = isocitrate dehydrogenase.

effect sizes for interaction and group).

Fatigue did not change over time (small effect size), but increased in the endurance and strengths training, while fatigue decreased in the active control condition (large effect size of interaction Fig. 2).

Insomnia scores did not change over time (small effect size), though insomnia scores decreased in the endurance training and active control condition, while insomnia scores increased in the strengths training condition (Fig. 3).

Physical fitness (number of completed lengths in the 6MWT) did not change over time (small effect size), but slightly increased in the active control condition (medium effect size of interaction).

Physical fitness (strengths in handgrip) increased over time (large effect size), but more so in the endurance training and active control condition, compared to the strengths condition (large effect size of interaction).

3.3. Symptoms of depression (experts' ratings; self-rating), stress, anxiety, fatigue, insomnia, and physical fitness (6min walking; handgrip test) over time and within the three study conditions; effect size calculations

Table 4 provides the overview of effect sizes of the dimensions related to psychological functioning, fatigue, insomnia, and physical fitness, separately for the three study conditions (endurance and strength straining; active control condition). Note that comparisons were made between the baseline and study end.

3.3.1. Endurance training

Self-rated symptoms of depression decreased dramatically (large effect size), while this was not the case for experts' ratings of symptoms of depression. Stress, state and trait anxiety, and insomnia decreased (medium to large effect sizes). Physical fitness indices did not change, and fatigue increased over time (medium effect size).

3.3.2. Strengths training

All effect sizes were trivial to small, or the other way around: dimensions of psychological functioning, insomnia, fatigue and physical fitness did neither improve, nor decrease over time.

3.3.3. Active control condition

Symptoms of depression, as rated by experts', decreased dramatically over time (large effect size); fatigue decreased dramatically over time (large effect size), and insomnia improved over time (medium effect size), while self-rated symptoms of depression, state and trait anxiety and physical fitness did not change over time.

4. Discussion

The aim of the present six-weeks lasting study was to investigate the impact of two exercising interventions (endurance; strengths) on dimensions of physical performance and psychological health among patients with high-grade glioma (WHO III and IV), always compared to an active control condition. The main findings were that after neurosurgery and undergoing radiochemotherapy, endurance training, strength training and an active control condition over a time lapse of six weeks impacted in a differentiated and complex fashion on dimensions of psychological functioning, fatigue, sleep and physical activity performance. More specifically, over time, symptoms of depression, as rated by experts, self-rated stress, fatigue, insomnia, and objectively assessed physical activity indices improved in the active control condition; symptoms of self-rated depression, stress, state and trait anxiety, and

Table 2
Overview of the descriptive statistics of the dependent variables separated by time timepoints (week 0, week 3, week 6) and study condition (endurance training, strength training, active control).

	Endurance training (n = 10)			Strength training (n = 11)			Active control (n = 8)		
	Week 0	Week 3	Week 6	Week 0	Week 3	Week 6	Week 0	Week 3	Week 6
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Depressive symptoms									
Experts' ratings	3.85 (3.46)	4.58 (2.30)	3.90 (2.95)	6.60 (4.39)	4.40 (3.13)	4.80 (6.02)	8.67 (1.88)	4.67 (1.88)	3.33 (0.82)
Self-rating	10.50 (2.56)	9.50 (4.95)	7.75 (3.28)	12.22 (5.21)	10.78 (5.17)	11.78 (6.10)	10.67 (2.53)	10.67 (2.53)	10.67 (2.53)
Stress	27.60 (3.64)	24.40 (3.82)	25.20 (4.25)	28.33 (4.45)	28.22 (5.38)	28.73 (4.26)	28.75 (3.94)	26.50 (4.85)	26.50 (4.85)
Anxiety									
State anxiety	54.40 (8.46)	47.00 (11.12)	46.75 (11.75)	41.78 (12.47)	39.64 (11.71)	41.91 (11.40)	44.00 (7.17)	44.00 (7.17)	39.75 (10.10)
Trait anxiety	46.00 (6.16)	42.25 (10.82)	39.75 (6.08)	37.75 (9.71)	38.88 (9.14)	43.13 (11.75)	35.25 (6.27)	35.00 (6.48)	33.50 (8.86)
Fatigue	3.07 (0.80)	3.71 (0.98)	3.71 (0.98)	5.01 (1.41)	5.16 (1.20)	5.49 (1.29)	4.78 (0.49)	3.60 (0.96)	3.81 (0.93)
Insomnia	11.50 (2.73)	6.50 (3.35)	7.00 (2.71)	6.89 (6.02)	10.56 (6.87)	9.56 (7.94)	9.25 (2.90)	7.75 (2.03)	7.75 (2.03)
Physical Fitness									
6MWT	15.90 (1.36)	15.40 (1.19)	15.30 (1.24)	17.72 (5.40)	17.56 (6.49)	17.33 (5.78)	17.00 (2.55)	17.00 (2.55)	17.17 (2.54)
Handgrip test	28.95 (6.20)	28.28 (6.40)	32.96 (9.69)	35.88 (12.60)	35.34 (14.29)	33.80 (14.09)	32.98 (7.42)	34.81 (8.24)	36.68 (9.09)

Table 3
Overview of the inferential indices.

	Factors					
	Time		Group		Time by Group interaction	
	F	Partial η^2	F	Partial η^2	F	Partial η^2
Depressive symptoms						
Experts' ratings[1]	10.76*	0.290 [L]	0.19	0.127 [M]	1.06	0.078 [M]
Self-rating	2.25	0.080 [M]	0.93	0.067 [M]	1.95	0.130 [M]
Stress	5.67**	0.179 [L]	1.16	0.082 [M]	1.88	0.126 [L]
Anxiety						
State anxiety	6.32**	0.196 [L]	2.01	0.134 [M]	3.35**	0.205 [L]
Trait Anxiety	0.43	0.016 [S]	2.29	0.963 [L]	5.05***	0.280 [L]
Fatigue	0.75	0.028 [S]	8.96***	0.408 [L]	7.56***	0.368 [L]
Insomnia	1.59	0.057 [S]	0.09	0.007 [S]	8.84***	0.405 [L]
Physical fitness						
6MWT	1.40	0.051 [S]	0.72	0.053 [S]	0.90	0.065 [M]
Handgrip test	4.74*	0.154 [L]	0.73	0.053 [S]	6.33***	0.328 [L]

Notes: [1] = ANOVA for repeated measures, with baseline scores as co-variate * = p < .05; ** = p < .01; *** = p < .001; [S] = large effect size; [M] = medium effect size; [L] = large effect size.

insomnia improved in the endurance condition, while no or unfavorable changes were observed in the strengths condition. Fatigue decreased in the active control condition, while fatigue increased in the endurance and strengths condition.

The present findings add to the current literature in six ways: First, the introduction of an active control condition enabled to sort out possible improvements under physical activity-conditions because of the mere amount and quality of social interaction. Second, a broad variety of psychological dimensions were assessed via self-rating. Third, experts' ratings further strengthened the quality of the data. Fourth, the impact of physical activity interventions on fatigue appeared to be critical. Fifth, while improvements were observed at the level of psychological functioning, changes in physical activity performance were trivial. Sixth, given this, in our opinion, these patterns of results also have clinical and practical importance.

Four hypotheses and one exploratory research question were formulated and each of these is considered now in turn.

With the first hypothesis we expected improvements in psychological functioning (depression, anxiety, stress) after a strengths and endurance training, compared to an active control condition, but data did not confirm this. Rather, self-rated depression, anxiety and stress improved in the endurance or in the active control condition or both, while neither improvements nor deteriorations were observed in the strengths condition. Given this, the observed general pattern is at odds with previous findings (Hansen et al., 2018, 2019, 2020; Levin et al., 2016; Troschel et al., 2019). Most importantly, symptoms of depression, as rated by experts, exclusively improved in the active control condition, while no changes were observed in the two physical activity conditions.

The quality of the data does not allow a deeper understanding of the underlying mechanisms, and the following assumptions are highly speculative.

First, given that self-rated psychological functioning improved in two completely different study conditions (endurance training; active control condition), these two conditions might inherently have similar psychophysiological mechanisms. Such mechanisms might be higher self-control, higher self-efficacy, higher self-acceptance, and higher commitment to self-paced goals (Knapen et al., 2005, 2015). However, if this assumption were fully true, one would have expected improvement in all study conditions.

Second, it is conceivable that participants in the endurance and active control condition benefited from the favorable impact of a confident, secure, stable and patient-centered relationship between the patient and the expert. Data on the importance of a confident, stable and secure patient-expert-relationship come from psychotherapy research (Grawe, 2004, 2007; Grawe et al., 1994; Kanfer et al., 2011). However, for the following two reasons this assumption appears problematic. First, if the patient-expert-relationship were key, then we should have observed improvements in all three study conditions, though, this was not the case. Second, specifically the active control condition was not intended as a *bona fide* intervention consisting of treatment elements that were truly intended to be therapeutic (Jasbi et al., 2018; Marcus et al., 2014; Sadeghi Bahmani et al., 2019b, 2020c, 2020d; Zakiei et al., 2021); participants were just encouraged to exchange daily life experiences.

Third, above all moderate to vigorous physical activity patterns as a

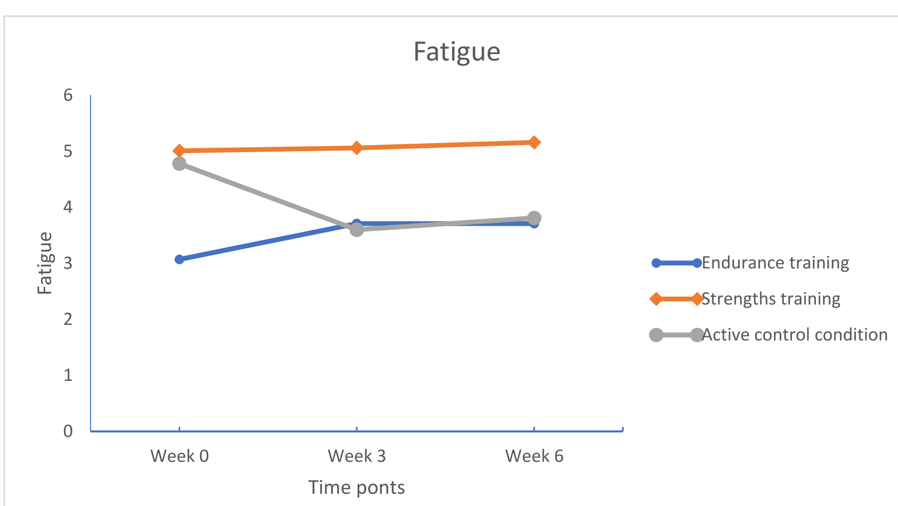

Fig. 2. Self-rated fatigue scores between and within the three study conditions (endurance training; strengths training; active control condition) at week 0, week 3 and week 6. Higher scores reflect higher fatigue. Points are means.

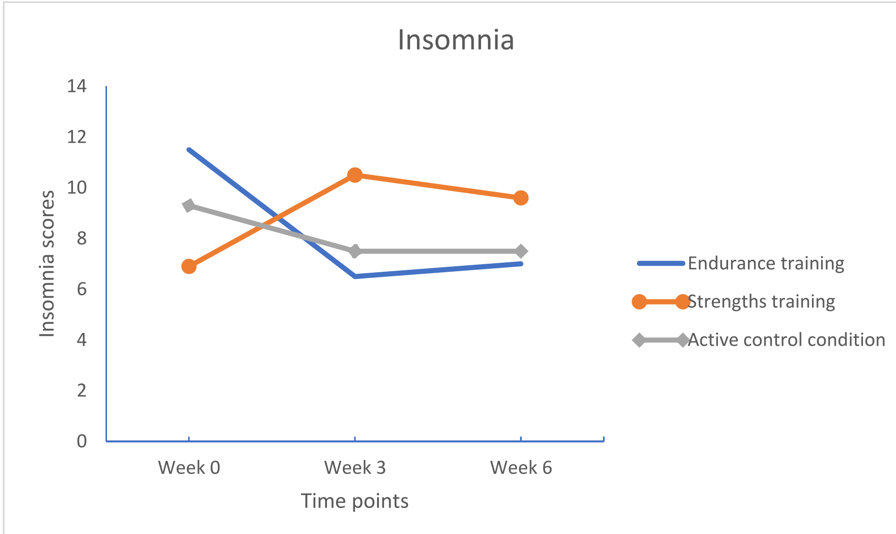

Fig. 3. Self-rated insomnia scores between and within the three study conditions (endurance training; strengths training; active control condition) at week 0, week 3 and week 6. Higher scores reflect higher insomnia. Points are means.

Table 4
Effect sizes for mean comparisons (depressive symptoms, stress, anxiety, fatigue, insomnia and physical fitness) from baseline to study end, separately for the three groups (endurance training, strength training, active control).

	Endurance training	Strength training	Active control
Cohen's d: Baseline vs. study end			
Depressive symptoms			
Experts' ratings	0.016 [T]	0.342 [S]	3.682 [L]
Self-rating	0.935 [L]	0.078 [T]	0.00 [T]
Stress	0.607 [M]	0.092 [T]	0.509 [M]
Anxiety			
State anxiety	0.747 [M]	−0.011 [T]	0.485 [S]
Trait Anxiety	1.021 [L]	−0.499 [S]	0.228 [S]
Fatigue	0.715 [M]	0.355 [S]	1.305 [L]
Insomnia	1.654 [L]	0.379 [S]	0.599 [M]
Physical fitness			
6MWT	0.461 [S]	0.070 [T]	0.067 [T]
Handgrip test	0.493 [S]	0.156 [T]	0.446 [S]

Notes: [T] = trivial effect size; [S] = small effect size; [M] = medium effect size; [L] = large effect size.

proxy of improved cardiorespiratory performance appeared to be particularly beneficial to improve behavioral and mental dimensions (Brand et al., 2010a, b; Brand et al., 2017; Brand et al., 2014; Ekelund et al., 2016; Sadeghi Bahmani et al., 2020a). However, a closer look at the objectively assessed physical activity performance of the present study showed that for the 6MWT, improvements were only observed in the active control condition, when compared to the other study conditions. Higher hand-grip strengths were observed in the endurance and active control conditions, always when compared between the study conditions; by contrast, no improvements (or impairments) were observed in the strengths condition. As such, beneficial changes in cardiorespiratory indices to explain changes in behavior and mental health are highly unlikely.

With the second hypothesis we assumed that compared to an active control condition, physical performance improved in the two physical activity conditions, and again, data did not confirm this: On the contrary, performance on the 6MWT test improved over time in the active control condition, when compared to the two physical activity interventions. Improvements on the handgrip test were observed in both the endurance and the active control condition, while this was not the case for the strengths condition. Thus, the present results are at odds with previous findings (Hansen et al., 2018, 2019, 2020; Levin et al., 2016; Troschel et al., 2019). Again, the quality of the data does not offer more insight into this unexpected results. We advance the following admittedly speculative assumptions:

First, the zero-improvement of the physical activity conditions could be associated with different diagnoses, surgical interventions, MGMT-status, IDH-type, or treatment regimen. However, as shown in Table 1, none of those dimensions differed between the groups.

Second, lower physical activity patterns were associated with fatigue (see also Tables 2–4; and see detailed discussion below). This assumption cannot be fully ruled out; fatigue increased in the physical activity conditions, while fatigue decreased in the active control condition. However, if fully true, then also handgrip performance should not have improved in the endurance condition.

Third, symptoms of depression unfavorably impacted on physical activity patterns. This assumption cannot be fully ruled out. However, self-rated symptoms of depression improved in the endurance training condition; as such, if symptoms of depression were associated with physical activity indices, one would have expected improvements at least in the endurance training condition. As regards symptoms of depression, no improvements were observed over time in the exercising conditions. To assess expert-based symptoms of depression, we employed the Hamilton Depression Rating Scale (HDRS): Compared to the Beck Depression Inventory (BDI) (Beck et al., 1961), which prevalently screens cognitive-emotional dimensions of depression, the HDRS emphasizes also somatic dimensions of major depressive disorders. As such, it is conceivable that participants in the exercising conditions experienced higher impairments on a somatic level; such an impairment could have been mirrored both in the HDRS and in the zero-improvements in the physical performance.

Fourth, by definition, it is conceivable that the current zero-improvements of the physical performance was obscured by further latent, but unassessed dimensions.

With the third hypothesis we assumed that insomnia as a proxy of subjective sleep improved in the physical activity conditions, compared to an active control condition, but data did only partially support this: Insomnia scores decreased over time in the endurance and active control conditions, but increased in the strengths condition. As such, the present pattern of results does only partially match with previous results observed among non-clinical and clinical samples of adolescents and adults (Chennaoui et al., 2015; Kalak et al., 2012; Kredlow et al., 2015; Sadeghi Bahmani et al., 2019a, 2019b, 2020a, 2020b). The present data expand upon previous studies, in that this was the very first study to prove that subjective sleep in patients with high-grade glioma after surgery and during radiochemotherapy can be improved both via regular endurance training and psychological counseling. Importantly, psychological counseling was not intended as *bona fide* intervention to be truly therapeutic (Jasbi et al., 2018; Marcus et al., 2014; Sadeghi Bahmani et al., 2019b, 2020c, 2020d; Zakiei et al., 2021). However, it is possible that psychological counseling improved patients' ability to get a deeper understanding of their current concerns and to accept their current situation in a broader context. As such, speculatively, it is conceivable that psychological counseling decreased psychological tension via decreased experiential avoidance and improved acceptance of the situation. This mechanism is well-known from the Acceptance and Commitment Therapy (ACT) (Salari et al., 2020; Zakiei et al., 2021).

With the fourth and last hypothesis we assumed that regular exercising improved fatigue, compared to an active control condition, though, data confirmed the opposite: Fatigue improved in the active control condition, while fatigue unfavorably increased in both the endurance and strengths condition. This pattern was against previous findings (Cramp and Byron-Daniel, 2012; Heine et al., 2015; Juvet et al., 2017; Kessels et al., 2018; Razazian et al., 2016, 2020; Rooney et al., 2019; Sadeghi Bahmani et al., 2019a; Safari et al., 2017; Wagoner et al., 2021). Again, the quality of the data does not allow a deeper understanding of the underlying psychophysiological mechanisms. The following admittedly speculative assumptions are conceivable:

First, the impact of the radiochemotherapy on fatigue in patients of the exercising conditions could have been particularly high (de Dreu et al., 2020; Ma et al., 2020; Valko et al., 2015), while the opposite was true for the active control condition. However, even if true, this does not answer the question why such an unbalanced fatigue load happened between the study conditions.

Second, exercising might increase fatigue at short-term; at least, this phenomenon is observed among individuals with multiple sclerosis (Giesser, 2015; Kalb et al., 2020). At middle- and long-term, in individuals with multiple sclerosis, regular exercising decreased fatigue (Razazian et al., 2016, 2020; Sadeghi Bahmani et al., 2019a) or not (Sadeghi Bahmani et al., 2019b). However, this does not explain, why fatigue decreased in the active control condition.

Third, as explained above, the active control condition was not intended as being truly a psychotherapeutic intervention. Nevertheless, we cannot rule out that psychological counseling improved participants' cognitive-emotional information processing such to coping and accepting in a more favorable fashion their current psychological and physical context; again, this phenomenon is observed in the field the ACT (Daly-Eichenhardt et al., 2016; Eifert, 2011; Harris, 2019; Hayes, 2019; Hayes et al., 2006, 2012).

The exploratory research question asked, if endurance or strengths training had a higher impact on participants' psychological functioning, insomnia, fatigue, and physical activity, and the answer was clear: While regular strengths training either had no favorable impact (depression, stress, anxiety, physical activity) or even an unfavorable impact on fatigue and insomnia, endurance training led to a broad variety of improvements (see Tables 2–4). Both the quality of the data and the theoretical background preclude straightforward assumptions to explain this pattern of results. While admittedly speculative, it appears that the intensity or further latent factors of strength training were such to preclude substantively favorable changes at participants' cognitive-emotional level. In this regard, Meyer et al. (2016) observed among women with major depressive disorders the following patterns: Compared to a preferred level of physical activity intensity, a higher prescribed intensity of physical activity had a larger impact on participants' mood both 10 and 30min after exercising. Given this, it is conceivable that a higher prescribed intensity of physical activity in the strengths condition might have had a more favorable impact on psychological functioning, including insomnia and physical activity patterns. However, it is important to mention that the present sample consisted of highly vulnerable individuals under a challenging radiochemotherapeutic treatment; as such, increasing the pace and intensity might have been inappropriate. Further, fatigue scores appear to preclude a higher physical activity intensity.

The novelty **of** the results of the present study should be balanced against the following limitations. First, the sample was small and we applied the intent-to-treat (ITT) with the last-observation-carried-forward (LOCF) statistical approach. However, we also emphasized on effect size calculations, which by definition are not sensitive to sample sizes. Relatedly, the decision was not to further explore possible differences between female and male participants. Second, it is highly conceivable that further latent and unassessed factors such as the intake of pain killers and antihistaminic medications might have biased two or more dimensions in the same or opposite directions. This holds particularly true as regards the possible impact of steroids on fatigue. We note that fatigue is a very common side-effect of cancer treatment; among others, methylphenidate is proposed to counterbalance cancer-related fatigue (Minton et al., 2008). Third, only patients from one study center were recruited. Fourth, similarly, it is conceivable that the pattern of results was biased because only participants able and willing to comply with the study conditions were enrolled. Fifth, insomnia was just subjectively, but not objectively assessed. However, there is sufficient evidence that subjective sleep quality, but not objective sleep duration, was associated with psychological functioning (Harvey and Tang, 2012; Lemola et al., 2013). Likewise, subjective data are as reliable as actigraphically assessed sleep continuity dimensions, at least among adolescents and at a level of large scale surveys (Wolfson et al., 2003). Sixth, a follow-up three, six, 12 and 24 months later would have allowed to explore, if and if so, to what extent current improvements remained stable over time. In our opinion, this research question is particularly important, if we consider that the time lapse of 12–16 months post-diagnosis is considered to be the peak incidence of mortality (Smoll et al., 2013), with a slow decline after that (Wang et al., 2015). Seventh, to assess strengths, we employed the handgrip test, while the so-called 1RM (One Repetition Maximum Test) is the gold standard assessment. However, to identify significant improvements, the IRM requires a single set of 6–12 repetitions with loads ranging from approximately 70-85% 1RM 2–3 times per week with high intensity of effort (reaching volitional or momentary failure) for 8–12 weeks (Androulakis-Korakakis et al., 2020). Clearly, the present study design including highly vulnerable participants did not meet such minimum requirements.

5. Conclusions

Among a sample of patients with high-grade glioma after neurosurgery and undergoing radiochemotherapy a six-weeks lasting endurance training and an active control condition impacted favorably on psychological dimensions and aspects of fatigue and insomnia. In contrast, strengths training appeared to have neither a beneficial nor a detrimental impact. Particular attention should be paid to fatigue. Overall, both endurance training and an active control condition deserve to be further promoted.

Declaration of competing interest

All authors declare no conflicts of interest. The study was performed without external funding.

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