J Neurooncol (2013) 114:93–100
DOI 10.1007/s11060-013-1153-z

CLINICAL STUDY

Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial

Chiara Zucchella · Annarita Capone · Valentina Codella · Alessandro Marco De Nunzio · Carmine Vecchione · Giorgio Sandrini · Andrea Pace · Francesco Pierelli · Michelangelo Bartolo

Received: 15 November 2012 / Accepted: 7 May 2013 / Published online: 16 May 2013

Abstract Cognitive impairment is one of the most common neurological disorders in neuro-oncological patients and exerts a deep negative impact on quality of life interfering with familiar, social and career-related activities. To test the effectiveness of early cognitive rehabilitation treatment for inpatients affected by primary brain tumors. Out of 109 consecutive patients enrolled in the study, 58 patients were randomly assigned to a rehabilitation group or to a control group. The rehabilitation consisted of 16 one-hour individual sessions of therapist-guided cognitive training, spread over 4 weeks, combining computer exercises and metacognitive training. Patients in the control group received usual care without cognitive training. All patients were evaluated by means of a comprehensive neuropsychological battery at the admission (T0) and after 4 weeks (T1). Patients in the rehabilitation group showed a significant improvement of cognitive functions. In particular, the domains that benefited most from the training were visual attention and verbal memory. The control group exhibited only a slightly, not statistically relevant, enhancement of cognitive performances. Cognitive rehabilitation for neuro-oncological inpatients resulted in a significant enhancement of cognitive performances after the training, also providing a foundation for early administration. Future research should be aimed to clarify the patients' characteristics that predict neuropsychological improvement, to identify the most effective elements in rehabilitative programs and to study the effects of treatment extension to everyday life.

Keywords Neuropsychology · Cognitive rehabilitation · Brain tumors · Quality of life · Neuro-oncology

C. Zucchella · A. Capone · V. Codella · F. Pierelli · M. Bartolo (✉)
Neurorehabilitation Unit, IRCCS Neurological Mediterranean Institute NEUROMED, Via Atinense 18, 86077 Pozzilli, Isernia, Italy
e-mail: bartolomichelangelo@gmail.com

C. Zucchella
Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

A. M. De Nunzio · M. Bartolo
Neurorehabilitation Unit, Laboratory of Multifactorial Biomechanics, IRCCS Neurological Mediterranean Institute NEUROMED, Via Atinense 18, 86077 Pozzilli, Isernia, Italy

C. Vecchione
Laboratory of Vascular Pathophysiology, IRCCS Neurological Mediterranean Institute NEUROMED, Via Atinense 18, 86077 Pozzilli, Isernia, Italy

C. Vecchione
Department of Medicine, University of Salerno, via S. Allende, 84081 Baronissi, Salerno, Italy

G. Sandrini
Neurorehabilitation Unit, IRCCS National Neurological Institute C. Mondino Foundation, via Mondino 2, 27100 Pavia, Italy

G. Sandrini
Department of Neurological Sciences, University of Pavia, via Mondino 2, 27100 Pavia, Italy

A. Pace
Neurology Unit, Regina Elena National Cancer Institute, via E. Chianesi 53, 00144 Rome, Italy

F. Pierelli
Department of Medical-Surgical Sciences and Biotechnology, University of Rome "La Sapienza", Corso della Repubblica 79, 04100 Latina, Italy

Introduction

Primary brain tumors (BTs) account for about 2 % of all malignancies, and are second only to stroke as the cause of death for neurologic disorders [1, 2]. Over the last years, therapeutic achievements in oncology have lengthened the life expectancy of neuro-oncological patients [3]; however, because of their longer progression-free survival, patients are more likely to experience physical and neurological deficits [4], including cognitive impairment [5–7].

Neurocognitive dysfunction in glioma patients has a multifactorial etiology, depending on localization and size of neoplastic lesion, symptomatic epilepsy, treatment side effects (neurosurgery, radiotherapy, chemotherapy, antiepileptics), patient-related factors such as age and psychological distress [8].

Regardless of the severity, cognitive disorders have a substantial negative impact on patients' daily lives [9–11], and are identified by both cancer patients and their caregivers as a significant factor interfering with familiar, social and career-related activities [12].

Cognitive function assessment has been widely employed, in clinical and pharmacological studies, to test the initial global cognitive level and to follow-up the clinical evolution [9, 13].

The early identification of neuropsychological changes in BT patients, may lead to improve the specificity and the final effectiveness of cognitive training. Moreover, this approach could represent a possible alternative or addition to pharmacological therapies (e.g. psychostimulants, acetylcholinesterase inhibitors) whose effects, up to date, lack of conclusive data [14, 15].

Despite cognitive rehabilitation effectiveness for patients with various neurological diseases has been widely demonstrated [16–20], only a few published studies have examined the potential benefits of such treatment for adults with BTs [21–26].

To the best of our knowledge, no previous studies have addressed cognitive rehabilitation in a neuro-oncological population in the early phase after surgical resection. To test the hypothesis that cognitive training can improve neuropsychological performance in early post-surgical BT patients, a randomized controlled trial was designed.

Materials and methods

Participants

The study enrolled consecutive post-neurosurgical patients referred to the Neurorehabilitation Unit of the IRCCS Neurological Mediterranean Institute NEUROMED, between November 2009 and October 2011. Medical inclusion criteria were as follows: age $\geq$18 years; diagnosis of primary BT, defined as the presence of a primary lesion on neuroimaging (CT or MRI), confirmed by histopathological examination. All the patients had been treated by maximal feasible tumor resection (biopsy, subtotal resection, gross total resection) and were admitted to the Neurorehabilitation Unit within two weeks after surgery. Neither adjuvant therapy, nor radiotherapy or chemotherapy was administered to the patients before or during the rehabilitation program.

The exclusion criteria were: aphasia, neglect, concomitant neurological or psychiatric disorders, inability to be examined due to severe disturbances in consciousness, motor impairment that could have affected the performance in some tests.

All the patients who fitted the clinical inclusion criteria, underwent the neuropsychological assessment for cognitive eligibility.

All patients, or their legal guardians, signed an informed consent form before entering the study. The study was approved by the local ethics committee board and was conducted in accordance with the revised version of the Helsinki Declaration.

Measures

The neuropsychological battery consisted of the Mini Mental State Examination (MMSE), a measure of global cognitive functioning [27], Digit Span and Corsi's Test for verbal and spatial immediate memory span [28], Rey Auditory Verbal Learning Test (RAVLT) and logical memory for verbal memory, immediate and delayed recall [29, 30], Raven's Coloured Progressive Matrices 47 (PM47) for non verbal reasoning [31], Frontal Assessment Battery (FAB) for frontal functionality [32], Trail Making Test A (TMTA) and Trail Making Test B (TMTB) for simple speed processing and complex attention [33], Attentive Matrices for visual selective attention [34], Rey-Osterrieth complex figure copy for visuo-constructional abilities [35] and verbal fluency (both phonological and semantic) [36]. The Esame Neuropsicologico per l'Afasia (E.N.P.A.) [37] was administered to all patients in order to disclose expressive and/or receptive language disturbances, before starting the neuropsychological evaluation.

Parallel versions of the RAVLT were used at follow-up assessments.

The neuropsychological battery included validated tests widely used in clinical practice, also suggested for studies of patients affected by BTs [38, 39]. Normative data are available for each test published.

The completion of the test battery required approximately 1 h, fulfilling the co-existing demands for brevity and sensitivity.

Cognitive training

The cognitive treatment was designed in accordance with the recent recommendations of Cicerone et al. [20], which underline the need to combine direct training of the impaired function with metacognitive training to promote development of compensatory strategies and generalization to real life.

The cognitive rehabilitation program was administered by two psychologists, experts in neuropsychology; it provided a total of 16 individual one-hour sessions, four sessions per week for 4 weeks.

During each session, patients performed 45 min of therapist-guided computer exercises with increasing difficulty levels, targeting different cognitive functions; the choice of treating different functions was based on the literature evidence that patients with BTs seem to experience mild and diffuse deficits in various cognitive domains [8]. During the computer exercises, the psychologist ensured that patients have understood task instructions and suggested metacognitive strategies to increase awareness, foster motivation and promote self-regulation (e.g. the psychologist asked patients to predict how they think they might perform on specific task, monitor and evaluate their performance, identify factors contributing to failures and success).

The computerized exercises included all the contents of the following softwares: "Training di riabilitazione cognitiva" [40] and "Una palestra per la mente" [41], and addressed different cognitive domains, as shown in the detailed list below:

Time orientation days of the week, months of the year, seasons, holidays and celebrations; anagrams of the days of the week, months, and seasons, signs of the zodiac; identification of temporal sequences within a story or performing activities of daily life; temporal sequences with images relating to activities of daily life;

Spatial orientation recognition of right and left; recognition and identification of cities, regions; wordsearch puzzle; placement of objects; observation of scenes and identification of the placement of objects; orienteering skills on pathways;

Visual attention searching for targets among distracters (stylized elements or objects); wordsearch puzzle; finding the differences between images/scenes; searching for things by categories;

Logical reasoning calculation; finding words in context; search for the outsider in categories; logical completion (metaphors and proverbs); categorization;

Memory recognition of pairs of words with or without logical connection; remembering lists; face recognition; memorization of scenes and stories answering a questionnaire; object location and object-seeking (like game memory cards).

Executive functions questions about a story; identification of the purpose/meaning of a story; pathways with rules; recognition of moods; mathematical logic; action planning; reordering the sequence of a story; critical judgement (give the pros and cons of ethical and social topics); problem solving.

During the last 15 min of the session, the psychologist discussed with the patient doubts or difficulties encountered in performing the exercises and explained the meaning of the exercises and how to contextualize them, transferring the strategies learned to everyday life (e.g.: patients were encouraged to adopt "associative techniques" and imagination to improve memory: "to avoid to forget your diary before going to the office, you must stop for a while (at least 10 s) to imagine the diary inside your bag. The association will become automatic and you will remember easily to take your agenda". Again, "to realize a recipe, close your eyes and try to imagine all the ingredients on the table. Focus your attention on each one, then try to recall the right sequence to use them").

To ensure inter-therapist reliability and to provide the same guidance during the training sessions, the psychologists followed written instructions and examples previously defined.

Study design and procedure

Among patients who underwent the baseline neuropsychological assessment (T0), only those who presented cognitive deficits (defined as test scores below population-based norms on at least 3 neuropsychological tests) were cognitively "eligible" for the study and randomly assigned to the treatment group or to the control group.

The randomization schedule was computer generated using a basic random number generator.

Randomization was stratified according to histology (high grade/low grade) and lesion side (right/left). For each stratum, random numbers were assigned to the participants and put into envelopes; it was determined randomly whether the even or odd number would enter the experimental group. Participants were assigned to the study according to the numbers they received on opening the envelopes. The different steps in this process were administered by different researchers who were blinded to the other processes.

Patients performed the baseline evaluation within three days after admission and cognitive treatment began immediately after the group assignment during the first week.

Both groups received usual rehabilitative care (medications, physiotherapy); the control group did not perform

cognitive training. Both groups were comparable in the distribution of therapies and daily timetable.

All patients were re-evaluated after 4 weeks (T1).

Pre- and post-treatment assessments were done by a psychologist blind to patient randomization and not involved in the care of the patients.

Statistical analysis

For neuropsychological measures, age-, gender- and education-corrected scores were calculated from the raw scores according to Italian population-based norms and only corrected scores were included in the statistical analysis.

Descriptive statistics, Mann–Whitney *U* test and the χ^2 were applied to characterize and compare demographic and clinical features of the two groups (treatment and control) at baseline. Changes within groups at different time points (T0 and T1) were investigated using the Wilcoxon signed-rank test. Comparisons of outcome measures between the two groups were performed using the Mann–Whitney *U* test.

As the neuropsychological tests provided non-normally distributed ordinal data, the non-parametric statistical tests were applied.

All computations were performed using the Statistical Package for the Social Sciences version 17.0 for Windows (version 17.0. SPSS Inc., Chicago, IL, USA). p value ≤ 0.05 was considered as statistically significant.

Results

Out of 109 consecutive patients who underwent the neuropsychological examination, 79 (72.4 %) showed evidence of cognitive impairment. According to the exclusion criteria 17 patients were excluded, respectively for aphasia (11), severe behavioral and psychiatric disorders (4), serious visual deficit (2). The remaining 62 patients were randomly assigned to the treatment group (30 patients) or to the control group (32 patients); 5 patients in the treatment group dropped out for deteriorating medical condition (2), renal failure (1), cardiovascular complications (1), death (1); while 4 dropped out of the control group for

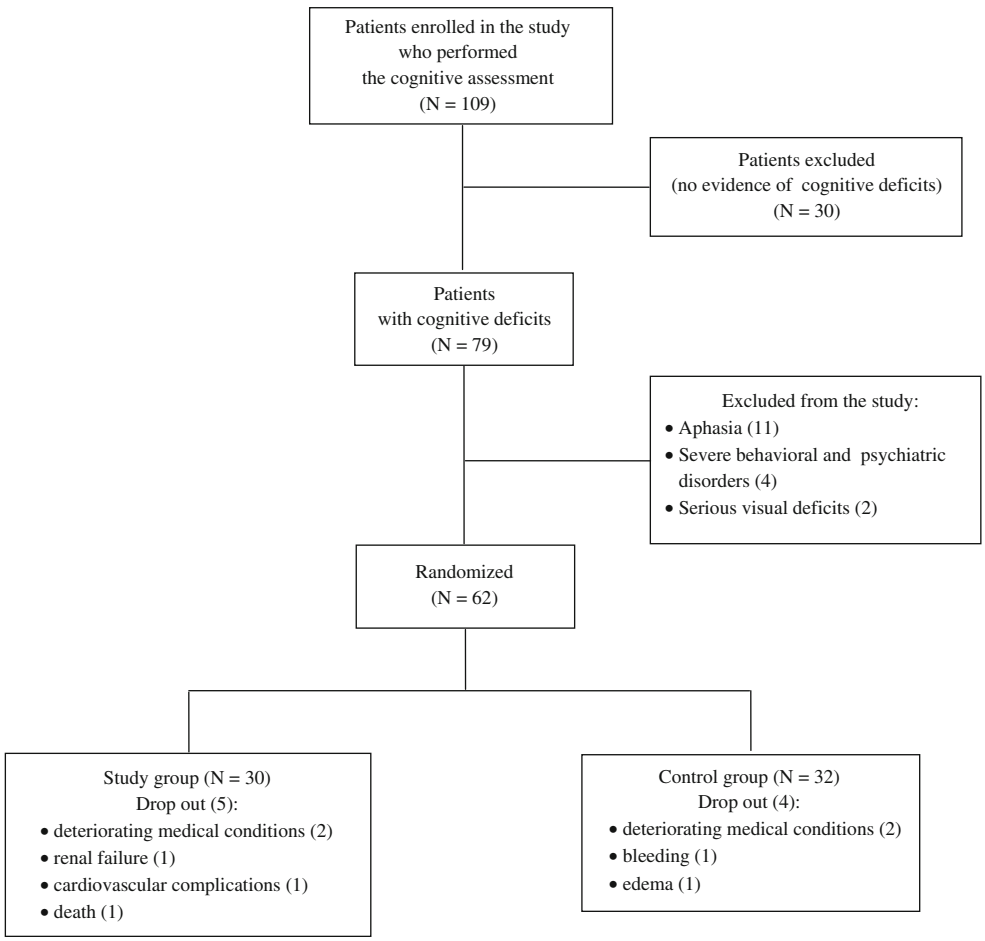

Fig. 1 Flow chart of the enrollment and randomization

Table 1 Demographic and clinical features

	Study group ($n = 25$)	Control group ($n = 28$)
Age (years) (mean ± SD)	58.7 ± 13.9	52.7 ± 17
Education (years) (mean ± SD)	9.6 ± 3.8	10.4 ± 4.5
Gender: female *n* (%)/male *n* (%)	11 (44)/14 (56)	15 (53)/13 (47)
Histology *n* (%)		
HGG	12 (48)	13 (46.5)
LGG	3 (12)	4 (14.3)
Meningioma	7 (28)	9 (32.1)
Other	3(12)	2(7.1)
Lesion side		
Right *n* (%)	14 (56)	16 (57)
Left *n* (%)	11 (44)	12 (43)
Location		
Frontal	8 (32)	11 (39.3)
Temporal	4 (16)	3 (10.7)
Parietal	–	2 (7.1)
Occipital	2 (8)	–
Fronto-temporal	4 (16)	5 (17.9)
Fronto-parietal	2 (8)	2 (7.1)
Temporo-parietal	–	1 (3.6)
Parieto-occipital	–	1 (3.6)
Temporo-parieto-occipital	2 (8)	1 (3.6)
Cerebellum	3 (12)	2 (7.1)
Lesion size (cm)		
≤3.5	10 (40)	9 (32.1)
>3.5	15 (60)	19 (67.9)
Antiepileptic drugs *n* (%)	11 (44)	9 (32.1)
Corticosteroids *n* (%)	5 (20)	7 (25)

HGG high grade glioma, *LGG* low grade glioma

worsening of the clinical conditions (2), bleeding (1), edema (1).

Therefore the final analysis was conducted on 25 cases and 28 controls (see flow of participants in Fig. 1).

At the time of inclusion, when socio-demographic and clinical characteristics of the two groups were checked, no significant differences were found, suggesting that the two groups were matched (Table 1). Moreover, there were no significant differences between the two groups in any of the neuropsychological tests (all p values ≥ 0.05).

The within-group analysis revealed a statistically significant improvement in all the neuropsychological measures at the end of the treatment period in the study group, while the control group showed a trend towards improvement, as indicated by the enhanced corrected scores at cognitive tests, without reaching statistical significance. Table 2 provides the means and standard deviation values for the intervention and control groups on the study variables at T0 and T1.

Comparison of the outcome measures of the two groups (Mann–Whitney U test) revealed that although the experimental group performed better than the control group in most of the neuropsychological tests, a statistically significant difference was found only in the domains of visual attention and verbal memory that improved more in the study group.

Differences in measures of logical-executive functioning were not statistically significant (Table 3).

Discussion

This study aimed at evaluating the effectiveness of an early cognitive training program for BT post-surgical inpatients. It showed that intervention markedly improved cognitive functioning in treated subjects, who performed significantly better in all the objective neuropsychological measures after training. Specifically, the most significant differences in favor of the treatment group were found in the domains of visual attention and verbal memory. The control group also showed a mild improvement: in fact, the corrected scores of all neuropsychological tests were slightly (but not statistically relevantly) enhanced.

Taken together, these data seem to confirm previous evidence that an approach based on retraining can improve cognitive performances, particularly in the attentional domain [42]; the retraining method in fact is based on the assumption that a "target process" can be enhanced by a repetitive stimulation, such as the one obtained by frequently practiced exercises [43]; such repetition is thought to make the skill more automatic, inducing a restitution of function. Usually the retraining method has been applied to rehabilitate mild cognitive deficits, showing positive effects particularly in the domain of attention, as for the patients observed in this study. Moreover, data are consistent with previous studies suggesting that attentive gains can provide a substrate that mediates the generalization of the improvements to other cognitive domains, such as memory [44, 45]. An explanation for the minor benefit observed in the logical-executive domain might be that it takes a longer time to learn strategies and to use them spontaneously.

It is likely that the mild cognitive improvement showed by the control group was due to the natural recovery occurring after the removal of the intracranial space occupying lesions and the relief of cerebral edema [46].

These data seem to provide a foundation for the administration of early inpatient cognitive rehabilitation after neurosurgery to BT patients. Unfortunately, cognitive and vocational rehabilitation are rarely offered to BT

Table 2 Baseline and post treatment outcome measures (mean ± SD): within-group analysis

	Study group			Control group		
	T0	T1	*p*	T0	T1	*p*
MMSE	21.8 ± 5.2	23.8 ± 5.4	0.000	23.9 ± 4.2	24 ± 4.1	n.s.
Digit Span	3.9 ± 0.6	4.5 ± 0.7	0.001	4.1 ± 0.6	4.2 ± 0.5	n.s.
Corsi's Test	3.6 ± 0.8	4.1 ± 0.8	0.005	3.7 ± 0.8	4 ± 0.9	n.s.
RAVLT – immediate recall	24.7 ± 10	29.7 ± 10.2	0.001	24.1 ± 10	24.3 ± 9.3	n.s.
RAVLT – delayed recall	4.2 ± 2.2	6.1 ± 3.1	0.001	3.4 ± 2.7	3.6 ± 2.5	n.s.
Logical memory—immediate recall	4.1 ± 2.1	5.3 ± 1.6	0.000	3.4 ± 1.4	3.6 ± 1.3	n.s.
Logical memory—delayed recall	3.5 ± 2.3	5 ± 2	0.000	2.6 ± 1.9	2.8 ± 1.7	n.s.
PM47	21.4 ± 5.7	24.8 ± 6.7	0.000	20.4 ± 6.1	20.9 ± 5.8	n.s.
FAB	12.8 ± 3.6	13.8 ± 3.8	0.001	13.8 ± 1.3	13.9 ± 1.8	n.s.
TMTA	126.8 ± 68.1	87.1 ± 48.9	0.000	119.6 ± 45.6	112.2 ± 38.8	n.s.
TMTB	271.1 ± 95.7	216.2 ± 102	0.000	304.5 ± 94.9	296.1 ± 87.7	n.s.
Attentive matrices	25.7 ± 12.6	36 ± 12.9	0.000	24.0 ± 11.5	25.3 ± 9.4	n.s.
Phonological fluency	16.8 ± 8.7	21.1 ± 11.1	0.013	19.9 ± 7.6	20.5 ± 6.7	n.s.
Semantic fluency	24.8 ± 11.1	31.1 ± 13.9	0.000	25.8 ± 9.3	27 ± 8.2	n.s.
Rey-Osterrieth figure, copy	17.8 ± 10.6	20.9 ± 11.2	0.000	21.7 ± 7.3	22.1 ± 7	n.s.

MMSE Mini Mental State Examination, *RAVLT* Rey Auditory Verbal Learning Test, *PM47* Progressive Matrices, *FAB* Frontal Assessment Battery, *TMTA* Trail Making Test Part A, *TMTB* Trail Making Test Part B

$p < 0.05$, *n.s.* not significant

Table 3 Post-intervention outcome measures (mean ± SD): between group analysis

Outcome measures	Study group	Control group	*p*
MMSE	23.8 ± 5.4	24 ± 4.1	n.s.
Digit span	4.5 ± 0.7	4.2 ± 0.5	n.s.
Corsi's test	4.1 ± 0.8	4 ± 0.9	n.s.
RAVLT—immediate recall	29.7 ± 10.2	24.3 ± 9.3	n.s.
RAVLT—delayed recall	6.1 ± 3.1	3.6 ± 2.5	0.004
Logical memory—immediate recall	5.3 ± 1.6	3.6 ± 1.3	0.000
Logical memory—delayed recall	5 ± 2	2.8 ± 1.7	0.000
PM47	24.8 ± 6.7	20.9 ± 5.8	n.s.
FAB	13.8 ± 3.8	13.9 ± 1.8	n.s.
TMTA	87.1 ± 48.9	112.2 ± 38.8	0.015
TMTB	216.2 ± 102	296.1 ± 87.7	0.009
Attentive matrices	36 ± 12.9	25.3 ± 9.4	0.005
Phonological fluency	21.1 ± 11.1	20.5 ± 6.7	n.s.
Semantic fluency	31.1 ± 13.9	27 ± 8.2	n.s.
Rey-Osterrieth figure, copy	20.9 ± 11.2	22.1 ± 7	n.s.

MMSE Mini Mental State Examination, *RAVLT* Rey Auditory Verbal Learning Test, *PM47* Progressive Matrices, *FAB* Frontal Assessment Battery *TMTA* Trail Making Test Part A, *TMTB* Trail Making Test Part B

$p < 0.05$, *n.s.* not significant

patients, and primary oncological settings are generally not familiar with these services, since cancer patients are not seen as potential clients because of their prognosis [47].

The novelty and, in our view, strength of this study is that the training was carried out during the acute phase; in this sense, the present study continues and extends a research field on early rehabilitation of neuro-oncological patients, an area in which studies are few and exclusively focused on motor recovery [48, 49].

As the brain displays a heightened sensitivity to rehabilitation in the early stages after the lesion, clinical guidelines in neuro-rehabilitation highlight that the training should begin as early as possible to improve the recovery process and reduce disability; the need for early intervention is even more pressing in the case of BT patients, as the deterioration of their condition is often much faster and their life expectancy shorter.

Moreover, the improvement of cognitive functions in this very early stage of patient care could provide patients with a cognitive reserve to balance or at least minimize the side effects of subsequent treatments; further longitudinal and instrumental studies are needed to test this hypothesis.

This study was designed as a randomized controlled trial (RCT). Despite the difficulties in applying this approach to neuropsychological rehabilitation, this design offers the study one strength: the methodology of an RCT should enhance the likelihood of the study generating unbiased and sufficiently precise results that can be applied in clinical practice [50].

The study presents some limitations, most notably the absence of follow-up monitoring and quality of life (QoL) assessment.

As regards the first point, since our institution does not provide radiotherapy and chemotherapy, the neuro-oncological patients were admitted for a set time (on average 4 weeks) before being discharged to start anti-cancer treatment in other hospitals, to which they were subsequently referred for periodic controls. As BTs, particularly malignant ones, have a tendency to recur, whether the gains recorded at the end of the early rehabilitation program are maintained is an important issue to be addressed in future studies.

As regards the second point, since QoL is a multidimensional concept in cancer patients that encompasses various dimensions related to evolving functional and social limitations, multiple treatment decisions and treatment side effects, we feel that, patients may not have been able to express a comprehensive and full opinion in the acute phase, which is the one we considered. Moreover, previous evidence suggested that patients with cognitive deficits may not be able to adequately assess QoL issues, providing subjective QoL scores not strongly related to outcome [51].

Although the study population included both gliomas and meningiomas, these were balanced and comparable between the two groups, permitting a statistical analysis on the whole sample. The expansion of the study sample will allow subgroup analysis, also considering histological type.

Finally, in this study we did not consider a "placebo" condition to rule out that the cognitive improvement in the intervention group could be due to non specific variables such as the attention given to patients, rather than the rehabilitation program itself. But we agree with previous authors that it is impractical and unethical to make patients work for so many hours without any rehabilitative goal [52].

In conclusion, as objective and subjective cognitive functions continue to gain recognition as a critical aspect of care for cancer patients and survivors, it is important to develop effective treatments to address this, and examine the mechanisms underlying their efficacy. The findings of this study provide an encouraging foundation for larger-scale studies on cognitive treatments for neuro-oncological patients; future research should be aimed at clarifying the patients' characteristics that predict neuropsychological improvement, identifying the most effective elements in rehabilitative programs and enhancing the occurrence of transfer of treatment effects to everyday life. Moreover, as neuro-oncological patients often show complex disabilities, also considering the close relationship between cognition and global functioning, it could be interesting to investigate the overall recovery effects of cognitive rehabilitation, also combined with other interventions (such as speech therapy, physiotherapy). Follow-up studies are also needed to test the maintenance of gains over time. Finally, the development of functional imaging techniques could bridge the gap between clinical practice and an understanding of the neural mechanisms underlying the recovery, making it possible to measure in vivo the re-emergence of lost functions.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Jensen OM, Estève J, Moller H, Renard H (1990) Cancer in the European Community and its member states. Eur J Cancer 26(11–12):1167–1256
2. Radhakrishnan K, Bohnen NI, Kurland L (1994) Epidemiology of brain tumors. In: Morantz RA, Walsh JW (eds) Brain tumors: a comprehensive text. Marcel Dekker, New York, pp 1–18
3. Meyers CA, Rock EP, Fine HA (2012) Refining endpoints in brain tumor clinical trials. J Neurooncol 108:227–230
4. Huang ME, Wartella JE, Kreutzer JS (2001) Functional outcomes and quality of life in patients with brain tumors: a preliminary report. Arch Phys Med Rehabil 82:1540–1546
5. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB (2001) Incidence of neurologic deficits and rehabilitation of patients with brain tumors. Am J Phys Med Rehabil 80:346–350
6. Hottinger AF, Yoon H, Deangelis LM, Abrey LE (2009) Neurological outcome of long-term glioblastoma survivors. J Neurooncol 95:301–305
7. Zucchella C, Bartolo M, Di Lorenzo C, Villani V, Pace A (2013) Cognitive impairment in primary brain tumors outpatients: a prospective cross-sectional survey. J Neurooncol 112(3):455–460
8. Taphoorn MJ, Klein M (2004) Cognitive deficits in adult patients with brain tumours. Lancet Neurol 3(3):159–168
9. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC (2003) Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. Int J Radiat Oncol Biol Phys 55:992–999
10. Giovagnoli AR, Silvani A, Colombo E, Boiardi A (2005) Facets and determinants of quality of life in patients with recurrent high grade glioma. J Neurol Neurosurg Psychiatry 76(4):562–568
11. Gustaffson M, Edvardsson T, Ahlstrom G (2006) The relationship between function, quality of life and coping in patients with low-grade gliomas. Support Care Cancer 14:1205–1212
12. Biegler KA, Chaoul MA, Cohen L (2009) Cancer, cognitive impairment, and meditation. Acta Oncol 48(1):18–26
13. Giovagnoli AR (2012) Investigation of cognitive impairments in people with brain tumors. J Neuroncol 108(2):277–283
14. Kim JH, Brown SL, Jenrow KA (2008) Mechanisms of radiation induced brain toxicity and implications for future trials. J Neurooncol 87:279–286
15. Gehring K, Sitskoorn MM, Aaronson NK, Taphoorn MJ (2008) Interventions for cognitive deficits in adults with brain tumours. Lancet Neurol 7:548–560
16. Levine B, Robertson IH, Clare L, Carter G, Hong J, Wilson BA, Duncan J, Stuss DT (2000) Rehabilitation of executive functioning: an experimental-clinical validation of goal management training. J Int Neuropsychol Soc 6:299–312
17. Kaschel R, Della Sala S, Cantagallo A, Fahlböck A, Laaksonen R, Kazen M (2002) Imagery mnemonics for the rehabilitation of memory: a randomised group controlled trial. Neuropsychol Rehabil 12:127–153
18. Sinforiani E, Banchieri L, Zucchella C, Pacchetti C, Sandrini G (2004) Cognitive rehabilitation in Parkinson's disease. Arch Gerontol Geriatr Suppl 9:387–391

19. Brissart H, Daniel F, Morele E, Leroy M, Debouverie M, Defer GL (2011) Cognitive rehabilitation in multiple sclerosis: a review of the literature. Rev Neurol (Paris) 167(4):280–290
20. Cicerone KD, Langenbahn DM, Braden C et al (2011) Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. Arch Phys Med Rehabil 92(4):519–530
21. Rao SM, Bieliauskas LA (1983) Cognitive rehabilitation two and one-half years post right temporal lobectomy. J Clin Neuropsychol 5(4):313–320
22. Sherer M, Meyers CA, Bergloff P (1997) Efficacy of postacute brain injury rehabilitation for patients with primary malignant brain tumors. Cancer 80(2):250–257
23. Locke DE, Cerhan JH, Wu W, Malec JF, Clark MM, Rummans TA, Brown PD (2008) Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumors: a pilot study. J Support Oncol 6(8):383–391
24. Duval J, Coyette F, Seron X (2008) Rehabilitation of the central executive component of working memory: a re-organisation approach applied to a single case. Neuropsychol Rehabil 18(4): 430–460
25. Gehring K, Sitskoorn MM, Gundy CM, Sikkes SA, Klein M, Postuma TJ, van den Bent MJ, Beute GN, Enting RH, Kappelle AC, Boogerd W, Veninga T, Twijnstra A, Boerman DH, Taphroon MJ, Aaronson NK (2009) Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. J Clin Oncol 27(22):3712–3722
26. Hassler MR, Elandt K, Preusser M, Lehrner J, Binder P, Dieckmann K, Rottenfusser A, Marosi C (2010) Neurocognitive training in patients with high-grade glioma: a pilot study. J Neurooncol 97(1):109–115
27. Folstein MF, Folstein SE, McHugh PR (1975) "Mini mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198
28. Orsini A, Grossi D, Capitani E, Laiacona M, Papagno C, Vallar G (1987) Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. J Neurol Sci 8(6): 539–548
29. Carlesimo GA, Caltagirone C, Gainotti G (1996) The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the standardization of the mental deterioration battery. Eur Neurol 36(6):378–384
30. Carlesimo GA, Buccione I, Fadda L, Graceffa A, Mauri M, Lo Russo S, Bevilacqua G, Caltagirone C (2002) Standardizzazione di due test di memoria per uso clinico: Breve Racconto e Figura di Rey. Nuova Rivista Neurol 12:1–13
31. Basso A, Capitani E, Laiacona M (1987) Raven's coloured progressive matrices and brain damage: normative values in 305 adult normal controls. Funct Neurol 2(2):189–194
32. Apollonio I, Leone M, Isella V, Piamarta F, Consoli T, Villa ML, Forapani E, Russo A, Nichelli P (2005) The frontal assessment battery (FAB): normative values in an Italian population sample. Neurol Sci 26:108–116
33. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E (1996) Trail making test: normative values from 287 normal adults controls. Ital J Neurol Sci 17: 305–309
34. Spinnler H, Tognoni G (1987) Standardizzazione e taratura italiana di test neuropsicologici. Ital J Neurol Sci 6(Suppl.8):1–120
35. Caffarra P, Vezzadini G, Dieci F, Zonato F, Venneri A (2002) Rey-Osterrieth complex figure: normative values in an Italian population sample. Neurol Sci 22:443–447
36. Novelli G, Papagno C, Capitani E, Laiacona M, Vallar G, Cappa S (1986) Tre test clinici di ricerca e produzione lessicale: taratura su soggetti normali. Archivio di Psicologia, Neurologia e Psichiatria 47:477–486
37. Capasso R, Miceli G (2001) Esame Neuropsicologico per l'Afasia (E.N.P.A.). Springer, Milano
38. Lageman SK, Cerhan JH, Locke DEC, Anderson SK, Wu W, Brown PD (2010) Comparing neuropsychological tasks to optimize brief cognitive batteries for brain tumors clinical trials. J Neurooncol 96(2):271–276
39. Papagno C, Casarotti A, Comi A, Gallucci M, Riva M, Bello L (2012) Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). J Neurooncol 108(2): 269–275
40. Powell T, Malia K (2009) Training di riabilitazione cognitiva, Erickson edn. Trento, Italia
41. Gollin D, Ferrari A, Peruzzi A (2011) Una palestra per la mente. Erickson, Trento
42. Kim YH, Yoo WK, Ko MH, Park CH, Kim ST, Na DL (2009) Plasticity of the attentional network after brain injury and cognitive rehabilitation. Neurorehabil Neural Repair 23:468–477
43. Petersen SE, van Mier H, Fiez JA, Raichle ME (1998) The effects of practice on the functional anatomy of task performance. Proc Natl Acad Sci USA 95:853–860
44. Solberg MM, Mater CA (2001) Improving attention and managing attentional problems. Adapting rehabilitation techniques to adults with ADD. Ann N. Y. Acad Sci 931:359–375
45. Robertson IH (2005) The rehabilitation of attention. In: Stuss DT, Winocur G, Robertson IH (eds) Cognitive neurorehabilitation. Cambridge University Press, New York, pp 302–313
46. Kolb B (1999) Synaptic plasticity and the organization of behaviour after early and late brain injury. Can J Exp Psychol 53:62–76
47. Giordana MT, Clara E (2006) Functional rehabilitation and brain tumor patients. A review of outcome. Neurol Sci 27:240–244
48. Geler-Kulcu D, Gulsen G, Buyukbaba E, Ozkan D (2009) Functional recovery of patients with brain tumor or acute stroke after rehabilitation: a comparative study. J Clin Neurosci 16: 74–78
49. Bartolo M, Zucchella C, Pace A, Lanzetta G, Vecchione C, Bartolo M, Grillea G, Serrao M, Tassorelli C, Sandrini G, Pierelli F (2012) Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. J Neurooncol 107(3): 537–544
50. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG (1998) The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 51:1235–1241
51. Meyers CA, Hess KR, Yung WK, Levin VA (2000) Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Clin Oncol 18(3):646–650
52. Gehring K, Aaronson NK, Gundy CM, Taphoorn MJB, Sitskoorn MM (2011) Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. J Int Neuropsychol Soc 17:256–266