Cognitive Rehabilitation

10

Chiara Zucchella

10.1 Epidemiology of Cognitive Disorders in Brain Tumours

In the last decades in western countries, the advances in diagnostic and therapeutic options have extended average life expectancies of neuro-oncological population [1]; specifically for patients affected by low to intermediate grade tumours the expected survival may reach 10–15 years, while for patients diagnosed with glioblastoma multiforme the median survival has increased to 18–24 months from 9 to 12 months in the years before the introduction of temozolomide in 2006 [2–4].

As survival has improved, long-term treatment and disease-related morbidity has gained more attention and cognitive dysfunction has been recognized as the most frequent complication among long-term survivors [5–7]. A growing literature in fact shows that impairment of cognitive functions, such as psychomotor slowing, attention and memory (working memory) deficits, executive dysfunction (cognitive control and flexibility, planning, and foresight) or focal deficits such as aphasia or apraxia may occur in most patients with brain tumours (BT) [8–11].

Rates of patients suffering from cognitive disorders evaluated through neuropsychological test assessments range from 29% in patients with non-irradiated low-grade glioma (LGG) to 50–90% in patients with diverse BT [12–16]. The lack of homogeneity in study populations and treatments as well as methodological issues such as the insensitivity of the assessment methods used, the duration of follow-up, the variability of normative data used to detect patients with cognitive impairments explain the variability of literature data.

Although the pathophysiology of cognitive impairment is not completely understood, several causes have been recognized, suggesting a multifactorial aetiology of neuropsychological deficits [5, 17–18].

First of all, the tumour itself, tumour progression, tumour-related neurological complications such as epilepsy can cause cognitive deficits. Although tumour type or

C. Zucchella (✉)
Neurology A – Verona University Hospital, Verona, Italy

M. Bartolo et al. (eds.), *Neurorehabilitation in Neuro-Oncology*,
https://doi.org/10.1007/978-3-319-95684-8_10

volume has not always been found to predict cognitive performance [19], cognitive impairments have been detected more frequently at diagnosis in rapid-growing tumours such as glioblastomas than in slow-growing ones such as LGG [20]. Nevertheless, recent literature underlined that also LGG can't be considered "tumour mass" as reported in the classic literature; instead, they represent an infiltrating chronic disease that invades the central nervous system, especially the subcortical connectivity known to be critical for brain and cognitive functions [21, 22]. Moreover, deficits in cognitive functions may indicate tumour recurrence, even before structural changes are evident on computerized tomography or magnetic resonance imaging [23, 24].

Apart from the tumour itself, also medical treatments contribute largely to the cognitive side effects: a wide literature in fact has documented that surgery, radiotherapy, chemotherapy, and antiepileptic drugs can all have adverse effects on cognitive functioning [5]. Cognitive impairments due to the damage to tumour surrounding tissue after surgical resection have been reported to be mild and transient in most cases [25]; however, the paucity of studies including pre- and post-surgical cognitive evaluations prevents from drawing definitive conclusions about the effect of surgery on cognitive functioning. Conversely, treatment-related neurotoxicity has been more widely explored. Radiation encephalopathy has been classified into three phases depending on the between the administration of radiotherapy and symptoms onset [26]. Actually, in a few days after the beginning of radiotherapy, acute radiation encephalopathy may occur, producing headache, somnolence, and worsening of pre-existing neurological deficits; similarly, within the first 6 months after completion of radiotherapy, early delayed radiation encephalopathy may develop. In both cases however, a return to normal baseline has been described. Conversely, late-delayed encephalopathy is an irreversible and serious disorder, occurring several months to many years after radiotherapy, that can manifest as local radionecrosis or diffuse leucoencephalopathy and cerebral atrophy. Cognitive disturbances are the hallmark of the diffuse encephalopathy [27–30]. Chemotherapy-related cognitive impairment, referred to as "chemobrain" (or chemofog), is the most widely reported source of cognitive deficits in neuro-oncological population. Animal models suggest vulnerability of neural stem cells to specific chemotherapy agents (carmustine, cisplatin, cytarabine, and methotrexate) with resultant cognitive deterioration [31, 32]; moreover, demyelination, inflammation, and microvascular injury have all been postulated as mechanisms underlying neurotoxicity of therapy [33, 34]. Combined injury may occur with concomitant or sequential administration of brain radiotherapy and chemotherapy because of alterations in blood brain barrier permeability and drug distributions.

Finally, the impact of emotional disturbances can't be neglected as emotional distress may affect attention, vigilance, and motivation, subsequently impairing cognitive performance [35].

10.2 Cognitive Impairments: Function, Participation, and Quality of Life

Although the severity of cognitive difficulty varies among patients, even the slightest deterioration in cognitive function can be devastating for the patient's quality of life (QOL), interfering with the patient's ability to function at premorbid levels

professionally and socially and therefore resulting in loss of functional independence [18]. The limited ability to undertake activities of daily living, reduced autonomy and inability to return to work may create an even greater restriction than a physical disability [36]. According to the International Classification of Functioning, Disability and Health proposed by the World Health Organization [37], functioning should be considered at three perspectives: body, person, and societal. At the most basic level, a problem in body function or structure is noted as *impairment* (i.e., cognitive impairment such as memory deficits, dysexecutive syndrome…) as a result of disease or injury. At the personal level, the patient's *activity limitations* reflect the consequences of the impairment in daily life (i.e., the patient with cognitive deficits is unable to remember things, to plan activities, to produce or to understand verbal messages…), whereas patient's *participation restrictions* reflects how the disability affects the patient's social interactions (i.e., the patient who suffers from cognitive impairments will be forced to leave work, school…).

Therefore the comprehensive concept of health-related QOL (HRQOL) that covers physical, psychological, and social domains, as well as symptoms induced by the disease and its treatment has been proposed to fully describe patients' functioning and well-being [38, 39]. In fact it is increasingly recognized that the benefits of treatments have to be carefully weighed against the side effects they produce [40] and that measures of HRQOL are important (secondary) outcome measure in clinical trials for BT patients, complementing traditional measures of survival or disease stability [41–43].

Considering the limited survival of neuro-oncological patients, this is an even more urgent issue.

10.3 Cognitive Rehabilitation

10.3.1 Main Features

In broad terms, rehabilitation principally focuses on the improvement of functioning and quality of life. While other branches of health care aim at the prevention and treatment of the disease, rehabilitation assumes that disability may be reduced even in presence of a permanent injury or chronic disease. Therefore, according to McLellan [44] rehabilitation may be defined as "an interactive process whereby people who are disabled by injury or disease work together with professional staff, relatives, and members of the wider community to achieve their optimum physical, psychological, social, and vocational well-being".

Despite most of rehabilitative studies and techniques addressed motor disability, rehabilitation is not only limited to improving physical deficits: Cognitive rehabilitation (CR) aims at enhancing cognitive functioning and independence through interventions that reduce the impairments or lessen the disabling impact of those impairments [45–48].

Differences among definitions of CR depend on theoretical differences regarding the underlying cognitive mechanisms that result in functional and behavioural deficits as well as on the contents of treatments. However, some basic distinctions, despite not mutually exclusive, are common among the

different approaches, including modular versus comprehensive, restorative (or remedial) versus compensative (or adaptive), and contextualized versus decontextualized approaches.

In *modular* approach usually the intervention focuses on the treatment of specific cognitive disturbances, while the term *comprehensive* approach refers to the treatments of patients suffering with multiple impairments (both cognitive and emotional or behavioural) by means of a combination of modular cognitive treatments as well as interventions addressing self-awareness of the impact of cognitive deficits and cognitive-behavioural intervention for emotional disturbances. This latter holistic approach is defined "neuropsychological rehabilitation" that, according to the definition proposed by Wilson [49], is broader than cognitive rehabilitation, as it is concerned with the amelioration of cognitive, emotional, psychosocial, and behavioural deficits caused by an insult to the brain.

Restorative interventions focus on the cause rather than the effect of a deficit and are aimed at reducing the severity of the deficit, enhancing (or normalizing if possible) specific impaired cognitive functions. These kind of interventions usually are based on the direct training of the impaired function through the repetitive and intensive use of exercises with growing levels of complexity and cognitive demands. Conversely, *adaptive or compensatory* therapies don't aim to correct the underlying deficit but to minimize its impact on everyday activities through the development of compensatory strategies or through the use of tools and aids to overcome the impairment [50, 51]. Ideally, the possibility to restore functions represents an appealing option affecting a broad range of activities damaged by the same impairment; on the contrary, compensatory strategies tend to be linked to specific activities, representing therefore more local solutions (although sometimes the only ones realistically achievable).

Finally, the distinction between contextualized versus decontextualized approaches refers to the degree in which they take place in the real world and use materials, activities, and tasks related to patient's everyday life. While *decontextualized* interventions are simpler to standardize but are more "artificial", *contextualized* approaches are more likely to enhance motivation and improve patient's self-awareness because they deal with personally relevant tasks within a familiar environment. Establishing meaningful and functionally relevant goals for rehabilitation linked to day-to-day activities represents a key point to restore patient's social participation.

Obviously, these attributes of CR are not mutually exclusive but can be combined in different ways: modular treatments, for example, may be aimed to either restoration or compensation as well as they can also be either contextualized or decontextualized; in any case, each patient should be carefully evaluated before starting the intervention in order to plan realistic rehabilitation goals, identify priorities for intervention, evaluate progress, break rehabilitation down into achievable steps, resulting in better outcomes [52]. Additionally as described by Sohlberg and Mateer [53] "there should be an emphasis to provide functional endpoints to a rehabilitation programme, so that impact on activities of daily living can be optimized. The ultimate measure of success of any cognitive rehabilitation program is

Table 10.1 Main components of cognitive rehabilitation

Component	Contents and aims
Education	Improvement of patient's understanding of the problem and its consequences as well as enhancement of awareness of cognitive weaknesses and strengths.
Process training	Improvement of skills through direct retraining of the impaired cognitive abilities to restore functions.
Strategy training	Use of environmental, internal, and external strategies to compensate the existing deficits, favouring an effective adaptation.
Functional activities training	Application of the other three components in everyday life to favour generalization of the improvements to activity of daily living.

Modified from Society of Cognitive Rehabilitation

improvement in an individual's ability to manage work, daily living or leisure activities, not simply on practiced therapy tasks".

Table 10.1 summarizes the main components of CR according to the Society for Cognitive Rehabilitation [54].

10.3.2 Literature Evidence

Despite CR programmes have been proven to be effective in the treatment of cognitive deficits in various populations of patients with neurological disorders, including those with traumatic brain injury, stroke, neurodegenerative disease, mainly Alzheimer's disease [48], few studies have investigated strategies to prevent or treat cognitive deficits in patients with BT [1, 55], likely because they are not seen as potential candidates due to their poor prognosis.

A single case study of a patient who suffered from cognitive deficits after right temporal lobectomy for an astrocytoma was the first report of a cognitive rehabilitation intervention in neuro-oncological patients [56]. After a 4-month intervention combining cognitive retraining with psychoeducational and compensation techniques, improvements were observed on follow-up neuropsychological data, behavioural observations made by the patient's wife, and efficiency on work-related tasks.

Subsequently, preliminary support for the effectiveness of postacute brain injury rehabilitation in the management of neuro-oncological patients was offered by a retrospective study published in 1997. Sherer and colleagues [57] showed that after an average of 2.6 ± 1.9 months of vocational rehabilitation performed both in individual and group sessions, primary BT outpatients enjoyed favourable community independence and employment outcomes. Moreover, gains made during treatment were generally maintained at follow-up evaluations performed an average of 8 months after discharge.

In the randomized controlled 2-week trial by Locke et al. [58] 13 pairs of BT patients and their caregivers underwent a combined cognitive-rehabilitation and problem-solving therapy intervention. After receiving the intervention, 88% of patients were able to learn the study specific strategies and to continue using the

strategies to some degree at the follow-up after 3 months. Also, 88% of those who received the intervention described it as helpful and indicated that they would recommend the intervention to other patients. Caregivers were similarly enthusiastic about the intervention strategies.

In a Dutch trial 140 patients with LGG and anaplastic gliomas, clinically stable (i.e., without any evidence of disease progression) for a minimum of 6 months before study entry, were recruited from 11 hospitals in the Netherlands and randomly assigned to an intervention group or to a waiting-list control group [59]. The intervention consisted of six weekly, individual sessions of 2 h each and included both computer-based attention retraining and compensatory skills training of attention, memory, and executive functioning. The weekly therapy sessions were combined with homework tasks including computer-based attention retraining exercises and of logs kept about experiences with applying compensatory strategies in daily life. The waiting-list control group received usual care and contact with the research staff was at similar intervals as the intervention group. At the immediate post-treatment evaluation, statistically significant intervention effects were observed for measures of subjective cognitive functioning and perceived burden, while at the 6-month follow-up, the intervention group performed significantly better on tests of attention and verbal memory and reported less mental fatigue.

In 2010 Hassler and colleagues [60] performed a small pilot study involving 11 patients with high-grade gliomas (HGG) to evaluate the effectiveness of 10 weekly group training sessions of 90 minutes, according to an holistic mnemonic training in which all aspects of mental activity were separately addressed, using exercises to train perception, concentration, attention, memory, retentiveness, verbal memory, and creativity. In the intervention group, comparison of mean group differences between baseline and at post-training evaluation after 12 weeks revealed improvement across all neurocognitive variables, especially attention and memory skills.

These positive results were further confirmed by an Italian randomized trial published in 2013 [61] that included 58 patients with primary BT who were randomly assigned to a rehabilitation group or to a control group, early after surgery. The intervention consisted of 16 one-hour individual sessions of therapist-guided cognitive training, spread over 4 weeks, combining computer exercises (remedial approach) and metacognitive training (compensatory approach). Patients in the control group received usual care without cognitive training. At the end of the intervention patients in the rehabilitation group showed a significant improvement of cognitive functions, especially in attentive and mnesic domains, while the control group exhibited only a slight, not statistically relevant, enhancement of cognitive performances.

To investigate whether virtual reality (VR) training will help the recovery of cognitive function in BT patients, a Korean group of researchers enrolled 38 patients with cognitive impairment who were randomly assigned to either VR group ($n = 19$) or control group ($n = 19$) [62]. Both VR training (30 min a day for 3 times a week) and computer-based cognitive rehabilitation program (30 min a day for 2 times) for 4 weeks were given to the VR group. The control group was given only the computer-based cognitive rehabilitation program (30 min a day for 5 days a week) for 4 weeks.

The VR group showed significantly ($p < 0.05$) better improvements than the control group in attentive measures, memory tests, and concentration, suggesting that VR training can have beneficial effects on cognitive improvement.

In the observational pilot study carried out by Maschio et al. [63] 16 patients affected by primary BT or cerebral metastases and tumour-related epilepsy performed a computerized remedial training consisting in one weekly individual session of 1 h, for a total of 10 weeks. Patients were evaluated with the same battery of tests used at baseline, directly after cognitive rehabilitation (T1), and at 6-month follow-up (T2). Statistical analysis showed that short-term verbal memory, episodic memory, fluency and long-term visuospatial memory improved immediately after the T1 and remained stable at T2.

Finally, Lo Buono et al. [64] described the effectiveness of a rehabilitative training based on cognitive retraining and motivational techniques performed by a young man after the removal and the treatment of a fibrillary grade II astrocytoma. After 3 months of training (2 times/week for a total of 24 sessions) the authors documented an improvement in memory, attention, shifting, and visual activities, in writing and reading, and in the ability to access the linguistic register.

The considered studies highlight the extreme heterogeneity of the available approaches that are included under the broad term of CR as well as the differences regarding the study design, the number of patients included in the trials, the diagnosis and the phase of the disease, and the measures used to assess cognitive functions and to evaluate the outcome. Despite such dissimilarity, all studies found evidence that CR was more effective than no rehabilitation or control to improve cognitive functions of BT patients, suggesting the need for further well-conceptualized, executed, and reported randomized controlled trials to clarify which are the most effective approach and the patients who can benefit from the intervention. Last but not least, also the impact of CR on daily function and quality of life is an urgent issue to deal with: in fact even highly efficacious treatments may induce enhancement only on specific measures of the targeted impairment but may fail to show improvement in real-world activities, participation or quality of life, resulting therefore scarcely useful. Actually some cognitive interventions appear to be more concerned with improving test scores than with reducing everyday problems [65], likely assuming that reducing impairments will reduce everyday problems. To date, however, there is little evidence that this actually happens [66].

The main results and limitations of the above-mentioned studies are listed in Table 10.2.

Based on evidence about CR and expert opinion, the Society for Cognitive Rehabilitation [54] provided a comprehensive list of recommendations for best practice whose main points are summarized below:

- The cognitive treatment plan must be defined on the basis of the results of a comprehensive neuropsychological assessment, that underlines patient's cognitive weaknesses and strengths.
- Whenever possible, assessment results and treatment plans should be explained and agreed with the patient and the caregiver; all rehabilitative

Table 10.2 Main studies on cognitive rehabilitation for brain tumour patients

Authors	Study design	Sample size and population	Type of training	Timing of training	Main Results	Limitations
Lo Buono et al. [64]	Case study	1 (grade II Astrocytoma)	Cognitive and motivational techniques	3 months (2 times/ week for a total of 24 sessions)	Improvement in memory, attention, shifting, and visual activities, in writing and reading, and in the ability to access the linguistic register.	Non-generalizable data
Maschio et al. [63]	Observational study	16 (4HGG, 2 GBM, 5 LGG, 2 MEN, 3 MET) + related epilepsy	Computerized remedial training (Training NeuroPsicologico—TNP®) software	Once a week for 10 weeks	Improvement in short-term verbal memory, episodic memory, fluency and long-term visuospatial memory after the training and at 6 month follow-up	No control group Small sample size
Yang et al. [62]	RCT	38 (5 GBM), 2 AST, 10 MEN, 6 MET, 15 other	*SG*: Virtual reality training + computer-based cognitive rehabilitation *CG*: computer-based cognitive rehabilitation	*SG*: VR training (30 min a day for 3 times a week) and computer-based cognitive rehabilitation program (30 min a day for 2 times) for 4 weeks *CG*: computer-based cognitive rehabilitation program (30 min a day for 5 days a week) for 4 weeks.	SG showed significant better improvements than the CG in attentive and memory tests and concentration	Small sample size No follow-up

Authors	Study design	Sample size and population	Type of training	Timing of training	Main Results	Limitations
Zucchella et al. [61]	RCT	58 (25 HGG, 7 LGG, 16 MEN, 5 other)	*SG*: combining computer exercises (remedial approach) and metacognitive training (compensatory approach) *CG*: usual care without cognitive training	16 one-hour individual sessions spread over 4 weeks	SG: significant improvement in attentive and mnesic domains CG: mild enhancement of cognitive performances, not statistically relevant	No follow-up
Hassler et al. [60]	Clinical trial	11 (6 GBM, 5 HGG)	*SG*: holistic mnemonic training	10 weekly group training sessions of 90 min	At post-training evaluation improvement across all neurocognitive variables, especially attention and memory skills.	No control group Small sample size
Gehring et al. [59]	RCT	140 (117 LGG, 23 HGG)	*SG:* both computer-based attention retraining and compensatory skills training of attention, memory, and executive functioning + weekly homework assignments *CG:* The waiting-list control group received usual care without cognitive intervention	6 weekly, individual sessions of 2 h each.	At the post-treatment evaluation, measures of subjective cognitive functioning and perceived burden significantly improved. At the 6-month follow-up, the SG performed significantly better on tests of attention and verbal memory and reported less mental fatigue	Patients with mild cognitive deficits

(continued)

Table 10.2 (continued)

Authors	Study design	Sample size and population	Type of training	Timing of training	Main Results	Limitations
Locke et al. [58]	RCT	19 pairs patient (13 HGG, 6 LGG)/ caregiver	SG: cognitive rehabilitation and problem-solving. CG: no cognitive training	6 sessions over the course of 2 weeks	88% of patients were able to learn to study specific strategies and to continue using the strategies to some degree after 3 months	Small sample size
Sherer et al. [57]	Retrospective study	13 (1 GBM, 9 LGG, 1 embryonal choriocarcinoma, 1 pineoblastoma, 1 anaplastic ependymoma)	Individualized vocational rehabilitation designed to decrease the impact of the patient's impairments on his/her functioning	Therapy was conducted in both individual and group settings The typical therapy day lasted 5 h. Patients received an average of 2.6 ± 1.9 months of rehabilitation	Patients enjoyed favourable community independence and employment outcomes. Gains were maintained at the follow-up after 8 months	Small sample size No control group No standardization of the training
Rao et al. [56]	Case study	1 (grade II–III Astrocytoma)	Retraining of simple cognitive capacities at home + psychoeducational and compensation techniques	4 months	Improvements in neuropsychological data, behavioural observations, and efficiency on work-related task	Non-generalizable data

HGG high-grade glioma, *GBM* glioblastoma, *LGG* low-grade glioma, *MEN* meningioma, *MET* metastasis, *RCT* randomized controlled trial, *SG* study group, *CG* control group

goals should be specific, measurable, and realistic as well as valuable and meaningful for the patient.
- CR treatments should encompass both attempts at restoration of impaired functions and teaching compensatory strategies to minimize cognitive deficits;
- The therapy has to be systematic, structured, and repetitive according to the patient's needs and it must be part of a multidisciplinary approach.
- Treatment goals should be directed towards enhancing the individual's ability to function as independently as possible; the goals of the intervention must focus on functional competence in real life.
- Opportunities to practice in real-life settings should be provided as part of the intervention to favour generalization and transfer of learning.
- Patient's awareness regarding the presence or severity of cognitive deficits represents the key to successful rehabilitation and should be directly worked on.
- Although cognitive deficits are the major focus of CR, emotional and psychosocial consequences of brain injury need to be addressed in rehabilitation programs. There is an interaction between these different functions, and it is not always easy to separate them from one another.

10.4 Theoretical Framework and Neural Plasticity

The heterogeneous array of interventions that are included within the term CR reflects the lack of a unified theoretical framework able to explain normal cognitive processes, how these are affected by brain injury and how recovery of cognitive processes may occur. In fact most of the neuropsychological models proposed by cognitive neuropsychologists try to explain the working of a normal brain and can detect if something is wrong, but are quite silent with respect to what to do about it [67]; conversely, a useful theory of cognitive rehabilitation should inform clinicians as when, how, and how much to treat to maximize recovery of functions.

As cognitive recovery requires re-learning of skills, theories of learning and memory are crucial for rehabilitation according to Baddeley [68] who claimed that "a theory of rehabilitation without a model of learning is a vehicle without an engine" (p. 235). In the last decades, behavioural experiments as well as careful and repeatable observations have clarified a lot of important principles about how people can learn and retain new information (operant and classical conditioning, shaping behaviours, intermittent reinforcement...); recently, the principle of errorless learning (i.e. preventing people, as far as possible, from making mistakes while they are learning a new skill or acquiring new information) has been highly influential in memory rehabilitation, proving to be particularly effective [69]. Models and theories from behavioural psychology have provided some of the most useful and influential theoretical contributions to rehabilitation, not only for the understanding, management, and remediation of disruptive behaviours, but also for the remediation of cognitive deficits [67]. Moreover, behavioural theories are especially valuable in cognitive rehabilitation because they inform assessment, treatment, and the measurement of rehabilitation efficacy.

Another approach that have revealed quite useful to simulate the mechanisms of learning of new information and specific cognitive tasks is represented by the connectionist models of learning that describe mental and behavioural phenomena as the emergent processes of interconnected networks of simple units. Among many forms of connectionism, the most common forms use neural network models, where units in the network represent neurons and the connections represent synapses. At any time, a network can change through the activation of a neural unit (or group of neural units) in the networks and the spread of the activation to all the other units connected to it. Memory, for instance, is created by modifying the strength of the connections between neural units, based on the principles of Hebb [70] who links learning to the synchronous firing of pre-and post-synaptic cells that leads to inter-neuron linkages through changes in synaptic strengths (*cells that fire together, wire together*), building a bridge between the behavioural/cognitive and the neurophysiological level of analysis.

However, considering the complexity of the field and the range of issues to be dealt with, CR needs a broad theoretical base incorporating frameworks, theories, and models from different areas in order to consider all the important aspects (cognitive, psychological, physical, social, and vocational) of patients' lives [67].

Starting from the concept of Hebbian learning, the following assumptions have been proposed by Robertson and Murre [71] to explain recovery after brain damage:

- The brain is capable of a large degree of self-repair through synaptic turnover (change in the dendritic branches of neurons and in the pattern of synaptic connectivity) and may be engaged in this, even in the absence of overt damage.
- This synaptic turnover is to some extent experience-dependent and is a key mechanism underlying both learning and recovery of function following brain damage.
- Recovery processes following brain damage share common mechanisms with normal learning and experience-dependent plasticity processes.
- Experience and inputs available to damaged neural circuits will shape synaptic interconnections and hence influence recovery.

Therefore, two neurons or groups of neurons that have been disconnected by an injury may become reconnected if they are activated together. Simultaneous activation will take place if both neurons are separately connected to a circuit whose neurons themselves are functionally interconnected. With several repetitions of this process, partially damaged neural circuits thus may become reconnected and cortical functions may be restored.

The capacity of the central nervous system to reorganize itself and adapt in response to changes in the environment or lesions is called *neural plasticity* [72]: results from neurophysiological and neuroanatomical experiments in animals and noninvasive neuroimaging and electrophysiological studies in humans in fact showed considerable plasticity of cortical representations with use or non-use, skill learning, or injury to the nervous system [73, 74].

Although plasticity has been mainly investigated in humans with acute strokes, a growing literature demonstrated that when a tumour invades part of the brain affecting

the underlying functions, the brain attempts to compensate for the functional deficit through cortical reorganization, or plasticity [75, 76]. Neural plasticity is therefore a continuous process allowing short-, middle-, and long-term remodelling with the aim to optimize the functioning of brain networks. To explain the pathophysiological mechanisms underlying cerebral plasticity, several hypotheses have been proposed involving both the microscopic (modulations of synaptic efficiency, unmasking of latent connections, phenotypic modifications, neurogenesis) and the macroscopic level (diaschisis, functional redundancies, compensatory recruitment of areas not initially dedicated to the impaired function) as well as morphological changes [25].

Functional imaging studies have shown that slow-growing lesions may induce major neural reorganization and are compensated for much more efficiently than acute lesions [77, 78]. Rearrangements observed in pre-operative studies in fact explain why most LGG patients appear either normal or only slightly impaired under standard neurological assessments [79, 80]. To compensate for LGG invasions different plastic processes have been described that seem to follow a hierarchic model, involving local compensation first with intrinsic reorganizations occurring within the injured and perilesional structures, and only at a later time the remote recruitment in the ipsi- and contra-lesional hemispheres [77, 81]. The post-operative literature reinforces the pre-surgical observations by suggesting that functional recovery involves a large array of complementary mechanisms.

Cerebral plasticity therefore represents the neural basis underlying any rehabilitative intervention and in the past few years it has become more and more evident that the understanding of these neuroplastic principles will address the development of more rational, hypothesis-driven strategies to promote and guide recovery of functions, likely resulting in improvements in patients' care.

10.5 Conclusions

Cognitive impairment is increasingly recognized as a relevant issue to consider in regard to the assessment of the impact and morbidity of a primary brain tumour. In the light of the deep impact of cognitive disturbances on patients' participation and quality of life, continued efforts are needed to assess the efficacy of interventions to improve cognitive functions. Although still preliminary, evidence suggests that multidisciplinary approaches to rehabilitation that encompasses adaptive, remedial, functional, and metacognitive interventions can optimize cognitive outcome.

References

1. Back M, Back E, Kastelan M, Wheeler H. Cognitive deficits in primary brain tumours: a framework for management and rehabilitation. J Cancer Ther. 2014;5:74–81.
2. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised Phase III study: 5-year analysis of the EORTC-NCIC Trial. Lancet Oncol. 2009;10(5):459–66.

3. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al. Phase III trial of chemoradiotherapy for anaplasticoligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31(3):337–43.
4. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, et al. Adjuvant procarbazine, lomustine, and vincristine chemo- therapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumour group study 26951. J Clin Oncol. 2013;31(3):344–50.
5. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004;3:159–68.
6. Fliessbach K, Rogowski S, Hoppe C, Sabel M, Goeppert M, Helmstaedter C, et al. Computer-based assessment of cognitive functions in brain tumor patients. J Neurooncol. 2010;100:427–37.
7. Bergo E, Lombardi G, Pambuku A, Della Puppa A, Bellu L, D'Avella D, et al. Cognitive rehabilitation in patients with gliomas and other brain tumors: state of the art. Biomed Res Int. 2016;2016:3041824. https://doi.org/10.1155/2016/3041824.
8. Giovagnoli AR. Investigation of cognitive impairments in people with brain tumors. J Neurooncol. 2012;108(2):277–83.
9. Monje M, Dietrich J. Cognitive side effects of cancer therapy demonstrate a functional role for adult neurogenesis. Behav Brain Res. 2012;227(2):376–9.
10. Gehrke AK, Baisley MC, Sonck ALB, Wronski SL, Feuerstein M. Neurocognitive deficits following primary brain tumour treatment: systematic review of a decade of comparative studies. J Neurooncol. 2013;115(29):135–42.
11. Day J, Gillespie DC, Rooney AG, Bulbeck HJ, Zienius K, Boele F, et al. Neurocognitive deficits and neurocognitive rehabilitation in adult brain tumours. Curr Treat Options Neurol. 2016;18(5):22.
12. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumours. Neurosurgery. 2000;47:324–33.
13. Klein M, Taphoorn MJ, Heimans JJ, van der Ploeg HM, Vandertop WP, Smit EF, et al. Neurobehavioural status and health-related quality of life in newly diagnosed high-grade glioma patients. J Clin Oncol. 2001;19:4037–47.
14. Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive function and progression in patients with brain metastases treated with wholebrain radiation and motexafin gadolinium: results of a randomized phase III trial. J Clin Oncol. 2004;22:157–65.
15. van Nieuwenhuizen D, Klein M, Stalpers LJ, Leenstra S, Heimans JJ, Reijneveld JC. Differential effect of surgery and radiotherapy on neurocognitive functioning and health-related quality of life in WHO grade I meningioma patients. J Neurooncol. 2007;84:271–8.
16. Zucchella C, Bartolo M, Di Lorenzo C, Villani V, Pace A. Cognitive impairment in primary brain tumors outpatients: a prospective cross-sectional survey. J Neuro-Oncol. 2013;112(3):455–60.
17. Bosma I, Vos MJ, Heimans JJ, Taphoorn MJ, Aaronson NK, Postma TJ, et al. The course of neurocognitive functioning in high-grade glioma patients. Neuro-Oncology. 2007;9(1):53–62.
18. Correa DD. Neurocognitive function in brain tumours. Curr Neurol Neurosci Rep. 2010;10:232–9.
19. Kayl AE, Meyers CA. Does brain tumour histology influence cognitive function? Neuro Oncology. 2003;5:255–60.
20. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC. Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumours. Int J Radiat Oncol Biol Phys. 2003;55:992–9.
21. Correa DD, Shi W, Thaler HT, Cheung AM, DeAngelis LM, Abrey LE. Longitudinal cognitive follow-up in low grade gliomas. J Neurooncol. 2008;86:321–7.
22. Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H. Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a "minimal common brain". NeuroImage. 2011;56:992–1000.
23. Meyers CA, Hess KR. Multifaceted end points in brain tumour clinical trials: cognitive deterioration precedes MRI progression. Neuro-oncology. 2003;5:89–95.

24. Armstrong CL, Goldstein B, Shera D, Ledakis GE, Tallent EM. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumour recurrence. Cancer. 2003;97:649–56.
25. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. Lancet Neurol. 2005;4:476–86.
26. Sheline G, Wara WM, Smith V. Therapeutic irradiation and brain injury. Int J Rad Oncol Biol Phys. 1980;6:1215–28.
27. Surma-aho O, Niemela M, Vilkki J, Kouri M, Brander A, Salonen O, et al. Adverse long-term effects of brain radiotherapy in adult lowgrade glioma patients. Neurology. 2001;56:1285–90.
28. Postma TJ, Klein M, Verstappen CC, Bromberg JE, Swennen M, Langendijk JA, et al. Radiotherapy-induced cerebral abnormalities in patients with low-grade glioma. Neurology. 2002;59:121–3.
29. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-Oncology. 2013;15(10):1429–37.
30. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol. 2017;13(1):52–64.
31. Dietrich J, Han R, Yang Y, Mayer-Pröschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and vivo. J Biol. 2006;5(7):22.
32. Dietrich J, Monje M, Wefel J, Meyers C. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. Oncologist. 2008;13:1285–95.
33. Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry. 2003;8:201–16.
34. Abrey LE. The impact of chemotherapy on cognitive outcomes in adults with primary brain tumours. J Neurooncol. 2012;108:285–90.
35. Anderson SI, Taylor R, Whittle IR. Mood disorders in patients after treatment for primary intracranial tumours. Br J Neurosurg. 1999;13:480–5.
36. Piil K, Jarden M, Jakobsen J, Christensen KB, Juhler M. A longitudinal, qualitative and quantitative exploration of daily life and need for rehabilitation among patients with high-grade gliomas and their caregivers. BMJ Open. 2013;3(7):e003183.
37. World Health Organization. International classification of functioning, disability, and health (ICF). Geneva: WHO; 2001.
38. Aaronson NK. Quality of life: what is it? How should it be measured? Oncology (Williston Park). 1988;2(5):69–76.
39. Dirven L, Reijneveld JC, Aaronson NK, Bottomley A, Uitdehaag BMJ, Taphoorn MJ. Health-related quality of life in patients with brain tumours: limitations and additional outcome measures. Curr Neurol Neurosci Rep. 2013;13(7):359.
40. Cheng J, Zhang X, Liu BL. Health-related quality of life in patients with high-grade glioma. Neuro-Oncology. 2009;11(1):41–50.
41. Bosma I, Reijneveld JC, Douw L, Vos MJ, Postma TJ, Aaronson NK, et al. Health-related quality of life of long-term high-grade glioma survivors. Neuro-Oncology. 2009;11(1):51–8.
42. Veilleux N, Goffaux P, Boudrias M, Mathieu D, Daigle K, Fortin D. Quality of life in neurooncology—age matters. J Neurosurg. 2010;113:325–32.
43. Giovagnoli AR, Meneses RF, Silvani A, Milanesi I, Fariselli L, Salmaggi A, et al. Quality of life and brain tumours: what beyond the clinical burden? J Neurol. 2014;261:894–904.
44. McLellan DL. Functional recovery and the principles of disability medicine. In: Swash M, Oxbury J, editors. Clinical neurology. Edinburgh, UK: Churchill Livingstone; 1991. p. 768–90.
45. Harley JP, Allen C, Braciszewski TL, Cicerone KD, Dahlberg C, Evans S, et al. Guidelines for cognitive rehabilitation. Neurorehabilitation. 1992;2(3):62–7.
46. Wilson BA. Cognitive rehabilitation: how it is and how it might be. J Int Neuropsychol Soc. 1997;3(5):487–96.

47. Katz DI, Ashley M, O'Shanick GJ, Connors SH. Cognitive rehabilitation: the evidence, the funding and case for advocacy in brian injury. Mc Lean, VA: Brain Injury Association of America; 2006.
48. Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, et al. Evidence-based cognitive rehabilitation: updated review of the literature from 2003 through 2008. Arch Phys Med Rehabil. 2011;92(4):519–30.
49. Wilson BA. Neuropsychological Rehabilitation. Annu. Rev. Clin. Psychol. 2008;4:141–62.
50. Sohlberg M, Mateer C. Introduction to cognitive rehabilitation theory and practice. New York: The Guilford Press; 1989.
51. Vargo M. Brain tumour rehabilitation. Am J Phys Med Rehabil. 2011;90(5):S50–62.
52. Nair KT, Wade DT. Satisfaction of members of interdisciplinary rehabilitation teams with goal planning meetings. Arch Phys Med Rehabil. 2003;84(11):1710–3.
53. Sohlberg M, Mateer C. Cognitive rehabilitation: an integrative neuropsychological approach. New York: The Guildford Press; 2001.
54. Society for Cognitive Rehabilitation, "What Is Cognitive Rehabilitation?" 2013. www.society-forcognitiverehab.org.
55. Gehring K, Sitskoorn MM, Aaronson NK, Taphoorn MJB. Interventions for cognitive deficits in adults with brain tumours. Lancet Neurol. 2008;7:548–60.
56. Rao SM, Bieliauskas LA. Cognitive rehabilitation two and one-half years post right temporal lobectomy. J Clin Neuropsychol. 1983;5:313–20.
57. Sherer M, Meyers CA, Bergloff P. Efficacy of postacute brain injury rehabilitation for patients with primary malignant brain tumours. Cancer. 1997;80:250–7.
58. Locke DEC, Cerhan JH, Wu W, Malec JF, Clark MM, Rummans TA, et al. Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumours: a pilot study. J Support Oncol. 2008;6:383–91.
59. Gehring K, Sitskoorn MM, Gundy CM, Sikkes SA, Klein M, Postma TJ, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. J Clin Oncol. 2009;27(22):3712–22.
60. Hassler MR, Elandt K, Preusser M, Lehrner J, Binder P, Dieckmann K, et al. Neurocognitive training in patients with high-grade glioma: a pilot study. J Neurooncol. 2010;97(1):109–15.
61. Zucchella C, Capone A, Codella V, De Nunzio AM, Vecchione C, Sandrini G, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumour: a randomized, controlled trial. J Neurooncol. 2013;114(1):93–100.
62. Yang S, Chun MH, Son YR. Effect of virtual reality on cognitive dysfunction in patients with brain tumour. Ann Rehabil Med. 2014;38(6):726–33.
63. Maschio M, Dinapoli L, Fabi A, Giannarelli D, Cantelmi T. Cognitive rehabilitation training in patients with brain tumour-related epilepsy and cognitive deficits: a pilot study. J Neurooncol. 2015;125:419–26.
64. Lo Buono V, Corallo F, De Cola MC, Chillemi A, Grugno R, Bramanti P, et al. Effect of cognitive rehabilitation in a case of thalamic astrocytoma. Appl Neuropsychol Adult. 2016;23(4):309–12.
65. Carney N, Chesnut RM, Maynard H, Mann NC, Patterson P, Helfand M. Effects of cognitive rehabilitation on outcomes for persons with traumatic brain injury: a systematic review. J Head Trauma Rehabil. 1999;14:277–307.
66. Wilson BA, Herbert CM, Shiel A. Behavioural approaches in neuropsychological rehabilitation: optimising rehabilitation procedures. Hove, UK: Psychology Press; 2003.
67. Wilson BA. Neuropsychological rehabilitation: theory and practice. Lisse, The Netherlands: Swets & Zeitlinger BV; 2003.
68. Baddeley AD. A theory of rehabilitation without a model of learning is a vehicle without an engine: a comment on Caramazza and Hillis. Neuropsychol Rehabil. 1993;3:235–44.
69. Kessels RP, de Haan EH. Implicit learning in memory rehabilitation: a meta-analysis on errorless learning and vanishing cues methods. J Clin Exp Neuropsychol. 2003;25(6):805–14.
70. Hebb DO. The organization of behavior; a neuropsychological theory. New York: Wiley and Sons; 1949.

71. Robertson IH, Murre JMJ. Rehabilitation of brain damage: brain plasticity and principles of guided recovery. Psychol Bull. 1999;125(5):544–75.
72. Sharma N, Classen J, Cohen LG. Neural plasticity and its contribution to functional recovery. Handb Clin Neurol. 2013;110:3–12.
73. Bütefisch CM. Plasticity in the human cerebral cortex: lessons from the normal brain and from stroke. Neuroscientist. 2004;10(2):163–73.
74. Nudo RJ, McNeal D. Plasticity of cerebral functions. Handb Clin Neurol. 2013;110:13–21.
75. Matthews PM, Honey GD, Bullmore ET. Applications of fMRI in translational medicine and clinical practice. Nat Rev Neurosci. 2006;7:732–44.
76. Fisicaro RA, Jost E, Shaw K, Brennan NP, Peck KK, Holodny AI. Cortical plasticity in the setting of brain tumours. Top Magn Reson Imaging. 2016;25(1):25–30.
77. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain. 2007;130:898–914.
78. Ghinda CD, Duffau H. Network plasticity and intraoperative mapping for personalized multimodal management of diffuse low-grade gliomas. Front Surg. 2017;4:3.
79. Duffau H, Capelle L. Functional recuperation following lesions of the primary somatosensory fields. Study of compensatory mechanisms. Neurochirurgie. 2001;47:557–63.
80. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Lopes M, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. J Neurol Neurosurg Psychiatry. 2003;74:901–7.
81. Heiss WD, Thiel A, Kessler J, Herholz K. Disturbance and recovery of language function: correlates in PET activation studies. Neuroimage. 2003;20(Suppl 1):S42–9.