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# Interventions for cognitive deficits in patients with a brain tumor: an update

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Patients with brain tumors may suffer from cognitive deficits caused by the disease and/or its treatment. Here, we review recent efforts in the research on prevention or treatment of cognitive deficits in these patients. We conclude that interest in this area is growing, but that methodological difficulties persist. In addition, we describe the recently completed first randomized controlled trial on the effectiveness of cognitive rehabilitation that we conducted in patients with brain cancer. By reflecting on the methodological challenges experienced in our trial, we hope to assist others in planning and conducting future studies on both pharmacological treatments and cognitive rehabilitation programs for cognitive deficits in this patient population. We conclude with suggestions for future research directions.

**KEYWORDS:** brain tumor • cognitive deficits • cognitive rehabilitation • intervention • neuropsychological impairment

Patients with primary brain tumors and those with brain metastases may suffer from cognitive deficits caused by the disease and/or its treatment. Deficits are often observed in the broad domains of attention, memory, executive functioning and language [1–3].

There is a good deal of variability across studies in the reported prevalence of cognitive deficits in these patient populations. The rates range from 29% in nonirradiated low-grade glioma patients [1] to approximately 90% in diverse brain tumor groups [1,4–6]. This variability may be due to differences in the specific populations of patients studied, tumor treatment variables, neuropsychological tests used, and cut-off scores and normative data used to establish ‘caseness’. Nevertheless, it is clear that patients with a brain tumor have cognitive deficits that are more prominent than in patients with extracranial malignancies with a similar prognosis [4,7].

Although the exact pathophysiology of the observed cognitive impairments is not entirely understood, several causes can be discerned, including the tumor (location, size, progression and growth rate), tumor-related neurological complications and epilepsy [8–13]. Cancer treatments, including surgery, radiotherapy and chemotherapy may (partially) alleviate cognitive deficits resulting from the tumor. However, these treatments can also have cognitive side

effects [11,14,15]. As compared with other causes, the pathogenesis of the cognitive side effects due to late radiation damage is relatively well known. Demyelination and microvascular injury, leading to necrosis [16,17], inflammation and impaired hippocampal neurogenesis, have been implicated in radiation-induced cognitive impairment [18–20]. Although the cognitive effects of chemotherapy are less clear, they might result from comparable mechanisms [21,22]. Antiepileptic drugs also have adverse effects [11,14,15,20,23]. Other medical factors and complications, including endocrine and metabolic disturbances, infection and anemia, can also contribute to the cognitive deficits [24–26]. Genetic risk factors are increasingly associated with individual neurotoxic reactions to invasive treatments such as chemotherapy [20]. Finally, psychological reactions to the disease such as anxiety and depression may also have cognitive effects [11,27]. A combination of these factors most probably explains the cognitive impairment observed in patients with brain tumors.

The cognitive deficits experienced by most patients with a brain tumor appear to be milder and more diffuse than would be predicted by site alone [28,29]. Nevertheless, these deficits can substantially impact on patients’ lives [30], and are particularly an issue in those patients with a more favorable prognosis, such as patients

with a lower grade glioma. After tumor treatment, many of these patients may live free from (severe) neurological symptoms for years until the disease progresses. During this period, as these patients attempt to resume family, work and social activities, they may begin to experience cognitive deficits. Cognitive symptoms are reported in as many as 80% of patients with a brain tumor, placing them among the most commonly reported neurological problems in this population of patients [25,31].

In the broad field of brain disorders and diseases, advances in treatment and the resulting improvement in survival rates has led to increased interest in developing effective physical, mental and cognitive rehabilitation programs. Two approaches are often undertaken in the treatment of cognitive deficits: pharmacological and neuropsychological (i.e., cognitive rehabilitation). While pharmacological treatment of cognitive deficits may be familiar to most readers, this may be less so for 'cognitive rehabilitation'. In short, cognitive rehabilitation refers to nonpharmacological interventions aimed at preventing or treating cognitive deficits. While not exhaustive, for illustrative purposes we will briefly describe five common types of cognitive interventions. First, the environment can be modified or restructured to help patients meet the demands of independent daily living by relying less upon their impaired cognitive abilities [32]. The nature or degree of such modifications will vary depending on the severity of the cognitive problems. Second, patients can be taught to make use of external aids and technology, such as electronic diaries. Third, via structured strategy training, patients can be taught to apply internal strategies to cope with their cognitive problems. This includes pacing of cognitive activities, preventing or minimizing distractions, anticipating and planning, or the use of mnemonics. Fourth, rehabilitation can focus on retraining specific cognitive skills by means of frequently practiced exercises ('repetitive stimulation'). Such retraining can, for example, focus on attention, memory or executive functioning. Finally, psychoeducation with regard to brain functioning, cognitive deficits and their consequences for daily life may be of value to patients and their families.

Studies among patient populations with other types of acquired brain injury, such as stroke and traumatic brain injury, have demonstrated the effectiveness of cognitive rehabilitation [33–39], with most programs combining strategy training and/or retraining with psychoeducation.

Specific to brain tumors, our previous review identified surprisingly few studies on pharmacological or neuropsychological interventions for cognitive deficits [40]. The few (predominantly Phase II) studies of pharmacological interventions and cognitive rehabilitation programs reported some degree of success. However, the results were often difficult to interpret owing to methodological limitations, some of which are common to Phase II trials, including nonrandomized study designs, failure to include a control group to rule out practice and other effects, small sample sizes, and absence of formal statistical testing. As a result, convincing evidence for a positive effect of pharmacological agents or cognitive rehabilitation on neuropsychological functioning could not be found.

Reasons for the paucity of cognitive intervention studies in this population compared with other types of acquired brain injury may include the relatively low incidence of brain tumors, their progressive nature and the relatively poor prognosis associated with the disease. Historically, research in brain cancer has been primarily focused on identifying treatments that are effective in terms of tumor control and survival. Gradually, as the rates of disease-free survival have increased, interest has expanded to include concern with long-term sequelae of the disease and its treatment, including cognitive impairment. At the same time, evidence for the efficacy of treatments for cognitive deficits in other patient populations has accumulated (e.g., see [33,41,42]), leading to a greater acceptance of cognitive rehabilitation as a legitimate goal in the treatment of brain cancer.

The mild-to-moderate global cognitive deficits seen in patients with brain cancer may be most amenable to cognitive treatment. Particularly in the case of low-grade gliomas, where the tumor grows slowly and infiltrates or displaces neuronal tissue without actually destroying it [8,28], some residual function may be maintained and/or reshaping or local reorganization of functional networks may take place [11,43,44].

In fact, studies of functional outcome after inpatient rehabilitation have indicated similar, or even better, outcomes for patients with a brain tumor than for individuals with traumatic brain injury or stroke, matched on demographic, medical and/or functional characteristics [45–47]. This suggests that patients with a brain tumor may also be good candidates for cognitive intervention.

In our previous review, we mentioned a number of forthcoming or ongoing studies (identified via Clinicaltrials.gov [201]) that were, at that time, not sufficiently mature to report results. In the current paper, we will review these studies and other recent pharmacological and cognitive rehabilitation approaches in patients with brain cancer. We will also summarize the results of a large randomized controlled trial (RCT) that we recently completed on the effectiveness of a cognitive rehabilitation program for patients with brain tumors [48], focusing in particular on some of the methodological issues arising from that study. Hopefully, the reflections on our experience in conducting such research will assist others in planning and conducting future studies in this area. Finally, we will provide some suggestions for future research directions.

### **Current state of research on interventions for cognitive deficits in patients with a brain tumor**

We will first discuss the results of the most recent studies of the prevention of cognitive deficits in patients with a brain tumor. This will be followed by an update on pharmacological and neuropsychological interventions for the treatment of cognitive deficits.

### **Novel studies of targeted brain tumor treatments**

Prevention studies are primarily focused on evaluating targeted anti-tumor treatments that may prevent or limit brain injury resulting from the (radiation) treatment itself (TABLE 1).

**Table 1. Recent and novel studies of targeted brain tumor treatments.**

Investigators (year; trial no.)	Design	n	Population	Intervention	Relevant outcome measures	Timing of assessments	Statistical analyses	Relevant results	Attrition/toxicities	Comments	Ref.
Gondi <i>et al.</i> (2010) in preparation of RTOG 0933 trial	Retrospective risk estimation	371	Patients with ≤10 BMs	None; estimation of perihippocampal metastasis risk in preparation of trial HA-WBRT	Axial images from pretreatment, postcontrast MRIs	NA	Correlations, backward logistic regression	Metastases within 5 mm of the hippocampus in 8.6% of patients, intracranial volume of metastatic disease predicted perihippocampal metastases	NA	HA-WBRT is safe for clinical testing	[49]
Anscher <i>et al.</i> (NCT00581113)	Phase III, randomized, open label	30	1–6 BMs	Neural stem cell-preserving WBRT vs standard WBRT	Cognitive tests	Until 12 months after completion of WBRT	NA	Study start: December 2007 Current status: terminated due to new research priorities	NA	No publication	[202]
Eisai Inc. (NJ, USA) (NCT00525590)	Phase II, no control group	75	1 BM	Surgery plus gliadel wafers	Cognitive tests	Unknown	NA	Study start: September 2007 Expected primary completion: March 2011 Current status: recruiting	NA	Estimated enrollment from 75 to 59 patients	[203]
Correa <i>et al.</i> (2009)	Phase II, prospective, no control group	12	Immunocompetent patients with newly diagnosed, histologically confirmed B-cell PCNSL	Induction CTX, reduced-dose WBRT and consolidation CTX	Cognitive tests, Q on depression and QoL; MRI	Baseline, postinduction CTX and prior to WBRT, 6, 12, 18 and 24 months after treatment	T-tests, correlations	No cognitive decline over 2 years post-treatment; mild increase of white matter disease until 18-month follow-up	7 drop-outs within 12 months and 3 drop-outs thereafter, with various reasons, among them 2 who declined cognitive testing		[50]

BM: Brain metastasis; CTX: Chemotherapy; HA-WBRT: Hippocampal avoidance during whole-brain radiation therapy; NA: Not applicable; PCNSL: Primary CNS lymphoma; Q: Questionnaire; QoL: Quality of life; RTOG: Radiation Therapy Oncology Group; WBRT: Whole-brain radiation therapy.

Radiation Therapy Oncology Group (RTOG) 0933 is a planned Phase II clinical trial of avoidance of the hippocampus plus a 5 mm margin during whole-brain radiotherapy (WBRT) to prevent radiation-induced cognitive decline in patients with brain metastases, without compromising intracranial disease control. In preparation for this trial, Gondi and colleagues sought to estimate the risk of disease progression within the hippocampal avoidance region to determine the safety profile of the intervention [49]. Axial images from pretreatment, postcontrast MRIs were retrospectively used to contour each metastasis and hippocampus in 371 patients. A total of 1133 brain metastases were identified. Metastases within 5 mm of the hippocampus were observed in 8.6% of the patients. Based on this perihippocampal metastasis risk of only 8.6%, the authors concluded that hippocampal avoidance during WBRT is safe for clinical testing. The trial on the cognitive effects of this more targeted tumor treatment is scheduled to open in 2010.

Another study of a comparable treatment was terminated “due to new research priorities” [202]. As discussed in our previous review, this planned Phase III randomized open-label study in 30 patients with one to six metastases was initiated to investigate whether neural stem cell-preserving WBRT would result in an improved cognitive profile over standard WBRT by minimizing radiation to brain areas where neural stem cells are located, such as the hippocampal area.

Correa and colleagues investigated a modified treatment regimen consisting of methotrexate-based chemotherapy incorporating rituximab, a chimeric monoclonal antibody, and reduced-dose WBRT aimed at improving efficacy and decreasing neurotoxicity in primary CNS lymphoma patients in a prospective, uncontrolled study [50]. Of the 19 patients with primary CNS lymphoma, 12 completed neuropsychological assessments at diagnosis, after induction chemotherapy and prior to reduced-dose WBRT and consolidation chemotherapy, and approximately 6 and 12 months after treatment. Seven patients dropped out for various reasons. Nine of the 12 patients completed additional cognitive evaluations (including tests of verbal memory, attention/executive functioning and motor speed) approximately 18 and 24 months post-treatment. Following treatment, cognitive functioning improved significantly, possibly owing to tumor treatment, discontinuation of some drugs, regression to the mean and/or practice effects. Up to 2-year follow-up, there was an absence of the significant decline of cognitive functioning that is frequently reported in studies of conventional combined-modality therapy. However, some difficulties in verbal memory and motor speed already observed at baseline persisted over the follow-up period. Furthermore, there was a mild increase in treatment-related white matter disease until 12 months post-treatment that did not increase further thereafter.

An uncontrolled Phase II study of the possible preservation of cognitive function by surgical intervention and insertion of gliadel wafers (wafers that slowly release the chemotherapy agent carmustine) [203] without postoperative WBRT aims to recruit 75 patients with brain metastases. Data collection is expected to be completed in March 2011.

### **Studies of pharmacological prevention in patients with brain tumors**

Research on pharmacological neuroprotective agents to protect healthy tissue against treatment-induced neuronal cell loss or degeneration is still in a predominantly preclinical phase (TABLE 2). The one study in humans was terminated early owing to slow accrual and high drop-out rates [51]. The data from planned or ongoing studies of neuroprotective agents in humans cited in our previous review are not yet available. The Phase I study on the efficacy of lithium in protecting normal cells from side effects of WBRT was completed in March 2009, having recruited 24 patients with multiple brain metastases [204]. The results have not yet been published.

The large-scale, randomized, double-blind, placebo-controlled study by Brown and colleagues on the efficacy of memantine, a NMDA receptor antagonist that is also used in Alzheimer's disease, in preventing cognitive deficits in patients with brain metastasis during and after WBRT, aims to recruit 536 patients [205]. This trial is anticipated to be completed in June 2012.

### **Studies of pharmacological treatment in patients with brain tumors**

In our previous review, it was not possible to draw any definitive conclusions about the efficacy of pharmacologic agents (e.g., methylphenidate) in the treatment of existing cognitive deficits in patients with brain tumors. In part, this was due to the methodological limitations of the studies reviewed.

Two of the trials mentioned in our earlier review have subsequently published their results. A trial on immediate-release methylphenidate, sustained-release methylphenidate and modafinil in patients with a primary brain tumor was closed early owing to poor accrual (TABLE 3) [206]. It was hypothesized that patients receiving methylphenidate would improve on memory, executive function and psychomotor processing speed measures, while patients receiving modafinil would improve on attention measures. Data from 24 patients enrolled in this trial suggested that methylphenidate improved psychomotor processing speed but did not result in differential change in memory or executive function measures [52]. The positive effects of modafinil on measures of attention could not be demonstrated.

The second trial, an uncontrolled investigation of liothyronine added to levothyroxine in improving cognitive deficits resulting from damage to the hypothalamic–pituitary axis due to the brain tumor and its treatment with external-beam irradiation was also terminated owing to slow accrual [207]. In the ten patients who were recruited into this study, liothyronine improved psychomotor processing speed, but not memory [53]. A trend toward improvement in executive function was also observed.

Two other pharmacological studies that we located on Clinicaltrials.gov have presumably been completed, but the results have not (yet) been published. The first is on hyperbaric oxygen therapy in patients with brain tumors and radiation necrosis (estimated study completion date: June 2005) [208]. The second is on bevacizumab to reduce radiation necrosis in patients with brain tumors or head and neck cancer (estimated primary completion date: September 2007) [210].

**Table 2. Recent and novel studies of pharmacological prevention of cognitive deficits in patients with brain tumors.**

Investigators (trial no.)	Design	n	Population	Intervention	Relevant outcome measures	Timing of assessments	Statistical analyses	Relevant results	Attrition/toxicities	Ref.
Brown <i>et al.</i> (NCT00566852)	Phase III, randomized, placebo-controlled, double-blind	536	BMs from solid tumors	Memantine during, and until 24 weeks after, WBRT	Cognitive tests, Q on QoL	BL, weeks 8, 16 and 24 of treatment, then every 4 months for 1 year, every 6 months for 2 years and every year thereafter	NA	Study start: March 2008 Estimated primary completion: June 2012 Current status: recruiting	NA	[205]
Lu <i>et al.</i> (NCT00469937)	Phase I, open label, no control group	24	Multiple BMs	Lithium 7 days before and during WBRT	Mental status and Q on QoL	BL, days 1, 8 and 15, 1 month after treatment and periodically thereafter	NA	Study start: February 2006 Current status: data collection completed March 2009	NA	[204]

BL: Baseline; BM: Brain metastasis; NA: Not applicable; Q: Questionnaire; QoL: Quality of life; WBRT: Whole-brain radiation therapy.

Several of the other clinical trials that we noted in our previous review are still ongoing. A double-blind, placebo-controlled randomized trial is being conducted to investigate the efficacy of donepezil, an acetylcholinesterase inhibitor in improving a neurocognitive symptom cluster (i.e., cognitive impairment, subjective confusion and fatigue) that has yielded positive results in Alzheimer's disease and vascular dementia [210]. Data collection on 200 irradiated patients with primary or metastatic brain tumors was scheduled to be completed by June 2010. Another uncontrolled study of the effects of donepezil for improvement of executive abilities and psychomotor speed in patients with brain tumors who have cognitive deficits (n = 30) is also expected to be completed this year [211].

A randomized, placebo-controlled, double-blind trial on the feasibility of the stimulant armodafinil in relieving radiation-induced fatigue was initiated in March 2010 [212]. In total, 54 patients with primary brain tumors will receive armodafinil or placebo beginning no later than the fifth fraction of brain radiotherapy and continuing for 9–11 weeks. In addition to fatigue, assessments will also include quality of life (QoL), and cognitive functioning at baseline and periodically during the study. Presence of cognitive deficits is not an inclusion criterion. Data collection is estimated to be completed in May 2011. Although the authors do not explicitly state that this is a prevention study, the timing of the armodafinil during radiotherapy suggests that the intervention is aimed at preventing fatigue and, possibly, cognitive deficits.

### **Studies of cognitive interventions in patients with brain tumors**

In our former review, only one study of a cognitive/vocational approach in brain tumor patients could be identified [54]. The (suggested positive) results of the study could not be fully interpreted owing to the absence of a control group and the failure to use formal statistical testing.

Duval and colleagues reported a case study in which a comprehensive program for the rehabilitation of working memory was employed in a young man who had undergone resection of a grade 2 ganglioglioma in the left temporal lobe (TABLE 4) [55]. The program consisted of two information sessions, 19 cognitive program sessions and seven ecological program sessions in 6 months. In total, 15 sessions of various neuropsychological evaluations and tests were held, including four sessions at a 3-month follow-up. Working memory deficits improved during and after the program. Subprocesses of working memory improved specifically after the corresponding rehabilitation components were completed. Subjective cognitive functioning also improved and there was a carry-over effect to, what the authors called, "tasks with an ecological dimension". The effects on neuropsychological test performance and subjective cognitive functioning were sustained until the 3-month follow-up.

Locke and colleagues conducted a pilot study of the feasibility and tolerability of a 2-week combined cognitive rehabilitation (particularly aimed at memory) and problem-solving intervention for pairs of patients with (predominantly newly diagnosed) primary brain tumors and their caregivers [56]. Patients were only

**Table 3. Recent and novel studies of pharmacological treatment of cognitive deficits in patients with brain tumors.**

Investigators (year; trial no.)	Design	n	Population	Intervention	Relevant outcome measures	Timing of assessments	Statistical analyses	Relevant results	Attrition/toxicities	Ref.
Wefel <i>et al.</i> (NCT00418691); Patwardhan <i>et al.</i> (2010)	Phase III; open label, randomized, no control group	24 out of 75	Primary or metastatic BT, postsurgery and post-RTX, reported cognitive decline	Methylphenidate (IR or SR) or modafinil, all for 4 weeks	Cognitive tests, Qs on symptoms such as fatigue and depression	BL, week 4	Likelihood ratio statistic, controlled for baseline performance, adjusted for multiple comparisons	Terminated owing to poor accrual (n = 24); methylphenidate improved psychomotor processing speed but not memory or executive function. No effect of modafinil	NV	[206] [52]
Levin <i>et al.</i> (NCT00488644); Wefel <i>et al.</i> (2009)	Open label; control group	10 out of 26	BT, hypothyroidism, post-RTX <sup>†</sup>	Liothyronine added to levothyroxine for 8 weeks	Cognitive tests, Qs on QoL and mood	BL, day 1 of treatment, and after 8 weeks	Paired t-tests, effect sizes	Terminated owing to slow accrual (n = 10); improved psychomotor processing speed, but not memory	NV	[207] [53]
Gesell <i>et al.</i> <sup>†</sup> (NCT00087815)	Pilot randomized, single blind, active control (CC)	30	BT, RN with progressive neurological symptoms, managed with steroid therapy <sup>†</sup>	CC plus hyperbaric oxygen therapy for ~3 months	Mental status, Q on QoL	BL, every month during treatment, end of treatment, and months 1, 2 and 4 thereafter	NA	Study start: September 2003 Expected primary completion: June 2005 Current status: ongoing, but not recruiting	NA	[208]
Loghin <i>et al.</i> <sup>†</sup> (NCT00492089)	Phase II, randomized, placebo controlled, crossover, double blind	16	Irradiated primary BT and head and neck cancer, RN with progressive neurological symptoms <sup>†</sup>	Bevacizumab for 6–12 weeks	Cognitive tests and QoL as secondary outcomes	BL, periodically during treatment, and weeks 12 and 24 after completion	NA	Study start: February 2007 Expected primary completion: September 2007 Current status: ongoing but not recruiting	NA	[209]
Rapp <i>et al.</i> <sup>†</sup> (NCT00369785)	Phase III, randomized, double blind, placebo controlled	200	Primary or metastatic BT, post-RTX, radiographically stable <sup>†</sup>	Donepezil for 24 weeks	Cognitive tests, Qs on subjective cognitive function, fatigue, mood and QoL	BL, weeks 12 and 24	NA	Study start: January 2008 Estimated primary completion: June 2010 Current status: recruiting	NA	[210]

<sup>†</sup>Presence of cognitive deficits not an inclusion criterion.

BL: Baseline; BT: Brain tumor; CC: Conventional care; CTX: Chemotherapy; IR: Immediate release; NA: Not applicable; NV: Not available; Q: Questionnaire; QoL: Quality of life; RN: Radionecrosis; RTX: Radiotherapy; SR: Sustained release.

**Table 3. Recent and novel studies of pharmacological treatment of cognitive deficits in patients with brain tumors.**

Investigators (year; trial no.)	Design	n	Population	Intervention	Relevant outcome measures	Timing of assessments	Statistical analyses	Relevant results	Attrition/toxicities	Ref.
Correa <i>et al.</i> <sup>†</sup> (NCT00594633)	Open label, no control group	30	BT, mild–moderate cognitive deficits, previous RTX, CTX or both	Donepezil for 24 weeks	Cognitive tests	BL, weeks 12 and 24, and 6 months after end of treatment	NA	Study start: October 2004 Estimated primary completion: October 2010 Current status: ongoing, but not recruiting	Estimated enrollment adjusted from 30 to 25 patients	[211]
Shaw <i>et al.</i> (NCT01032200)	Randomized, placebo controlled, double blind	54	Patients with primary BT undergoing RTX <sup>†</sup>	Armodafinil or placebo for 9–11 weeks	Cognitive tests, Qs on fatigue and QoL	BL and periodically during the study	NA	Study start: March 2010 Estimated primary completion: May 2011 Current status: not yet recruiting	NA	[212]

<sup>†</sup>Presence of cognitive deficits not an inclusion criterion.  
BL: Baseline; BT: Brain tumor; CC: Conventional care; CTX: Chemotherapy; IR: Immediate release; NA: Not available; NV: Not applicable; Q: Questionnaire; QoL: Quality of life; RN: Radionecrosis; RTX: Radiotherapy; SR: Sustained release.

included if they had mild-to-moderate cognitive impairment. A total of 19 patient–caregiver dyads were enrolled, of which 16 were randomized to receive the intervention or standard medical care, and three were assigned directly to the intervention group. The intervention consisted of six sessions of cognitive rehabilitation and six sessions of problem-solving therapy that were provided concurrently with radiation therapy over the course of 2 weeks. Both study groups were reassessed immediately after the intervention and at 3-month follow-up, with primary outcome measures of QoL and functional capacity, and secondary outcome measures of cognitive functioning, caregiver burden, mood, fatigue, intervention feedback and the use of compensation techniques. The intervention group also completed a questionnaire for feedback on the intervention.

Although the authors concluded that patient participation was feasible, accrual was low (19 out of 160 patients). One of the main reasons for this was a low prevalence of cognitive deficits (38%) in patients. The authors suggested that the patients, who were newly diagnosed were too early in their disease and treatment course to expect measurable impairment. Other major reasons for the low accrual were patient decline of referral to the clinical neuropsychologist (16%) and a competing QoL research protocol in the cancer center (10%). A total of 13 patients completed the entire study through the 3-month follow-up. Four out of 12 patients who were enrolled in the intervention group did not complete the intervention for various reasons. Seven of the eight dyads who completed the program found the intervention to be helpful. There was no significant intervention effect on the primary outcome measures of QoL and functional capacity, and too few patients completed the neuropsychological follow-up to allow for any statistical analysis of the neuropsychological test data.

In another pilot study, Hassler and colleagues evaluated the feasibility of group training sessions of Stengel's holistic mnemonic training in patients with high-grade gliomas who were treated with maximal tumor resection, radiation and chemotherapy [57]. Six patients with glioblastoma multiforme and five with WHO grade III gliomas and good performance underwent the intervention consisting of ten 90-min sessions over 12 weeks. It was not required that participants had cognitive deficits. There was no control group. Neuropsychological assessments were performed pre- and postintervention. On four out of five test variables of various cognitive domains, patients showed variability in their performance, with worsening, improvement and stabilization of test scores. A significant group improvement in a verbal learning test variable was observed. The authors stated that all patients showed some improvement (although 'improvement' was not defined) in at least one of the four tests "and not the lack of improvement in repetitive testing which is frequently seen in patients with cognitive sequelae after systemic cancer therapy". However, closer inspection of the studies they refer to shows that some included only one assessment (in which it is not possible to measure effects due to repetitive testing) and others used intervals between assessments of longer than 3 months, in which practice effects may be smaller.

**Table 4. Recent and novel studies of cognitive rehabilitation for cognitive deficits in patients with brain tumors.**

Investigators (year; trial no.)	Design	n	Population	Intervention	Relevant outcome measures	Timing of assessments	Statistical analyses	Relevant results	Attrition/toxicities	Comments	Ref.
Duval <i>et al.</i> (2008)	Case study	1	Man with resection of ganglioglioma grade 2 in left temporal lobe	Rehabilitation of central-executive component of working memory, consisting of information, cognitive and ecological sessions, several per week, for 6 months	Cognitive and ecological tests, Q on subjective cognitive functioning	Complex time-frame, with 15 different evaluation points, until 3 months after completion of rehabilitation	Both comparison to normative groups, and nonparametric $\chi^2$ tests	Improvement of working memory deficits, subjective cognitive functioning and on ecological tasks. Effects on cognitive tests and subjective cognitive functioning maintained at 3-month follow-up	NA		[55]
Locke <i>et al.</i> (2008)	Pilot open label, randomized controlled for first 16 dyads, another three assigned to intervention group	19	Dyads of newly diagnosed primary BT, during RTX, having mild-moderate cognitive deficits, and their caregivers	12 sessions of cognitive-rehabilitation and problem-solving therapy intervention (n = 12) vs standard medical care (n = 7) over 2 weeks	Qs on compensation techniques, intervention feedback, QoL, and functional status, cognitive tests	Baseline, postintervention, and 3-month follow-up	Wilcoxon signed-rank test	88% used compensation strategies and 88% found intervention helpful (n = 13); no significant intervention-related improvement in QoL and functional status; no analysis of cognitive data	Low accrual, 5 pairs dropped out before postintervention assessment, 1 pair did not complete follow-up	Feasibility and tolerability study	[56]
Hassler <i>et al.</i> (2010)	Pilot, no control group	11	Patients with grade 3 gliomas and glioblastomas multiforme, postsurgery RTX and CTX; KPS: 80–100*	Ten sessions of holistic mnemonic group training of attention, verbal and memory skills over 12 weeks	Three cognitive tests	Pre- and postintervention	Paired t-tests	Significant improvement in a verbal memory test	None		[57]

\*Presence of cognitive deficits not an inclusion criterion.

ANCOVA: Analysis of covariance; BT: Brain tumor; CTX: Chemotherapy; KPS: Karnofsky performance score; NA: Not applicable; Q: Questionnaire; QoL: Quality of life; RTX: Radiotherapy.

Table 4. Recent and novel studies of cognitive rehabilitation for cognitive deficits in patients with brain tumors.

Investigators (year; trial no.)	Design	n	Population	Intervention	Relevant outcome measures	Timing of assessments	Statistical analyses	Relevant results	Attrition/toxicities	Comments	Ref.
Brigidi et al. (NCT00849498)	Open-label, randomized, controlled	20	Dyads of patients with high-grade glioma, and depression, fatigue, sleep problems and/or cognitive impairment, and their caregivers	Coping skills training including problem solving, communication and skills and managing activities for 3 months vs usual care	Adherence, cognitive tests, Qs on cognitive functioning and symptoms	Baseline, postintervention, and every 4 months thereafter up to 2 years	NA	Study start: December 2008 Estimated study completion date: December 2011 Current status: recruiting	NA	Coping skills include cognitive rehabilitation strategies	[213]
Taphoorn et al. (NCT00256425); Gehring et al. (2009)	Open label, randomized, controlled	140	Low-grade gliomas, anaplastic gliomas (age <50 years and KPS >70), subjective and objective cognitive symptoms	Six sessions of cognitive rehabilitation (retraining and compensation) in 7 weeks	Cognitive tests, Qs on cognitive functioning, mental fatigue, community integration and QoL	Baseline, immediately after training and 6-month follow-up	Doubly multivariate repeated measures ANCOVAs	Postintervention improvement of subjective cognitive functioning, longer term improvement in attention, verbal memory and mental fatigue	13 patients dropped out between baseline and follow-up		[214] [48]

<sup>†</sup>Presence of cognitive deficits not an inclusion criterion.

ANCOVA: Analysis of covariance; BT: Brain tumor; CTX: Chemotherapy; KPS: Karnofsky performance score; NA: Not applicable; Q: Questionnaire; QoL: Quality of life; RTX: Radiotherapy.

Brigidi and colleagues are currently recruiting 20 dyads of patients with a high-grade (III or IV) glioma and a life expectancy of at least 6 months and their caregivers to a trial in which they will be randomized to coping-skills training, including problem solving, communication skills and managing activities, or a usual care control group [213]. Evidence of problems in depression, fatigue, sleep disturbance and/or cognitive impairment as indicated by the treating neuro-oncologist is one of the inclusion criteria. The study is expected to be completed by December 2011.

#### **RCT on cognitive rehabilitation in patients with low-grade & anaplastic gliomas**

We recently reported on the first RCT that evaluated the effects of a multifaceted cognitive rehabilitation program on cognitive functioning and selected QoL domains in 140 adult patients with low-grade and anaplastic gliomas, favorable prognostic factors, and both subjective cognitive symptoms and objective cognitive deficits [48,214]. Patients were randomized to an intervention group or a waiting list control group. Most patients had undergone either biopsy (29%) or resection (66%), 61% had undergone radiotherapy, and 11% had had chemotherapy. The cognitive rehabilitation program that we developed consisted of six-weekly, 2-h individual sessions plus homework, and incorporated both computer-based attention retraining (C-Car) and psychoeducation on and compensatory skills training of attention, memory and executive functioning (strategy training; see [GEHRING K, AARONSON NK, TAPHOORN MJB, SITSKOORN MM. A COGNITIVE REHABILITATION PROGRAM FOR PATIENTS WITH MILD TO MODERATE COGNITIVE DEFICITS EVALUATED IN PATIENTS WITH BRAIN TUMORS. MANUSCRIPT SUBMITTED]) for more details on the program). The mean total time devoted to the entire cognitive rehabilitation program was 35 h over a period of 6 weeks; almost 6 h for the C-Car component and up to 30 h for the strategy component.

Participants completed a battery of neuropsychological tests and self-report questionnaires on cognitive functioning, fatigue, mental health-related QoL and community integration at baseline following completion of the program and at 6-months follow-up. For the primary statistical analysis of the result at the group level, a hierarchical approach of doubly multivariate repeated-measure analysis of covariance was used.

Although the intervention group reported a significant improvement in subjective cognitive functioning early on, and this was largely maintained through to the 6-month follow-up, the control group exhibited a smaller, more gradual improvement in

self-reported cognitive functioning over time. This improvement might reflect a combination of regression to the mean [58], response shift [59] and natural recovery (e.g., see [60,61]). As a result, differences in subjective cognitive functioning between the two groups diminished over time.

With regard to the objective neuropsychological test scores, no significant group differences were observed at immediate post-intervention. Closer inspection of the test scores suggested that improvement due to practice effects or regression to the mean in both groups may have initially overwhelmed any intervention effect in the experimental group. At the 6-month assessment, the intervention group exhibited continued improvement in objective cognitive performance on six neuropsychological measures of attention and verbal memory, while the control group did not. Significant intervention effects were also found for longer term mental fatigue scores.

In summary, the results of this RCT at the group level indicated a positive effect on short-term cognitive complaints, and longer term cognitive performance and mental fatigue level. The large majority of the participants indicated that they found most of the program elements to be very useful [GEHRING *ET AL.* MANUSCRIPT SUBMITTED]. A substantial percentage (36%) of the participants indicated that the strategy training involved a great deal of homework, although only a few indicated that it was too burdensome. Older patients had more difficulty with the amount of homework involved than younger participants.

### Expert commentary

Many of the published studies and those currently being carried out on the prevention or treatment of cognitive deficits in patients with brain tumors have methodological limitations that impact on both the quality of the research and the ability to draw firm conclusions. In our own research, we were also confronted with a number of methodological challenges and problems. In this section, we will address the most important of these methodological issues, with an eye toward informing future research on both pharmacological and neuropsychological approaches to the cognitive rehabilitation of this patient population.

Among the methodological limitations, perhaps the most important is the failure to employ an appropriate control group in order to rule out practice effects (i.e., improved neuropsychological test performance due to repeated testing over time), and other effects such as regression to the mean or spontaneous recovery. Although it appears that more recent studies have employed a randomized controlled design more frequently, based on our own experiences, we would again like to emphasize the importance of the control group. In our RCT, we observed an initial improvement in test performance in the intervention group. Without the inclusion of a control group, we would have attributed this positive effect to the cognitive rehabilitation program. However, the fact that there was a similar improvement in the control group suggested a practice effect. The inclusion of a control group proved to be essential. Bruera and colleagues had a comparable experience when testing methylphenidate for cancer fatigue [62,63]; although in their initial pilot study the scores on a fatigue scale improved

significantly (by 17 points), the overall effects were markedly lower in their RCT (7.5 points for placebo and 9.6 points for methylphenidate). They stated that this lower improvement was probably the result of the double-blind controlled nature of their study and concluded that their findings reinforce the importance of conducting placebo-controlled trials to assess symptomatic outcomes.

In studies where, for whatever reason, use of a control group is not possible, there are two alternatives:

- The use of multiple baseline assessments, as practice effects are most likely to occur between the first and second testing sessions;
- The use of parallel neuropsychological tests (tests with alternate forms) [64] that are alternately administered to the diverse groups.

In studies in which several groups are being compared, it is of course highly desirable to assign patients by means of randomization. In our RCT, we employed a 'pseudorandomized' method called 'minimization'. For relatively small trials, this method has proven to provide more balanced groups when compared with both restricted (stratified) and unrestricted (simple) randomization, and is able to incorporate more prognostic factors [64]. Disadvantages of the method are that assignment can be predictable, that statistical testing assumptions of randomized allocation may be compromised due to the 'pseudorandom' allocation adopted, and that it is organizationally more complex [64,65]. However, these disadvantages are also true of other allocation methods such as stratification and, for some, adjustments can be made [64]. Other authors suggest that minimization may be the platinum standard if randomization is the gold standard [66]. Free software for carrying out minimization is available on the internet. Researchers are referred to the website of John Martin Bland, Professor of Health Statistics, with an overview of links to randomization (including minimization) software and services [215].

Problems with patient accrual and attrition over time have been reported in many trials. In some cases, this may be due to logistical barriers, such as inconvenient timing of neuropsychological testing, or the patient having to travel to a hospital to undergo cognitive rehabilitation and/or to be tested. Most interventions were carried out in patients with a history of treatment, in particular of radiation therapy. One might argue that the cognitive deficits (whether caused by the tumor itself or by treatment) are most prevalent and severe at this stage of the illness trajectory, when treatment has been completed. Intervention at an earlier stage may be problematic. For example, Locke and colleagues indicated that problems with recruitment into a study of cognitive rehabilitation in patients with newly diagnosed brain tumors was largely due to the fact that patients were relatively early in their disease and treatment trajectory, and thus measurable cognitive impairment was limited [56].

Arranging for the training and assessments to take place at the patient's home may be an effective means of limiting both problems with accrual and with loss to follow-up. In our RCT, less than 10% of patients in both the intervention and the control group dropped out during the 8-month study period. We are convinced that the home-based nature of the intervention and of

the assessments played an important role in this high, sustained rate of participation. At the same time, facilitating training and assessment at home requires a larger travel budget, places greater demands on personnel, and requires flexibility on the part of both the researchers and the patients and their families to create optimal circumstances for carrying out training and assessments.

Alternatively, with respect to cognitive rehabilitation, internet-based programs may also overcome these impediments. We are aware of only one completed study on internet-based cognitive rehabilitation [67], which was conducted in patients with memory impairments after severe traumatic brain injury. In this study, although there were no significant differences observed between the active and control conditions on the primary outcome measures (patient- and family-rated mood and memory), the authors suggest that the internet may still be a useful means of delivering compensatory cognitive rehabilitation [67]. They also report that patients were highly satisfied with the treatment [68].

Many studies have been conducted on internet-based cognitive behavioral therapy. Although this type of therapy has a different purpose and targets a different patient population, the successes observed in these studies suggest that internet-based cognitive rehabilitation should be considered as a serious option for future research [69]. We are currently investigating the possibilities of adapting both the retraining and strategy components of our cognitive rehabilitation program to an internet-based platform.

With regard to data analysis, the employment of multivariate techniques can be important in longitudinal studies with repeated measures and a battery of outcome measures. By means of these approaches the specific effects for the different groups over time can be tested. They may in part account for multiple statistical testing and thereby minimize the risk of type I errors.

Furthermore, although results at the group level (e.g., statistical comparisons of group means) are very informative in studies of treatment effectiveness, they may also mask the variability in individual responses to interventions [70].

Defining responsiveness to an intervention or change over time at the individual patient level, that is, defining criteria on which to dichotomize change into 'success' or 'failure' of a treatment, is, however, complicated by the fact that the reliability of (neuro) psychological measures can be compromised by such factors as practice effects and regression to the mean. To prevent arbitrariness of the responsiveness criteria, more sophisticated methods than, for example, percentages of change have been proposed. In recent years, the Reliable Change Index has been introduced [71]. It represents a stringent measure of improvement at the individual level in the context of observed changes over time in a control group [72], and reflects the individual change beyond that which can be attributed to measurement error and practice effects. Other measures with terms such as clinical significance, clinically meaningful change and minimum clinically important difference (e.g., see [72–74]) have also been introduced.

Additional analyses may help to identify the specific patient characteristics that predict positive individual response to a pharmacological or neuropsychological intervention. The knowledge gained can be used to inform future patients about the likelihood

that they will benefit (or not) from that intervention, and that it is worth the investment in time and effort. Conversely, if we can identify patients who are less likely to benefit from the intervention under study, we can advise them accordingly. Perhaps more importantly, and in particular for cognitive rehabilitation programs, we can use the knowledge to adapt our interventions to yield optimal benefit for a larger percentage of the target population. We are currently conducting analyses on the possible sociodemographic, clinical, subjective cognitive symptom and neuropsychological baseline predictors of individual improvement based on a modification of the original Reliable Change Index in the participants of the cognitive rehabilitation program.

Another issue that is commonly encountered in many studies of cognitive functioning in chronically ill patients is the discrepancy observed between the subjective (self-report) and objective (neuropsychological testing) measures of cognitive functioning [75–81]. The results of our trial suggest that this disconnect between subjective experience and test-based indicators of cognitive functioning not only applies in cross-sectional assessments, but also in assessing change in cognitive functioning over time. The moderate ecological validity of neuropsychological tests [82] and test situations may not entirely explain this discrepancy (e.g., [80]). For example, in patients with multiple sclerosis, it was found that patients' performance on a battery of cognitive tests did, in fact, correlate with spouses' and caregivers' perceptions of patients' daily cognitive functioning [83]. In another study in the same population, Middleton suggested that correlations between perceptions of daily cognitive functioning and objective scores are higher for healthy controls than for patients [80]. Thus, the cause of the discrepancy may be found in the perceptions of patients themselves. In fact, it has been generally observed that self-reported cognitive functioning tends to correlate more highly with self-reported measures of emotional distress and well-being than with objective neuropsychological test performance [75,76,78,80,81].

A related issue concerns the common failure to include the presence of cognitive deficits as an inclusion criterion for studies designed to test the efficacy of cognitive rehabilitation. In order to be able to measure an effect of an intervention, whether pharmacological or neuropsychological, patients need to exhibit some minimal level of cognitive impairment. Furthermore, the awareness that we must not rely on the Mini-Mental State Examination [84] as the only measure of cognitive functioning has grown in recent years. As this measure has an unacceptably low sensitivity [85], we would again advise not to use it as the only screening and/or evaluation measure.

In addition, it may be appropriate to screen patients not only for objectively determined cognitive impairment, but also for self-reported cognitive complaints, and to only recruit patients who exhibit both. In particular, the experience of cognitive symptoms may be crucial in motivating patients to adhere to medication regimens and to undergo time-consuming cognitive rehabilitation programs. This 'two-step' screening process reflects, in fact, what often takes place in clinical practice. The problems reported in recruiting and keeping patients in trials designed to prevent

cognitive deficits in patients undergoing anticancer therapy may, at least in part, be due to the fact that the patients are not yet experiencing cognitive symptoms, and thus may not be motivated to participate in a cognitive intervention or to adhere to the program once enrolled.

With respect to the assessment of outcome in cognitive intervention studies, we would point out that, although improvements in neuropsychological test performance and subjective cognitive symptoms are desirable results, improvement at the level of functional abilities may be the ultimate goal. For the purpose of evaluating functional outcome in individuals with cognitive deficits, questionnaires on instrumental activities of daily living, including tasks such as housekeeping, shopping and managing finances, are often used. The problem with most of these questionnaires is that the activities that they measure may not be sensitive enough to detect changes (improvement) in the relatively mild-to-moderate cognitive deficits experienced by patients with brain tumors who are candidates for cognitive rehabilitation. In our own research, as an alternative to measures of instrumental activities of daily living, we employed the Community Integration Questionnaire, which assesses productive activity, independent living and social activity [86]. We also used a measure of fatigue, and found some evidence that mental fatigue improves following cognitive rehabilitation.

It should also be noted that maintaining rather than improving neuropsychological functioning may be a legitimate goal of a cognitive intervention in patients with brain tumors. This may particularly be the case when cognitive decline is expected (e.g., with measurements over a longer interval, in which practice effects may be diminished).

A recommendation that is based on both our experience and that of others, is that studies of cognitive rehabilitation programs should take into account the possibility of a 'delayed' intervention effect on cognitive test performance. We observed this in our RCT, and it has also been reported in earlier studies of cognitive rehabilitation in other patient populations [87–90]. It has been suggested that patients may require a longer period of time to integrate learned strategies into their daily routine.

Finally, future cognitive rehabilitation studies in patients with brain tumors will face the problem, common for all behavioral treatment studies, that it is not feasible to incorporate a 'placebo' condition in which patients are required to attend a series of sessions (comparable to the intervention group) in which no truly substantive rehabilitation program is offered. As a consequence, it will be difficult to exclude the possibility that the positive results of the cognitive rehabilitation are not only attributable to the cognitive treatment itself, but also to other nonspecific factors such as attention [91,92]. At the same time, careful analysis of trial data can provide some insight into the probability of a placebo effect. For example, in our study, we could not exclude the possibility that the immediate decline in subjective cognitive symptoms could be due to nonspecific treatment effects. However, nonspecific treatment effects as the sole or even primary explanation for the improvements in objective test performance was less likely, considering the initially equal improvement in neuropsychological

performance for both groups, and the intervention effect after a 6-month interval, in which possible placebo effects may be assumed to be absent. Moreover, it has been suggested that non-specific treatment effects, such as social support and a credible treatment rationale, form an integral part of the treatment, and that results from trials without placebo are more generalizable to clinical practice [93].

### Five-year view

In recent years, the interest in interventions for tumor- or treatment-related cognitive deficits in patients with brain tumors has clearly grown, resulting in an expansion of novel studies of this subject. Identification of studies on Clinicaltrials.gov shows that important data will become available in the next few years. It is therefore expected that insight in this topic will grow considerably.

First, the identification of more targeted brain tumor treatments is anticipated. Results from the study on gliadel wafers [203] are forthcoming and a trial on avoidance of the hippocampus during WBRT in patients with brain metastases is opening soon [49].

With regard to prevention studies in patients with brain tumors, the results of a RCT on the possible preventive effects of memantine [205] will become available in the next few years. Studies of pharmacological treatment of cognitive deficits that have been conducted in patients with cancers outside the CNS [77,94–96] suggest that it might be worthwhile to determine the preventive effects of erythropoietin or similar stimulating agents in these patients and in those with brain cancer.

The number of successful studies of pharmacological agents for the treatment of existing cognitive deficits in patients with brain tumors is still very low. In the coming years, the results of RCTs on donepezil [210] and armodafinil [212] in patients with brain tumors are anticipated. Indeed, modafinil has been found to be effective in recent studies in patients with cancers outside the CNS [97–99] who have cognitive deficits, which suggests that the cognitive effects of this agent should be investigated more thoroughly in these populations.

Cognitive rehabilitation programs in patients with brain tumors have only recently been the subject of study [48,56,57]. Results show that they are feasible and that they yield positive effects, even in the long term. Replication of studies that have provided positive results and further refinement of available programs is, however, still needed.

Moreover, we expect that studies on cognitive rehabilitation may have higher success rates than pharmacological and/or prevention studies. Previous studies that offered cognitive intervention during tumor treatment (most often prevention studies), although suffering less from logistical barriers to patient enrollment and adherence, have faced problems with patient willingness to participate. The reason for this is presumably that cognitive problems, if present at all at this stage, are not among patients' main concerns. Furthermore, with regard to pharmacological treatment or prevention of cognitive deficits, patients may be reluctant to take (additional) medication during or after tumor treatment. Internet-based cognitive rehabilitation programs, preferably combined with some personal contact, may be a more

convenient and flexible alternative to in-clinic programs, although their efficacy needs to be tested. Other approaches to improving cognitive functioning in patients with a brain tumor should also be considered. For example, it has been suggested that (offline repetitive) transcranial magnetic stimulation might be useful in the rehabilitation of cognitive functions [100,101], although evidence of long-term effects is needed [101].

Recent findings also suggest that physical exercise may be effective in delaying or ameliorating cognitive decline in older adults with and without cognitive decline [102–104]. The evidence stems from epidemiologic [105,106], experimental [107], neuro-anatomical [108] and animal studies [107,109]. Furthermore, the benefits of physical activity on fatigue, depression, fitness and happiness have frequently been demonstrated in patients with diverse cancer types (other than brain cancer) [110–112]. The effects of physical exercise on cognitive functioning in patients with a brain tumor have yet to be investigated. Our group is preparing a study of the feasibility and effectiveness of physical exercise in predominantly low-grade glioma patients in improving cognitive functioning, fatigue, mood and QoL.

Future research on cognitive interventions should continue to be based on a clear (albeit sometimes preliminary) rationale, employ randomized or well-matched controlled designs and a

comprehensive neuropsychological test battery, and analyze data with multivariate statistics at the group level and preferably individual measures of improvement. In order to avoid or minimize problems with enrollment and adherence, and to yield optimal treatment effects, future studies should consider screening patients for the presence of both subjective and objective cognitive problems, and take logistical considerations concerning planning and location of assessments (and, if applicable, training sessions) into account.

In this way, clear insights into the treatment of cognitive deficits in patients with a brain tumor will be obtained and become applicable in clinical practice.

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## Key issues

- Cognitive deficits resulting from a brain tumor or its treatment can substantially impact on patients' lives.
- Until recently, relatively few studies investigated prevention or treatment of cognitive deficits in patients with brain tumors.
- The interest in interventions for tumor- or treatment-related cognitive deficits in brain tumors has clearly grown, and data of promising novel studies are anticipated.
- Although methodologies have also become stronger, many studies have methodological limitations, of which the most important is the failure to employ an appropriate control group in order to rule out practice effects.
- The effects of erythropoietin and similar agents in the pharmacological prevention of cognitive deficits need to be determined.
- Potentially successful pharmacological treatments for cognitive deficits may be modafinil and similar agents.
- However, pharmacological prevention and treatment studies suffer from problems with patient enrollment and attrition.
- Research experience and results suggest that cognitive rehabilitation is a very promising method of treating cognitive deficits. However, studies should be replicated and cognitive rehabilitation programs should be further refined.

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