

8.03.10 Cognitive Rehabilitation			
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Policy Statement

Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) may be considered **medically necessary** in the rehabilitation of patients with cognitive impairment due to traumatic brain injury.

Cognitive rehabilitation (as a distinct and definable component of the rehabilitation process) is considered **investigational** for all other applications, including, but not limited to:

- Aging population, including patients with Alzheimer disease
- Autism spectrum disorder
- Multiple sclerosis
- Patients with cognitive deficits due to brain tumor or previous treatment for cancer
- Postencephalitic or postencephalopathy patients
- Seizure disorders
- Stroke

Policy Guidelines

For services to be considered medically necessary, they must be provided by a qualified licensed professional and must be prescribed by the attending physician as part of the written care plan. Additionally, there must be a potential for improvement (based on preinjury function), and patients must be able to participate actively in the program. (Active participation requires sufficient cognitive function to understand and participate in the program, as well as adequate language expression and comprehension, i.e., participants should not have severe aphasia.) Ongoing services are considered necessary only when there is demonstrated continued objective improvement in function.

Duration and intensity of cognitive rehabilitation therapy programs vary. One approach for comprehensive cognitive rehabilitation is a 16-week outpatient program comprising 5 hours of therapy daily for 4 days each week. In another approach, cognitive group treatment occurs for three 2-hour sessions weekly and three 1-hour individual sessions (total, 9 hours weekly). Cognitive rehabilitation programs for specific deficits (e.g., memory training) are less intensive and generally have 1 or 2 sessions (30 or 60 minutes) a week for 4 to 10 weeks.

Coding

The following CPT code is specific to cognitive rehabilitation:

- **97127:** Therapeutic interventions that focus on cognitive function (e.g., attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (e.g., managing time or schedules, initiating, organizing and sequencing tasks), direct (one-on-one) patient contact

Sensory integration therapy, explicitly identified by CPT code 97533, is addressed separately in Blue Shield of California Medical Policy: Sensory Integration Therapy and Auditory Integration Therapy.

Description

Cognitive rehabilitation is a therapeutic approach designed to improve cognitive functioning after central nervous system insult. It includes an assembly of therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory,

reasoning, problem-solving, and executive functions. Cognitive rehabilitation comprises tasks to reinforce or reestablish previously learned patterns of behavior or to establish new compensatory mechanisms for impaired neurologic systems. Cognitive rehabilitation may be performed by a physician, psychologist, or a physical, occupational, or speech therapist.

Related Policies

- Sensory Integration Therapy and Auditory Integration Therapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Cognitive rehabilitation is not subject to regulation by the U.S. Food and Drug Administration.

Rationale

Background

Cognitive rehabilitation is a structured set of therapeutic activities designed to retrain an individual's ability to think, use judgment, and make decisions. The focus is on improving deficits in memory, attention, perception, learning, planning, and judgment. The term *cognitive rehabilitation* is applied to various intervention strategies or techniques that attempt to help patients reduce, manage, or cope with cognitive deficits caused by brain injury. The desired outcomes are improved quality of life and function in home and community life. The term *rehabilitation* broadly encompasses reentry into familial, social, educational, and working environments, the reduction of dependence on assistive devices or services, and general enrichment of quality of life. Patients recuperating from traumatic brain injury have traditionally been treated with some combination of physical therapy, occupational therapy, and psychological services as indicated. Cognitive rehabilitation is considered a separate service from other rehabilitative therapies, with its own specific procedures.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the

intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

This review evaluates evidence for cognitive rehabilitation delivered by a qualified professional; studies of self-administered computer programs are not considered cognitive rehabilitation for this evidence review and are not assessed here.¹⁻⁵ Short-term improvements in cognitive test performance measured postintervention alone will not be considered a health outcome for this review. Measurements of daily functioning and quality of life (QOL) are the primary health outcomes of interest. Improvements should be demonstrable after longer term follow-up postintervention, preferably greater than 6 months.

This evidence review was initially informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1997).⁶ The Assessment addressed a broad range of patient indications resulting from neurologic insults, including traumatic brain injury (TBI), stroke, postencephalopathy, and aging (including Alzheimer disease [AD]). Eighteen controlled trials were reviewed, primarily focusing on stroke and TBI. No controlled trials were available that specifically addressed other patient indications. No clear answer on the efficacy of cognitive rehabilitation emerged from the Assessment. The evidence was conflicting either because of study designs, low power to detect differences or variations in treatment. The Assessment concluded that data in the published peer-reviewed literature were inadequate to validate the effectiveness of cognitive rehabilitation as an isolated component or as a component of a multimodal rehabilitation program.

The American Congress of Rehabilitation Medicine (ACRM) published a systematic review (2013) of cognitive rehabilitation on medical conditions affecting cognitive function.⁷ Literature was searched through the end of 2008. Of 11 clinical conditions reviewed (anoxia/hypoxia, encephalitis, epilepsy, HIV-AIDS encephalopathy, Huntington disease, systemic lupus erythematosus, Lyme disease and other tick-borne encephalopathy, neoplasms, Parkinson disease, metabolic encephalopathy), evidence supported only a practice guideline for children and adolescents with brain tumors who underwent surgical resection and/or radiotherapy (see Practice Guidelines and Position Statements section). The evidence for patients with seizure-related cognitive impairments is discussed in a later section herein.

Traumatic Brain Injury

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in patients with cognitive deficits due to traumatic brain injury.

The question addressed in this evidence review is: does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with cognitive deficits due to traumatic brain injury.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life.

Timing

The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to traumatic brain injury has varying lengths of follow up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, a minimum of 6 months of follow-up is considered necessary to demonstrate efficacy.

Setting

Patients with cognitive deficits due to traumatic brain injury are actively managed by neurologists, psychologists, psychiatrists, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- d. Studies with duplicative or overlapping populations were excluded

Systematic Reviews

A 2013 Cochrane review assessed cognitive rehabilitation for executive dysfunction (planning, initiation, organization, inhibition, problem-solving, self-monitoring, error correction) in adults with nonprogressive acquired brain damage.⁸ Sixteen RCTs (total N=660 patients; 395 TBI, 234 stroke, 31 other acquired brain injury) were included in pooled analyses. No statistically significant effects on measures of global executive function or individual component functions were found.

A TEC Assessment (2008) evaluated cognitive rehabilitation specifically for adults with TBI.⁹ The objective of this Assessment was to determine whether the evidence showed that cognitive rehabilitation improved health outcomes. Eleven RCTs for specific cognitive deficits showed inconsistent support for cognitive rehabilitation. Of these 11 studies, eight reported daily functioning or quality of life (QOL) outcomes. Three studies showed statistically significant differences between intervention groups and control groups on 1 outcome. However, 2 studies were extremely small. Findings were inconsistent across other outcomes measured, and, in 1 study, significant findings after the intervention were no longer present at 6-month follow-up. All 11 trials also reported outcomes of various cognitive tests. These trials had numerous methodologic limitations, such as small sample sizes, lack of long-term follow-up, minimal interventions, and multiple outcomes. In summary, the RCTs considered in this Assessment did not show strong evidence for efficacy in the treatment of TBI.

Randomized Controlled Trials

RCTs not included in the Cochrane systematic review or TEC Assessment are described next. Cicerone et al (2008) reported on an RCT comparing a comprehensive neuropsychologic rehabilitation program with standard rehabilitation.¹⁰ Sixty-eight patients were randomized to the 2 intervention groups for 16 weeks of treatment. Principal outcomes were the Community Integration Questionnaire (CIQ) and the Perceived Quality of Life Scale scores. Treatment effectiveness was evaluated by an interaction between intervention pre- and posttreatment. Such an interaction was significant for CIQ scores ($p=0.042$) and Perceived Quality of Life Scale scores ($p=0.049$) but not for any of the secondary neuropsychologic outcomes. The proportion of patients having a clinically significant improvement in CIQ score (4.2 points) was not reported. Follow-up assessments were done at 6 months posttreatment, but were not subjected to formal statistical analysis. The standard treatment group had further improvements in CIQ scores such that its mean follow-up CIQ score was very similar to that of the intervention group (12.9 vs 13.2). For Perceived Quality of Life Scale scores, the differences observed at the end of treatment were maintained or had increased by 6 months. This RCT, thus, had mixed findings on the efficacy of comprehensive neuropsychologic rehabilitation for TBI.

Chiaravalloti et al (2016) conducted an RCT evaluating the Story Memory Technique (SMT) to improve learning and memory in subjects with TBI.¹¹ Sixty-nine subjects were randomized to treatment or control. Assessments were performed at the end of treatment (5 weeks) and 6 months posttreatment. Statistically significant outcomes favored the treatment group for several measures assessing memory at 5 weeks, while results at 6 months were less definitive.

Section Summary: Traumatic Brain Injury

Although some RCTs have shown improvements in some outcomes with cognitive rehabilitation, systematic reviews have provided mixed findings, with no consistent evidence of efficacy in patients with TBI.

Dementia, Including Alzheimer Disease Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in patients with cognitive deficits due to dementia.

The question addressed in this evidence review is: does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with cognitive deficits due to dementia.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life.

Timing

The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to dementia has varying lengths of follow up, ranging from 3 months to 2 years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Setting

Patients with cognitive deficits due to dementia are actively managed by neurologists, psychologists, psychiatrists, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- d. Studies with duplicative or overlapping populations were excluded

Systematic Reviews

Huntley et al (2015) performed a meta-analysis of cognitive interventions in dementia.¹² Thirty-three studies were included. Interventions were divided into categories such as cognitive training, cognitive stimulation, and cognitive rehabilitation. Studies classified as cognitive stimulation had a significant effect as measured on the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale. Reviewers concluded that benefits measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale were generally not clinically significant.

In a Cochrane review, Bahar-Fuchs et al (2013) evaluated the use of cognitive training (task-focused) or rehabilitation (strategy-focused) in AD and vascular dementia.¹³ Evidence from 11 RCTs did not demonstrate improved cognitive function, mood, or activities of daily living in patients with mild-to-moderate AD or vascular dementia with cognitive training. Reviewers cited a 2010 high-quality RCT¹⁴ of cognitive rehabilitation in 69 patients with early-stage AD, which showed short-term improvements in patient-rated outcomes. A 2011 Cochrane review assessing interventions for persons with mild cognitive impairment concluded that there was little evidence on the effectiveness or specificity of such interventions because improvements observed were similar to effects seen with active control interventions.¹⁵

Randomized Controlled Trials

Ameiva et al (2016) reported on results from the ETNA3 multicenter RCT that compared 4 therapies strategies: standardized programs of cognitive training (group sessions), reminiscence therapy (group sessions), individualized cognitive rehabilitation program (individual sessions), and usual care.¹⁶ Six hundred fifty-three patients with mild-to-moderate AD were randomized in a 1:1:1:1 ratio at 40 French clinical sites. We focus on the cognitive rehabilitation program and usual care arms. The primary outcome was the rate of survival without moderately severe to severe dementia at 2 years. Secondary outcomes were cognitive impairment, functional disability, behavioral disturbance, apathy, QOL, depression, caregiver burden, and resource utilization. Participants and clinical staff were not blinded to treatment assignment, but outcome assessments were done by blinded physicians and psychologists. The cognitive rehabilitation therapy consisted of a "made-to-measure" program conducted in

individual sessions and adapted to patients' cognitive abilities, with goals selected to be personally relevant to the patient. Intention-to-treat analyses were performed using "missing equal failure" to replace missing values. Approximately 90% of participants had the 3-month follow-up visit, and 72% had the 24-month visit. There was no difference between the cognitive rehabilitation group and the usual care group with respect to the primary outcome. However, patients who received cognitive rehabilitation therapy had a less functional decline at 24 months compared with the usual care group, as measured by one of the 2 scales assessing functional abilities: the Autonomie G rontologique Groupes Iso-Ressources scale ($p=0.02$). The rate of institutionalization was lower in the cognitive rehabilitation therapy group (27%) than in the usual care group (19%). These results are promising but, given the lack of consistency in benefits on the 2 functional scales, replication is needed to confirm positive findings. Regan et al (2017) reported on an RCT of a home-based, 4-session, goal-oriented cognitive rehabilitation program vs usual care in 55 patients with mild cognitive impairment and early AD.¹⁷ Patients were community-dwelling with a diagnosis of mild cognitive impairment or AD within 6 months of enrollment and an MMSE score greater than 20. The intervention group received 4 weekly 1-hour therapy sessions delivered by experienced therapists with a focus on addressing personally meaningful goals. All participants identified at least 1 goal for improvement. The usual care group had no contact with the research team between their initial and final assessments. The primary outcome measures were goal performance and satisfaction scores on the Canadian Occupational Performance Measure. Twelve participants in the intervention group and 3 participants in the control group discontinued study participation and were excluded from the final, per-protocol analysis. For the first identified goal, the intervention group had significantly greater improvements in performance and satisfaction on the Canadian Occupational Performance Measure than the control group. There were no differences in secondary measures of QOL or anxiety and depression. The per-protocol results were biased due to the high rate of missing data.

Thivierge et al (2014) in Canada reported on a small ($N=20$), assessor-blinded, block-randomized, crossover trial of an individualized memory rehabilitation program in patients with mild-to-moderate AD.¹⁸ The Memory Rehabilitation Program comprised 4 weeks of training by a patient's caregiver to improve performance of an instrumental activity of daily living selected by the patient and caregiver. Errorless learning (assistance provided to minimize errors) and spaced retrieval (expanded delays, from 30 seconds to 8 minutes, between each correct performance of the task) were used to facilitate learning at each patient's own pace. The primary outcome was a measure of assistance required to perform the task correctly at 1, 4, and 8 weeks after training. Compared with untrained (in period 1) or previously trained (in period 2) controls, statistically, significant improvements in performance were observed at posttreatment week 1 in both periods and at posttreatment week 4 in period 2. A statistically significant (vs baseline) improvement in performance occurred in period 1 controls. Performance of the target instrumental activity of daily living declined within 2 to 3 months posttraining. Improvements in other outcomes (general memory and cognitive ability, overall function, QOL, and behavioral/psychological symptoms¹⁸) were not observed.

Individual randomized trials have shown variable outcomes of cognitive rehabilitation. For example, Kurz et al (2012) conducted an RCT of patients with AD and early dementia.¹⁹ The population comprised 201 patients with clinical evidence of dementia and an MMSE score of at least 21 (of 30 points) who were randomized to a 12-week cognitive rehabilitation program or standard medical management (site-specific). There were no between-group differences on any outcome measure. There also were no group differences on subgroup analyses by age, sex, education level, or baseline cognitive ability, except depression scores, which improved significantly for females, but not males, in the intervention group.

Another randomized study of 54 patients, Chapman et al (2004) evaluated the combined effect of a cognitive-communication therapy plus an acetylcholinesterase inhibitor vs drug treatment alone.²⁰ A positive effect for the inhibitor cognitive rehabilitation group was found for discourse

abilities, functional abilities, emotional symptoms, and overall global performance. Beneficial effects were reported up to 10 months after active intervention.

Spector et al (2003) published an RCT on 115 patients assigned to a cognitive stimulation program or a control group.²¹ The intervention program ran for 7 weeks, and patients were only evaluated at completion. The treatment group had significantly higher scores on the principal outcome (MMSE), with a group difference of 1.14 points. Differences were also significant for secondary outcomes, a QOL score for AD and an AD assessment scale. The trialists limited assessment of outcomes to the 7-week period of treatment, and concluded that the intervention would need to be continued on a regular basis beyond 7 weeks.

Table 1. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	X	Interventions	X.1	X.2	X.3	X.4	X.5	X.6
						Therapy 1	Therapy 2		Therapy 3		Therapy 4	
Amieva (2016) ¹⁶	France	40	2008-2009	Patients diagnosed with Alzheimer disease	CTT (n=170)		RT (n=172)	ICRT (n=157)		Usual medical care (n=154)		
Thivierge (2014) ²²	Canada	NR	2008-2011	Patients with Alzheimer disease (n=20)		ELL and SR cognitive techniques	Controls		NR		NR	
Kurz (2012) ¹⁹	Germany	NR	NR	Patients with mild Alzheimer disease (n=201)		12-week cognitive rehabilitation program (n=100)	Standard medical management (site-specific; n=101)		NR		NR	
Chapman (2004) ²⁰	US	NR	1999-2001	Patients with mild to moderate Alzheimer disease (n=54)		Combined cognitive-communication therapy plus an acetylcholinesterase inhibitor (n=28)	Drug treatment alone (n=26)		NR		NR	
Spector (2003) ²¹	UK	23	NR	Patients with dementia		Cognitive stimulation therapy (n=115)	Control (n=86)		NR		NR	

RCT: randomized controlled trial; CTT: cognitive training therapy; RT: reminiscence therapy; ICRT: individualized cognitive rehabilitation therapy; ELL: errorless learning; SR: spaced retrieval.

Table 2. Summary of Key RCT Results

Study	Rate of patients alive and without moderately severe/severe dementia at 24 months	Survival rate at 24 months	Direct measure of training	Functional ability score at 9 months (mean SD)	Overall cognitive functioning at 1 year	Change in MMSE scores from baseline to 7 weeks
Amiev a (2016) ¹⁶						
CTT	81(47.7%)	124 (72.9%)				
RT	78 (45.4%)	118 (68.6%)				
ICRT	85 (54.1%)	121 (77.1%)				
Control	74 (48%)	109 (70.8%)				
Thivierge (2014) ²²						
Therapy			86.78			
Control			81.12			
Kurz (2012) ¹⁹						
Therapy				0.729+/-1.82		
Control				0.857+/-1.59		
P-Value				0.64		
Chapman (2004) ²⁰						
Therapy					24.62	
Control					26.96	
Spector (2003) ²¹						
Therapy						0.9
Control						-0.4
P-Value						0.044

CTT: cognitive training therapy; RT: reminiscence therapy; ICRT: individualized cognitive rehabilitation therapy

Table 3. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Amiev a (2016) ¹⁶					
Thivierge (2014) ²²			4. Not the intervention of interest		1,2. Follow-up only 24 weeks
Kurz (2012) ¹⁹					1,2. Follow-up only 9 months
Chapman (2004) ²⁰					
Spector (2003) ²¹					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Follow-Up ^d	Power ^e	Statistical ^f
Amiev a (2016) ¹⁶	2. Allocation not concealed	1. Participants and clinical staff not blinded				
Thivierge (2014) ²²	2. Allocation not concealed	1,2. No blinding				
Kurz (2012) ¹⁹	2. Allocation only concealed from outcome raters	1. Not blinded to treatment assignment				
Chapman (2004) ²⁰	1. Randomization process not described					
Spector (2003) ²¹	3. Allocation concealment unclear	1,2,3. Blinding not clear				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Dementia, Including Alzheimer Disease

Systematic reviews of RCTs have generally shown no benefit of cognitive rehabilitation or effects of clinical importance. Most randomized trials either have not shown effects, shown only short-term effects, or did not evaluate long-term outcomes. One large RCT with a goal-oriented cognitive rehabilitation program has reported significantly less functional decline on 1 of 2 functional scales and institutionalization in the cognitive rehabilitation group compared with usual care at 24 months.

Stroke

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in patients with cognitive deficits due to stroke.

The question addressed in this evidence review is: does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with cognitive deficits due to stroke.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life.

Timing

The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to stroke has varying lengths of follow up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting

Patients with cognitive deficits due to stroke are actively managed by neurologists, psychologists, psychiatrists, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- d. Studies with duplicative or overlapping populations were excluded

Systematic Reviews

Four Cochrane reviews have assessed the effectiveness of cognitive rehabilitation for recovery from stroke.²³⁻²⁶ The reviews evaluated spatial neglect, attention deficits, and memory deficits. The most recent updates of these reviews for these 3 domains drew the following conclusions:

- Spatial neglect: A 2013 update identified 23 RCTs with 628 patients.²³ There was very limited evidence for short-term improvements on tests of neglect with cognitive rehabilitation. However, for reducing disability due to spatial neglect and increasing independence, the effectiveness of cognitive rehabilitation remained unproved.
- Attention deficit: A 2013 update identified 6 RCTs with 223 patients.²⁴ There was limited evidence of short-term improvement in divided attention (ability to multitask), but no indication of short-term improvements in other aspects of attention. Evidence for persistent effects of cognitive rehabilitation on attention or functional outcomes was lacking.
- Memory deficit: A 2016 update identified 13 trials with 514 patients.²⁶ There were statistically significant benefits in subjective measures of memory in the short-term (i.e., the first assessment measurement after the intervention) but not in the longer term (i.e., the second assessment measurement after the intervention). The quality of the evidence ranged from very low to moderate; there was poor quality of reporting in many studies, lack of consistency in the choice of outcome measures, and small sample sizes.

Gillespie et al (2015) published an overview of Cochrane reviews and a more recent RCT assessing rehabilitation for poststroke cognitive impairment.²⁷ Data from 44 trials (total >1500 patients) were summarized. In addition to poststroke spatial neglect and attention and memory deficits (addressed in the 3 Cochrane publications previously described), poststroke perceptual disorders, motor apraxia, and executive dysfunction were reviewed. Conclusions were:

- Very little high-quality evidence exists for the effectiveness of cognitive rehabilitation for poststroke cognitive deficits.
- Current evidence has shown that cognitive rehabilitation for spatial neglect, attention deficits, and motor apraxia improve standardized assessments of impairment immediately after treatment. However, the durability and clinical significance of these improvements are unclear.
- Evidence for the effectiveness of cognitive rehabilitation for poststroke memory deficits, perceptual disorders, or executive dysfunction was not identified.

A 2001 review of the rehabilitative management of poststroke visuospatial inattention also concluded that the long-term impact of visual scanning and perceptual retraining techniques on overall recovery and functional outcome were unclear.²⁸

Randomized Controlled Trials

Zucchella et al (2014) conducted an assessor-blinded RCT of comprehensive cognitive rehabilitation, combining computer training and metacognitive strategies within 4 weeks after stroke.²⁹ Of 288 consecutive stroke survivors admitted to a neurorehabilitation unit in Italy, 92 (32%) met inclusion criteria and were randomized to cognitive rehabilitation (n=45) or control (n=47). At the end of treatment (i.e., at week 4), statistically significant differences were found between groups on some measures of memory and visual attention. The clinical significance of these short-term outcomes is unclear.

Section Summary: Stroke

Recent systematic reviews have generally reported limited effects of cognitive rehabilitation in stroke patients.

Multiple Sclerosis

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in patients with cognitive deficits due to multiple sclerosis.

The question addressed in this evidence review is: does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with cognitive deficits due to multiple sclerosis.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life.

Timing

The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to multiple sclerosis has varying lengths of follow up, ranging from 6 months to 1 year. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 1 year of follow-up is considered necessary to demonstrate efficacy.

Setting

Patients with cognitive deficits due to multiple sclerosis are actively managed by neurologists, psychologists, psychiatrists, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- Studies with duplicative or overlapping populations were excluded

Systematic Reviews

Three Cochrane reviews have evaluated cognitive rehabilitation for patients with multiple sclerosis (MS) and cognitive impairments.³⁰⁻³² In an update, das Nair et al (2016) included 15 studies with 989 patients. There were no differences in subjective reports of memory functioning or mood.³² There was some evidence of a significant effect of the intervention on objective assessments of memory in both the immediate and long-term follow-up and QOL in intermediate follow-up. However, this effect on objective memory outcomes and QOL was no longer statistically significant when studies at high risk of bias were excluded.

Rosti-Otajarvi and Hamalainen (2014) conducted a Cochrane review of neuropsychological rehabilitation in MS.³¹ Twenty RCTs met inclusion criteria (total N=986 patients), including 7 of the 8 trials in the das Nair Cochrane review. Overall quality and comparability of included trials were low due to methodologic limitations and variations in interventions and outcome measures across trials, respectively. In meta-analysis, statistically significant improvements in memory span (based on 2 low-quality trials, n=150 patients; standardized mean difference, 0.54; 95% confidence interval, 0.20 to 0.88; p=0.002; I²=0%) and working memory (3 very low-quality trials, n=288 patients; standardized mean difference, 0.33; 95% confidence interval, 0.09 to 0.57; p=0.006; I²=0%) were observed with cognitive training compared with controls. Statistically significant improvements in attention, information processing speed, immediate verbal memory, executive functions, and depression were not observed.

Table 5. SR&MA Characteristics

Study	Dates	Trials	Participants	Intervention	N (Range)	Design	Duration
Rosti-Otajarvi (2014) ³¹	1993-2013	20	Patients with	Neuropsychological rehabilitation	986 (15-240)	RCTs and quasi-	Mean 9.5 weeks

Study	Dates	Trials	Participants	Intervention	N (Range)	Design	Duration
			multiple sclerosis			randomized trials	
Das Nair (2016) ³²	1993-2015	15	Patients with multiple sclerosis	Cognitive rehabilitation	989 (19-240)	RCTs and quasi-randomized trials	NR

Table 6. SR&MA Results

Study	Memory Span Improvement (SMD)	Working Memory Improvement (SMD)	Objective Assessment of Memory (SMD)	Activities of Daily Living (SMD)
Rosti-Otajarvi (2014) ³¹	0.54	0.33	NR	NR
95% CI	0.2-0.88	0.09-0.57	NR	NR
P-v alue	0.002	0.006	NR	NR
Das Nair (2014) ³²	NR	NR	0.26	-0.33
95% CI	NR	NR	0.03-0.49	-0.63 to -0.03
P-v alue	NR	NR	0.03	0.03

P-v alue NR 0.03

SMD: standardized mean difference; CI: confidence interval.

Randomized Controlled Trials

Chiaravalloti et al (2005) conducted 2 RCTs in patients with primarily relapsing-remitting MS in the United States (total N=117 patients).^{33,34} In the 2005 RCT, included in both Cochrane reviews previously described, 29 (67%) of 43 screened patients who met inclusion criteria were randomized to 8 biweekly 45-minute cognitive rehabilitation sessions (n=15) or to control sessions with the same therapist at the same frequency, engaging in nontraining tasks (e.g., reading and recalling a story; n=14).³³ All patients demonstrated baseline impairment in new learning ability in the presence of intact attention/concentration and language comprehension. Cognitive rehabilitation comprised training in the SMT; during weeks one and two, patients used imagery to facilitate recall, and during weeks three and four, patients used context to aid new learning. Neuropsychologic assessments in 7 domains (attention/concentration, language, intelligence, information processing, emotional functioning, episodic memory, meta-memory [self-assessment]) were made at baseline, immediately after treatment (week 5), and 5 weeks later (during week 11). At 5 and 11 weeks, there were no statistical differences between groups in new learning (episodic memory) or emotional functioning. Self-reported improvements in memory were greater in the cognitive rehabilitation group than in the control group at both time points. Results for other neuropsychological assessments were not reported. Analysis of subgroups defined by the level of cognitive impairment (mild vs moderate-severe) showed statistically significant between-group differences in episodic memory, but because patient numbers were very small and there was no correction for multiple testing, this analysis was exploratory.

Chiaravalloti et al (2013) randomized 88 patients with MS to 10 biweekly, 45- to 60-minute sessions of modified SMT (mSMT) training (n=46) or control (n=42).³⁴ All patients in this RCT demonstrated new learning impairment on baseline neuropsychological screen. The mSMT training and the control interventions were carried out as previously described, with the addition of 2 sessions for patients in the treatment group to apply mSMT to real-world settings. The primary outcome was learning efficiency (rate of improvement in objective memory) during the first 8 sessions of training at 5 weeks (immediately after treatment) and at 6-month follow-up. At 5 weeks, learning efficiency was greater in the cognitive rehabilitation group than in controls. Improvements in objective everyday memory, general contentment (subjective everyday cognition and emotional functioning), apathy, and executive dysfunction also were greater in the cognitive rehabilitation group. Between-group differences in awareness level, depression, or anxiety were not statistically significant. At 6-month follow-up, the only persistent between-group difference was general contentment.

Rosti-Otajarvi et al (2013)³⁵ reported on 1-year follow-up results to a multicenter RCT included in the later Rosti-Otajarvi (2014) Cochrane review previously described. Patients with relapsing-remitting MS and attentional deficits (N=102) were randomized 3:2 to strategy-oriented neuropsychological rehabilitation (13 weekly 60-minute sessions) or no intervention. In the 2014 trial, neuropsychological rehabilitation did not improve cognitive performance immediately after the intervention (at week 13) or at 6 months, but statistically significant improvements in perceived cognitive deficits were observed at both time points.³⁶ In this follow-up report, statistically significant differences in perceived cognitive deficits persisted for an additional 6 months (1 year from baseline). However, only 78 (76%) of 102 randomized patients completed 1-year follow-up, and dropout was differential (83% completers in the neuropsychological rehabilitation group vs 67% in the control group). Due to the possibility that dropout was related to the outcome of interest (e.g., patients with perceived cognitive decline might have been more likely to drop out), findings should be interpreted cautiously.

Hanssen et al (2016) conducted an RCT evaluating cognitive rehabilitation for patients with MS.³⁷ One hundred twenty patients were randomized to 4 weeks of multidisciplinary cognitive rehabilitation or 4 weeks of standard rehabilitation. Outcomes for executive function did not differ significantly between groups at 4 or 7 months after the start of the intervention. Only a health-related QOL measure relating to psychological health showed a difference between intervention and control, favoring intervention.

Section Summary: Multiple Sclerosis

Although numerous RCTs have investigated cognitive rehabilitation in MS, large, high-quality trials are lacking. The ability to draw conclusions based on the overall body of evidence is limited by the heterogeneity of patient samples, interventions, and outcome measures. Further, results of the RCTs evaluated are mixed, with positive studies mostly reporting short-term benefits. Evidence for clinically significant, durable improvements in cognition is currently lacking.

Other Cognitive Deficit Conditions

Clinical Context and Therapy Purpose

The purpose of cognitive rehabilitation delivered by a qualified professional is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation, in patients with cognitive deficits due to epilepsy, autism spectrum disorder, postencephalopathy, or cancer.

The question addressed in this evidence review is: does cognitive rehabilitation delivered by a qualified professional improve the net health outcome in individuals with cognitive deficits?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with cognitive deficits due to epilepsy, autism spectrum disorder, postencephalopathy, or cancer.

Interventions

The therapy being considered is cognitive rehabilitation delivered by a qualified professional. Cognitive rehabilitation is designed to improve cognitive functioning after central nervous system insult. It includes therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem-solving, and executive functions.

Comparators

Comparators of interest include standard rehabilitation (e.g., physical therapy, occupational therapy) without specific focus on cognition, or no rehabilitation. Treatment includes counseling, physical and psychological therapy, and dieting and exercise.

Outcomes

The general outcomes of interest are functional outcomes and quality of life.

Timing

The existing literature evaluating cognitive rehabilitation delivered by a qualified professional as a treatment for cognitive deficits due to epilepsy, autism spectrum disorder, postencephalopathy, or cancer has varying lengths of follow up, ranging from 2 to 6 months. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 6 months of follow-up is considered necessary to demonstrate efficacy.

Setting

Patients with cognitive deficits due to epilepsy, autism spectrum disorder, postencephalopathy, or cancer are actively managed by neurologists, psychologists, psychiatrists, physical therapists, and primary care providers in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs
- b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies
- c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought
- d. Studies with duplicative or overlapping populations were excluded

Epilepsy/Seizure Disorders

Farina et al (2015) in Italy conducted a systematic review of the literature on cognitive rehabilitation for epilepsy.³⁸ Literature was searched through December 2013, and 18 articles of different types (reviews, methodologic papers, case reports, experimental studies) were identified. Studies were heterogeneous for patient characteristics (type of epilepsy, type of previous treatment [surgery, antiepileptic drugs]), intervention modalities (e.g., holistic, focused) and duration, and outcome measures. Reviewers considered the overall quality of evidence to be moderate to low, and results inconsistent (e.g., not all studies showed benefit; some showed greater benefit in left-sided seizures, and others showed greater benefit in right-sided seizures).

The 2013 updated systematic review by ACRM evaluated cognitive rehabilitation in epilepsy.⁷ Based on 2 comparative studies (1 randomized; total N=156), ACRM recommended cognitive rehabilitation for attention and memory deficits as a "possibly effective" practice option for seizure-related attention and memory deficits. The RCT by Engelberts et al (2002) prospectively enrolled 50 patients with focal seizures who were receiving carbamazepine monotherapy.³⁹ Patients were randomized to a retraining method, aimed at retraining impaired cognitive functions (n=19); to a compensation method, aimed at teaching compensatory strategies (n=17); or to a wait-list control group (n=8). Both interventions focused on divided attention (ability to multitask). At 6-month follow-up, performance on cognitive tests improved more in both intervention groups than in the control group. No differences in inhibitory capacity were observed. Self-reported cognitive complaints, absentmindedness, and QOL improved more with cognitive rehabilitation. Overall, the different rehabilitation methods were similarly effective.

Helmstaedter et al (2008), in a nonrandomized study, assessed the short-term effects of cognitive rehabilitation on memory deficits in 2 retrospective, matched cohorts of temporal lobe epilepsy surgical patients.⁴⁰ Mean age was 36 years; mean age at onset of epilepsy was 4 years; and mean IQ was 105. Patients who received cognitive rehabilitation (n=55) participated in a 1-month program comprising educational sessions about brain function and cognitive exercises. A cohort of 57 patients received no cognitive rehabilitation. Statistically significant improvements in verbal learning and recognition were observed in right-resected patients who received cognitive rehabilitation. Cognitive rehabilitation had nonsignificant effects in left-resected patients. Study limitations included its retrospective design and baseline imbalances in patients' memory and attention deficits (more severe deficits in the control cohort). The limited evidence base precludes conclusions about cognitive rehabilitation for this indication.

Autism Spectrum Disorder

Reichow et al (2013) reported on a systematic review of psychosocial interventions administered by nonspecialists for children and adolescents with intellectual disability (IQ<70) or lower functioning autism spectrum disorder (ASD).⁴¹ Five comparative trials in patients with ASD (total N=255 patients) who received cognitive rehabilitation, training, and support were included. Improvements in school performance and developmental outcomes were inconsistent across trials.

Wang and Reid (2013) conducted a pilot study of a novel virtual reality-cognitive rehabilitation intervention in 4 children (mean age, 7.4 years) with ASD.⁴² Children with autism, who are difficult to engage, may respond better to virtual reality approaches than to traditional cognitive rehabilitation. Mean nonverbal IQ ranged from 93 to 139. Each child viewed training programs on laptop computers equipped with tracking webcams; the child's image and movements were projected into virtual environments where he/she was required to manipulate virtual objects. Outcomes were measures of contextual processing, defined as "the ability to determine an object's meaning or relevance in a particular context," and of abstraction and cognitive flexibility, with executive functions considered components of contextual processing. After 4 to 6 weeks, all children demonstrated statistically significant improvements in contextual processing and cognitive flexibility. Abstraction scores at baseline were at or close to maximum.

Eack et al (2013) conducted a feasibility study of a comprehensive cognitive rehabilitation intervention, called Cognitive Enhancement Therapy, in 14 "high-functioning" adults (mean age, 25 years) with ASD.⁴³ Cognitive Enhancement Therapy, originally developed for patients with schizophrenia, provides social interaction and cognitive training focused on attention, memory, and problem solving. Mean full scale IQ of the patient sample was 118 (range, 92-157). Eleven (79%) of 14 patients completed 18 months of treatment. Statistically significant changes from baseline were observed in mean composite measures of neurocognition, cognitive style, social cognition, and social adjustment. All components of neurocognition (e.g., processing speed, working memory) improved statistically, except attention/vigilance.

Postencephalitis

The 2013 updated ACRM systematic review also evaluated cognitive rehabilitation for postencephalitis cognitive deficits.⁷ Eight identified studies were considered poor quality evidence and considered insufficient for forming conclusions.

Cancer

Cognitive rehabilitation has been investigated in 2 cancer-related settings: in patients with brain tumors and in cancer survivors whose cognitive deficits are attributed to cancer treatment.

Brain Tumors

The 2013 ACRM systematic review evaluated cognitive rehabilitation for adults with brain tumors.⁷ In 5 case reports and case series (total N=36 patients), some patients showed benefit with various cognitive rehabilitation interventions. This evidence was considered insufficient to support any recommendations.

Zucchella et al (2013) conducted an RCT of cognitive rehabilitation in adults after neurosurgery at a single rehabilitation facility in Italy.⁴³ Time since craniotomy was not reported. Adjuvant chemotherapy or radiotherapy was not administered until after the trial. Of 109 consecutive patients screened for participation, 62 (57%) met minimum cognitive deficit and other criteria and were randomized to usual rehabilitative care with (n=30) or without (n=32) cognitive rehabilitation. Treatment sessions were held 4 times a week for 4 weeks and comprised 45 minutes of therapist-guided computer exercises in 6 cognitive domains (time and spatial orientation, visual attention, logical reasoning, memory, executive function) and 15 minutes of cognitive strategizing. At the end of treatment (i.e., at week 4), statistically significant improvements in visual attention and verbal memory were observed in the treatment group compared with controls. Improvements in logical reasoning and executive function were not statistically significant. Limited study follow-up makes the clinical significance of these findings unclear.

Cancer Survivors

Systematic Reviews

Zeng et al (2016) published a meta-analysis of a neuropsychologic intervention for cognitive function in cancer survivors.⁴⁴ Three case-control studies and 7 RCTs with 433 patients (range, 22-98 patients), published between January 2010 and September 2015, were included. Most trials assessed the effects of the intervention immediately postintervention or at short-term follow-up (%±6 months). More than half of the trials were conducted in breast cancer survivors. Three trials assessed the effects of cognitive rehabilitation programs and the weighted mean difference for the intervention effect at postintervention follow-up was -0.19 (95% CI, -2.98 to 2.61).

The 2013 systematic review by ACRM evaluated cognitive rehabilitation for cognitive impairments in adult and pediatric cancer survivors.⁷ A German RCT, by Poppelreuter et al (2008), showed no benefit with cognitive rehabilitation in 157 adult inpatients who had cognitive impairments after hematopoietic cell transplantation.⁴⁵ In children and adolescents, 2 prospective, comparative studies (one an RCT by Butler et al [2008]⁴⁶) evaluated cognitive rehabilitation in treatment survivors (resection, cranial radiotherapy, and/or chemotherapy) involving the central nervous system (total N=192 patients). Reviewers concluded that process-based cognitive rehabilitation techniques (e.g., strategy acquisition, corrective feedback) were "probably effective" in treating attention and memory deficits in these patients. However, the Butler et al RCT had several methodologic limitations.⁴⁶ It randomized 161 pediatric survivors of treatment for brain tumors, leukemia, bone marrow transplant involving total body irradiation, and non-Hodgkin lymphoma 2:1 to a cognitive remediation program (n=108) or wait-list controls (n=53). Documented attentional deficit was required for trial eligibility. The cognitive remediation program comprised 2-hour weekly sessions of practice, strategy acquisition, and cognitive-behavioral interventions for up to 20 sessions. Both groups were assumed to receive special education services if needed; this factor was not analyzed in the results. The primary outcome was change from baseline in 5 investigator-developed, multitest indices (academic achievement, brief focused attention, working memory, memory recall, vigilance) at approximately 6 months after baseline assessments. These indices incorporated results from 11 validated scales completed by blinded study assessors and unblinded parents, teachers, and patients. Mean patient age was 11 years. Sixty percent of patients in the cognitive remediation group completed the entire program; 80% completed 75% (15 sessions). Six-month follow-up was differential between groups (83% in the cognitive remediation group vs 98% in the control group). The analysis was intention-to-treat. The statistically greater improvement was observed in the cognitive remediation group than in the control group only in academic achievement, although the treatment effect was small (standardized mean difference, 0.24) and of uncertain clinical relevance. Given the lack of improvement on the neurocognitive scales, it did not appear that improved academic achievement was due to improved neurocognitive function.

Randomized Controlled Trials

Cherrier et al (2013) evaluated group cognitive rehabilitation in adult cancer survivors.⁴⁷ Patients in 1 region who completed cancer treatment 6 or more months previously (median, 3 years) and had subjective concerns about cognitive decline related to their cancer diagnosis or treatment were eligible. Primary cancer diagnoses included breast, bladder, prostate, colon, and uterine. Of 53 patients screened, 28 (53%) patients were randomized to 7 weekly, hour-long workshops focusing on memory and attention techniques, or to a wait-list control group. Four patients in the treatment group who attended fewer than 2 group sessions were excluded from analysis. One to 2 weeks after completion of 7 treatment sessions (7-8 weeks after baseline assessments for controls), there were statistically greater improvements in cognition-related QOL measures in the cognitive rehabilitation group than in controls, but most neurocognitive testing showed no statistical difference between groups.

Ercoli et al (2015) conducted an RCT of cognitive rehabilitation in breast cancer survivors.⁴⁸ Patients with subjective concerns about memory or mental abilities were randomized to a 5-week program of group training or a wait-list control. Outcomes were assessed with an instrument evaluating patient self-reported difficulties with mental tasks. At the 2-month follow-up, the cognitive rehabilitation group showed greater improvements in self-reported mental ability and memory scores. Quantitative electroencephalographic findings also showed some significantly different results. Trial outcomes reported were of uncertain clinical significance.

Table 7. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	Comparator
Cherrier (2013) ⁴⁷	US	NR	NR	Adult cancer survivors (n=28)	Active 7-wk cognitive rehabilitation intervention	Wait list control group
Ercoli (2015) ⁴⁸	US	NR	2012-2013	Adult breast cancer survivors	cognitive rehabilitation intervention (n=32)	Wait list control group (n=16)

RCT: randomized controlled trial.

Table 8. Summary of Key RCT Results

Study	Improvement in FACT-Cog F Score	Improvement in Neurocognitive Tests ¹	ES for Changes in PAOFI Scores	ES for changes in RAVLT Scores
Cherrier (2013) ⁴⁷	5.66	4.197		
P-v value	<0.01	<0.01		
Ercoli (2015) ⁴⁸				
CR			0.9	0.57
Control			0.15	0.3
P-v value			0.01	0.02

CR: cognitive rehabilitation; ES: effect size; FACT-Cog: Functional Assessment of Cancer Therapy-Cognition; PAOFI: Patient's Assessment of Own Functioning Inventory; RAVLT: Rey Auditory Verbal Learning Test.

¹Measured by digit span backward and the digit span total score F.

Table 9. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Cherrier (2013) ⁴⁷	4. Small study population			1. Only significant outcomes reported and only for the treatment group	1,2. Follow-up only 8 weeks

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
				5. Clinical significant difference not specified	
Ercoli (2015) ⁴⁸					1,2. Follow-up only 2 months

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 10. Study Design and Conduct Gaps

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Follow-Up ^d	Power ^e	Statistical ^f
Cherrier (2013) ⁴⁷	1. Randomization process not described					
Ercoli (2015) ⁴⁸	3. Allocation concealment unclear	1,2. Blinding unclear				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Other Cognitive Deficit Conditions

Systematic reviews of cognitive rehabilitation for a number of conditions, including epilepsy, ASD, spectrum disorder, postencephalopathy, and cancer, have generally concluded that there is no strong evidence supporting the efficacy of cognitive rehabilitation. Randomized trials of cognitive rehabilitation have numerous methodologic flaws that preclude strong conclusions about its efficacy.

Summary of Evidence

For individuals who have cognitive deficits due to traumatic brain injury who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, case series, and systematic reviews. Relevant outcomes are functional outcomes and quality of life. The cognitive rehabilitation trials have methodologic limitations

and have reported mixed results, indicating there is no uniform or consistent evidence base supporting the efficacy of this technique. Systematic reviews have generally concluded that efficacy of cognitive rehabilitation is uncertain. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cognitive deficits due to dementia who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, case series, and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Systematic reviews of RCTs have generally shown no benefit of cognitive rehabilitation or effects of clinical importance. One large RCT evaluating a goal-oriented cognitive rehabilitation program reported a significantly less functional decline in 1 of 2 functional scales and lower rates of institutionalization in the cognitive rehabilitation group compared with usual care at 24 months. These results need replication. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have cognitive deficits due to stroke who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Four systematic reviews evaluating 3 separate domains of cognitive function have shown no benefit of cognitive rehabilitation or effects of clinical importance. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cognitive deficits due to MS who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes and quality of life. Systematic reviews of RCTs have shown no significant effects of cognitive rehabilitation on cognitive outcomes. Although numerous RCTs have investigated cognitive rehabilitation for MS, high-quality trials are lacking. The ability to draw conclusions based on the overall body of evidence is limited by the heterogeneity of patient samples, interventions, and outcome measures. Further, results of the available RCTs have been mixed, with positive studies mostly reporting short-term benefits. Evidence for clinically significant, durable improvements in cognition is currently lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cognitive deficits due to epilepsy, ASD, postencephalopathy, or cancer who receive cognitive rehabilitation delivered by a qualified professional, the evidence includes RCTs, nonrandomized comparison studies, and case series. Relevant outcomes are functional outcomes and quality of life. The quantity of studies for these conditions is much less than that for the other cognitive rehabilitation indications. Systematic reviews generally have not supported the efficacy of cognitive rehabilitation for these conditions. Relevant RCTs have had methodologic limitations, most often very short lengths of follow-up, which do not permit strong conclusions about efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies and 5 academic medical centers in 2015. Input was mixed on cognitive rehabilitation for patients with stroke, multiple sclerosis, brain tumors, or cognitive impairments after previous treatments for cancer.

2009/2010 Input

In response to requests from Blue Cross Blue Shield Association, input was received from 2 physician specialty societies and 5 academic medical centers in 2010. The strongest support was for the use of cognitive rehabilitation as part of the treatment of those with traumatic brain injuries. The level of support varied for other diagnoses (e.g., use in poststroke patients).

Practice Guidelines and Position Statements**American Congress of Rehabilitation Medicine**

Based on a 2013 systematic review, the American Congress of Rehabilitation Medicine recommended process-based cognitive rehabilitation strategies (e.g., attention process training, strategy acquisition and internalization, self-monitoring, corrective feedback) to treat attention and memory deficits in children and adolescents with brain cancers who undergo surgical resection and/or radiotherapy.⁷

National Institute for Health and Care Excellence

National Institute for Health and Care Excellence guidance (2013) on stroke rehabilitation recommended cognitive rehabilitation for visual neglect and memory and attention deficits that impact function.⁴⁹ Interventions should focus on relevant functional tasks (e.g., "errorless learning") and "elaborative techniques" (e.g., "mnemonics," "encoding" strategies) for memory impairments.

Institute of Medicine

The Institute of Medicine published a report in 2011 on cognitive rehabilitation for traumatic brain injury that included a comprehensive review of the literature and recommendations.⁵⁰ The report concluded that "current evidence provides limited support for the efficacy of CRT [cognitive rehabilitation therapy] interventions. The evidence varies in both the quality and volume of studies and therefore is not yet sufficient to develop definitive guidelines for health professionals on how to apply CRT in practice." The report recommended that standardization of clinical variables, intervention components, and outcome measures was necessary to improve the evidence base for this treatment. The Institute of Medicine also recommended future studies with larger sample sizes and more comprehensive sets of clinical variables and outcome measures.

Veterans Administration

The Veterans Administration/Department of Veterans Affairs published guidelines on the treatment of concussion and mild traumatic brain injury in 2009,⁵¹ which were updated in 2016.⁵² These guidelines addressed cognitive rehabilitation in the setting of persistent symptoms. The 2016 guidelines stated:

"Individuals with a history of mTBI [mild traumatic brain injury] who present with symptoms related to memory, attention, and/or executive function problems that do not resolve within 30 to 90 days and have been refractory to treatment for associated symptoms should be referred as appropriate to cognitive rehabilitation therapists with expertise in TBI rehabilitation. The Work Group suggests considering a short-term trial of cognitive rehabilitation treatment to assess the individual patient responsiveness to strategy training, including instruction and practice on use of memory aids, such as cognitive assistive technologies (AT). A prolonged course of therapy in the absence of patient improvement is strongly discouraged."

The strength of the recommendation was rated as "weak."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02265757	Comparative Effectiveness of Behavioral Interventions to Prevent or Delay Dementia (CEBIPODD)	600	Dec 2018 (ongoing)
NCT03306875	Impact of Brain Connectome and Personality on Cognitive Rehabilitation in Multiple Sclerosis	50	Oct 2018 (ongoing)
NCT01138020	Cognitive Rehabilitation of Blast-induced Traumatic Brain Injury	120	Oct 2020
NCT01788618	Cancer and Disorders of Cognitive Functions and Quality of Life: "Cognitive Rehabilitation in Patients Suffering From Cancer and Treated With Chemotherapy"	168	July 2017 (ongoing)
NCT03237676	The Effect of Cognitive Rehabilitation Therapy in Improving Cognitive Function of Attention Following Mild Traumatic Brain Injury	100	Oct 2019
NCT03215342	Cognitive Rehabilitation in Pediatric Acquired Brain Injury - a Randomized Controlled Trial	80	Jan 2020
NCT03168360	Effect of Intensive Cognitive Rehabilitation in Subacute Stroke Patient	150	Dec 2021

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - o Reason for cognitive rehabilitation

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	97127	Therapeutic interventions that focus on cognitive function (e.g., attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (e.g., managing time or schedules, initiating, organizing and sequencing tasks), direct (one-on-one) patient contact
HCPCS	G0515	Development of cognitive skills to improve attention, memory, problem solving (includes compensatory training), direct (one-on-one) patient contact, each 15 minutes
ICD-10 Procedure	F06ZDZZ	Swallowing Dysfunction Treatment
	F07Z4ZZ	Wheelchair Mobility Treatment
	F08Z6ZZ	Psychosocial Skills Treatment

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/15/1997	BCBSA Medical Policy adoption	Medical Policy Committee

Effective Date	Action	Reason
06/28/2007	Policy Review Statement unchanged, but clarification added "for all other indications that the procedure is investigational."	Medical Policy Committee
04/02/2010	Policy revision without position change	Medical Policy Committee
10/25/2010	Policy revision with position change	Medical Policy Committee
03/14/2011	Administrative update	Administrative Review
07/31/2015	Coding update	Administrative Review
10/30/2015	Policy revision with position change	Medical Policy Committee
05/01/2016	Policy revision without position change	Medical Policy Committee
05/01/2017	Policy revision without position change	Medical Policy Committee
01/01/2018	Coding update	Administrative Review
03/01/2018	Coding update	Administrative Review
05/01/2018	Policy revision without position change	Medical Policy Committee
05/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.