Cognitive Rehabilitation

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

Number: 0214

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Scope of Policy

This Clinical Policy Bulletin addresses cognitive rehabilitation.

1. ### Medical Necessity

   Aetna considers cognitive rehabilitation as adjunctive treatment of cognitive deficits (e.g., attention, language, memory, reasoning, executive functions, problem solving, and visual processing) medically necessary when performed by a licensed health care professional acting within their scope of practice and *all* of the following are met:

   1. Neuropsychological testing has been performed and neuropsychological results will be used in treatment-planning and directing rehabilitation strategies; *and*
   2. The cognitive deficits have been acquired as a result of neurologic impairment due to moderate to severe traumatic brain injury, brain surgery, stroke, or encephalopathy; *and*
   3. The member has been seen and evaluated by a psychiatrist or psychologist; *and*
   4. The member is able to actively participate in a cognitive rehabilitation program (eg, is not comatose or in a vegetative state); *and*
   5. The member is expected to make significant cognitive improvement.

   Note: Rehabilitation for visuo-spatial deficits generally entails 20 1-hour sessions delivered over the course of 4 weeks. For language and communication deficits, persons usually receive 8 hours of weekly therapy, beginning at 4 weeks post-onset and continuing up to 48 weeks post-onset.

2. ### Experimental, Investigational, or Unproven

   The following cognitive rehabilitation indications, programs, services are considered experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

   1. Cognitive rehabilitation for the following indications (not an all-inclusive list):

      1. Behavioral/psychiatric disorders such as addiction, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, depression, schizophrenia, social phobia, substance use disorders (SUD), and autism spectrum disorders (ASD);
      2. Cerebral palsy;
      3. Cognitive decline in multiple sclerosis (MS) and chronic obstructive pulmonary disease (COPD);
      4. Dementia (e.g., from Alzheimer's disease, HIV-infection*, or Parkinson's disease);
      5. Intellectual disability;
      6. Learning disabilities;
      7. Long COVID / COVID "brain fog";
      8. Memory deficit in multiple sclerosis;
      9. Mild traumatic brain injury (TBI) (including sports-related concussion);
      10. Treatment of epilepsy/seizure disorders;
      11. Wernicke encephalopathy;

2. Coma stimulation, also known as the "Responsiveness Program" (cognitive remediation of comatose persons), coma arousal program/therapy, sensory stimulation, and multi-sensory stimulation programs for coma and persistent vegetative state;
3. Combined motor and cognitive rehabilitation for individuals with mild cognitive impairment (MCI);
4. EyeBox device for the diagnosis of mild traumatic brain injury (TBI) or concussion;
5. Transcranial electrical stimulation for facilitation of post-stroke CR;
6. Virtual reality therapy for the rehabilitation of acquired cognitive disorders (e.g., stroke, traumatic brain injury, and neurodegenerative diseases).

*__Note__: Cognitive rehabilitation is considered medically necessary for encephalopathy due to HIV when medical necessity criteria in section I above are met.

3. **Policy Limitations and Exclusions**

   1. Cognitive rehabilitation may be performed by a occupational therapist, physical therapist, speech/language pathologist, neuropsychologist or other psychologist, or a neuropsychiatrist, psychiatrist or other physician.
   2. Coverage of outpatient cognitive rehabilitation is subject to applicable benefit plan terms and limitations for physical and occupational therapy. Please check benefit plan descriptions for details.

4. **Related Policies**

   - CPB 0250 - Occupational Therapy
   - CPB 0325 - Physical Therapy

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
97129	Therapeutic interventions that focus on cognitive function (eg, attention, memory, reasoning, executive function, problem solving, and/or pragmatic functioning) and compensatory strategies to manage the performance of an activity (eg, managing time or schedules, initiating, organizing, and sequencing tasks), direct (one-on-one) patient contact; initial 15 minutes
+97130	each additional 15 minutes (List separately in addition to code for primary procedure)
97537	Community/work reintegration training (e.g., shopping, transportation, money management, avocational activities and/or work environment/modification analysis, work task analysis, use of assistive technology device/adaptive equipment), direct one-on-one contact by provider, each 15 minutes

CPT codes not covered for indications listed in the CPB:

0615T	Eye movement analysis test without spatial calibration
0770T	Virtual reality technology to assist therapy (List separately in addition to code for primary procedure)

Other CPT codes related to the CPB:

96132 - 96133	Neuropsychological testing evaluation services by physician or other qualified health care professional, including integration of patient data, interpretation of standardized test results and clinical data, clinical decision making, treatment planning and report, and interactive feedback to the patient, family member(s) or caregiver(s), when performed
96146	Psychological or neuropsychological test administration, with single automated, standardized instrument via electronic platform, with automated result only

HCPCS codes not covered for indications listed in the CPB:

A4596	Cranial electrotherapy stimulation (ces) system supplies and accessories, per month
E0732	Cranial electrotherapy stimulation (ces) system, any type
S9056	Coma stimulation per diem

ICD-10 codes covered if selection criteria are met:

Code	Code Description
F07.81	Postconcussion syndrome
G92.00 - G92.9	Toxic encephalopathy
G93.1	Anoxic brain damage, not elsewhere classified
G93.40 - G93.49	Other and unspecified encephalopathy
I60.00 - I62.9	Nontraumatic subarachnoid, intracerebral hemorrhage and other and unspecified intracranial hemorrhage and cerebral infarction
I65.01 - I66.9	Occlusion and stenosis of precerebral and cerebral arteries, not resulting in cerebral infarction
I67.0 - I67.9	Cerebral atherosclerosis, other cerebrovascular disease, and hypertensive encephalopathy
I69.00 - I69.028, I60.10 - I69.128, I69.20 - I69.228, I69.30 - I69.328, I69.80 - I69.828, I69.90 - I69.928	Sequelae of nontraumatic subarachnoid hemorrhage, nontraumatic intracerebral hemorrhage, intracranial hemorrhage, cerebral infarction, and other and unspecified cerebrovascular diseases
S02.0xxS - S02.119S	Fracture of skull, sequela

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

B20	Human immunodeficiency virus [HIV] disease
E51.2	Wernicke's encephalopathy
F01.50 - F07.0, F07.89 - F99	Mental disorders
G10 - G14	Systemic atrophies primarily affecting the central nervous system
G20.A1 – G20.C	Parkinson's disease
G21.0 – G26	Extrapyramidal and movement disorders
G30.0 - G30.9	Alzheimer's disease
G31.84	Mild cognitive impairment of uncertain or unknown etiology
G35	Multiple sclerosis
G36.0 – G37.9	Demyelinating diseases of the central nervous system
G40.001 - G40.919	Epilepsy and recurrent seizures
G60.0 – G65.2	Polyneuropathies and other disorders of the peripheral nervous system
G70.00 – G73.7	Diseases of myoneural junction and muscle
G80.0 - G80.9	Cerebral palsy
I63.00 – I63.9	Cerebral infarction
I68.0 – I68.8	Cerebrovascular disorders in diseases classified elsewhere
I69.031 – I69.098, I69.131 – I69.198, I69.231 – I69.298, I69.331 – I69.393, I69.831 – I69.898, I69.931 – I69.998	Sequelae of cerebrovascular disease
I69.398	Other sequelae of cerebral infarction [facilitation of post-stroke CR]
J41.0 - J47.9	Chronic lower respiratory diseases
R40.20 - R40.2444	Coma
R40.3	Persistent vegetative state
R41.840 - R41.89	Other symptoms and signs involving cognitive functions and awareness
R62.50, R62.59	Other and unspecified lack of expected normal physiological development in childhood
S06.0X0A – S06.0X0S	Concussion without loss of consciousness [mild traumatic brain injury (including sports-related concussion)]
S06.0X1A – S06.9X9S	Intercranial injury
S06.A0XA – S06.A1XS	Traumatic brain compression and herniation
U09.9	Post COVID-19 condition, unspecified [long covid / covid “brain fog”]

Background

Cognitive rehabilitation offers retraining in the ability to think, use judgment, and make decisions. The focus is on correcting deficits in memory, concentration and attention, perception, learning, planning, sequencing, and judgment. A neuropsychologist, aided by other specialists (e.g., occupational therapists, speech and language pathologists) may be asked to evaluate the level and kind of cognitive dysfunction following traumatic brain injury (TBI), and they may re-assess the individual over time to measure recovery.

The goals of cognitive rehabilitation are to enhance the person's capacity to process and interpret information and to improve the person's ability to function in all aspects of family and community life. Restorative training focuses on improving a specific cognitive function, whereas compensatory training focuses on adapting to the presence of a cognitive deficit. Compensatory approaches may have restorative effects at certain times. Some cognitive rehabilitation programs rely on a single strategy (e.g., computer-assisted cognitive training), while others use an integrated or inter-disciplinary approach. A single strategy program can target either an isolated cognitive function or multiple functions concurrently.

Although the interventions falling under the rubric of cognitive rehabilitation are heterogeneous, a Consensus Panel convened by the National Institutes of Health noted that these interventions share certain characteristics in that they are structured, systematic, goal-directed, and individualized and they involve learning, practice, social contact, and a relevant context.

A report of a consensus conference sponsored by the National Institute of Child Health and Human Development (NIH, 1999) concluded that, despite many descriptions of specific strategies, programs, and interventions, limited data on the effectiveness of cognitive rehabilitation programs are available because of heterogeneity of subjects, interventions, and outcomes studied. Outcome measures present a special problem, since some studies use global "macro"-level measures (e.g., return to work), while others use "intermediate" measures (e.g., improved memory). These studies also have been limited by small sample size, failure to control for spontaneous recovery, and the unspecified effects of social contact. Nevertheless, a number of programs have been described and evaluated. Despite these limitations in evidence, the consensus conference report concluded: "Evidence supports the use of certain cognitive and behavioral rehabilitation strategies for individuals with TBI [traumatic brain injury] in particular circumstances. These interventions share certain characteristics in that they are structured, systematic, goal-directed, and individualized and they involve learning, practice, social contact, and a relevant context."

Cognitive exercises, including computer-assisted strategies, have been used to improve specific neuropsychological processes, predominantly attention, memory, and executive skills. A NIH Consensus Statement notes that both randomized controlled studies and case reports have documented the success of these interventions using intermediate outcome measures. Certain studies using global outcome measures also support the use of computer-assisted exercises in cognitive rehabilitation. An AHCPR Evidence Report/Technology Assessment concluded that there is some evidence that compensatory cognitive rehabilitation reduces anxiety and improves self-concept and relationships for people with TBI.

Compensatory devices, such as memory books and electronic paging systems, are used both to improve particular cognitive functions and to compensate for specific deficits. Training to use these devices requires structured, sequenced, and repetitive practice. According to a NIH Consensus Statement, the efficacy of these interventions has been demonstrated.

Interventions in cognitive rehabilitation are being developed and have only recently been subjected to the scientific inquiry. The efficacy of cognitive rehabilitation so far has been measured by its objective influence on function and the subjective value of these changes to the individual. An NIH Consensus Conference Report (NIH, 1999) stated: "It is important to recognize that a great deal of the scientific evidence to support the use of these approaches derives from relatively limited studies that should be replicated in larger, more definitive clinical trials."

According a review article on cognitive rehabilitation (Ciceron et al, 2000), rehabilitation for visuo-spatial deficits generally entails 20 1-hour sessions delivered over the course of 4 weeks. For language and communication deficits, patients usually receive 8 hours of weekly therapy, beginning at 4 weeks post-onset and continuing up to 48 weeks post-onset.

Amato et al (2006) stated that despite its frequency and high functional impact, very little is known about effective strategies for managing cognitive impairment in patients with multiple sclerosis (MS). Disease-modifying drugs may prevent or reduce the progression of cognitive dysfunction by containing the development of new cerebral lesions. Available evidence has provided inconsistent findings, with neuropsychological effects documented only in 1 trial. Moreover, pilot studies have tested symptomatic therapies for fatigue, a frequent symptom in MS, which may share a common physiopathological substrate with cognitive dysfunction. Small studies with amantadine, pemoline, 4-aminopyridine and 3-4 aminopyridine have provided mainly negative results. Acetylcholinesterase inhibitors used to treat Alzheimer's disease (e.g., donepezil, rivastigmine, and galantamine) have recently been tested in other cognitive disorders, including MS. The majority of pilot trials with acetylcholinesterase inhibitors in MS have provided promising results, and the donepezil study recently published by Krupp and colleagues represented a major development in this field. As for non-pharmacological interventions based on cognitive rehabilitation, few studies have used an experimental approach and, in general, results have been disappointingly negative. The authors noted that further research is clearly needed in this area.

In an evidenced-based review of cognitive rehabilitation for persons with MS, O'Brien et al (2008) concluded that cognitive rehabilitation in MS is in its relative infancy. More methodologically rigorous research is needed to determine the effectiveness of various cognitive rehabilitation interventions.

A Cochrane systematic evidence review by Thomas et al (2006) found "some evidence of effectiveness" of cognitive rehabilitation on cognitive outcomes in persons with MS who have cognitive impairments, although the authors found that "this was difficult to interpret because of the large number of outcome measures used".

A systematic evidence review by the BlueCross BlueShield Association Technology Evaluation Center (BCBCA, 2008) concluded that cognitive rehabilitation for traumatic brain injury does not meet the TEC criteria. An important weakness in the literature on cognitive rehabilitation is that many clinical trials report impacts of cognitive rehabilitation on cognitive tests rather than on health outcomes. The assessment stated that "[d]emonstration of the effectiveness of cognitive rehabilitation ... requires prospective, randomized designs that employ validated measures of health outcomes."

Coma stimulation refers to clinical intervention related to cognitive rehabilitation by attempting to improve or increase the rate of recovery and arousal of the comatose patient through increasing sensorimotor input. It has been suggested that increasing baseline stimulation to critical brain structures, including the reticular activating system in particular, promotes arousal and recovery of these patients. Suggestive findings of such approaches include reports of increased arousal and improvement in findings on electroencephalograms in prolonged vegetative states following dorsal column stimulation and improvement of the comatose patient's condition. However, there are no published studies that confirm the overall efficacy of such approaches in altering the recovery patterns of comatose patients. A Cochrane systematic evidence review (Lombardi et al, 2002) concluded that "there is no reliable evidence to support the effectiveness of multisensory programmes in patients in coma or vegetative state."

A guideline of "Guidance on diagnosis and management of the vegetative state" from the Royal College of Physicians (2003) concluded that "there is no evidence that constant stimulation of someone who is in a vegetative state can bring about improvement in the long-term outcome."

In a randomized, controlled study, Incalzi et al (2008) examined the effects of cognitive training in patients with hypoxemic chronic obstructive pulmonary disease (COPD). This study consisted of 105 COPD patients with at rest (n = 36) or effort (n = 69) hypoxemia and free from concurrent dementing diseases. Neuropsychological assessment included a screening test, the Mini Mental State Examination (MMSE), and a standardized confirmatory battery of neuropsychological tests, the Mental Deterioration Battery (MDB). After baseline assessment, patients were randomized to receive standardized multi-dimensional care (standardization of pharmacological therapy, health education, selection of inhalers according to patient's ability, respiratory rehabilitation, nutritional counseling, oxygen therapy, and control visits) with (n = 53) or without (n = 52) cognitive training aimed at stimulating attention, learning, and logical-deductive thinking. Cognitive performance was re-assessed after 1.5, 4, and 6 months. The analysis of variance for repeated measures (ANOVA) having the group membership (study versus control) as grouping factor was used to assess changes in cognitive performance. Both intervention and control groups showed no significant changes in cognitive performance except for a trend toward improvement in verbal fluency and verbal memory, but cognitive intervention had no significant effect. The authors concluded that cognitive training seems ineffective in COPD.

Brissart and colleagues (2011) noted that cognitive impairment is now well-known in MS. However, few rehabilitation interventions are proposed or really efficient. These investigators presented a review of cognitive rehabilitation intervention research conducted in people with MS, regarding different findings about episodic memory, working memory, attention and executive function disorders in MS. A search of Medline (yield 20 papers) and of PsychInfo (yield 1 article), using combinations of the following terms: cognitive rehabilitation, multiple sclerosis, cognitive therapy, neuropsychological rehabilitation, in the title or in the abstract, from 1960 to March 2010, excluding animal studies. Episodic memory rehabilitation studies appear to be promising. Programs on working memory, attention and executive functions are in the very early phases. The authors concluded that results are encouraging and allow specific recommendations for future research regarding:

1. inclusion criteria, often not defined,
2. a specific baseline adapted to the program of rehabilitation,
3. a control measure regarding program efficiency,and
4. a role for the psychologist (presence and advice during the program).

Note: Cognitive rehabilitation should not be confused with cognitive behavior therapy. Cognitive behavior therapy (also known as cognitive therapy) is a form of psychotherapy that emphasizes the role of thought patterns in moods and behaviors.

Georgiopoulos et al (2010) performed a systematic review of the proposed medical or surgical treatments in patients in chronic vegetative state (VS) or minimally conscious state (MCS), as well as of their mechanisms of action and limitations. For this review, these researchers have agreed to include patients in VS or MCS having persisted for over 6 months in post-traumatic cases, and over 3 months in non-traumatic cases, before the time of intervention. Searches were independently conducted by 2 investigators between May 2009 and September 2009 in the following databases: Medline, Web of Science and the Cochrane Library. The electronic search was complemented by cross-checking the references of all relevant articles. Overall, a total of 16 papers were eligible for this systematic review. According to the 16 eligible studies, medical management by dopaminergic agents (levodopa, amantadine), zolpidem and median nerve stimulation, or surgical management by deep brain stimulation, extra-dural cortical stimulation, spinal cord stimulation as well as intra-thecal baclofen have shown to improve the level of consciousness in certain cases. The authors concluded that the treatments proposed for disorders of consciousness have not yet gained the level of "evidence-based treatments". Moreover, the studies to-date had led to inconclusiveness. They stated that the published therapeutic responses must be substantiated by further clinical studies of sound methodology.

The American Academy of Neurology's practice parameters on "Assessment and management of patients in the persistent vegetative state" (AAN, 2006) did not mention the use of coma stimulation as a treatment modality. Also, the American Occupational Therapy Association's practice guideline on "Adults with traumatic brain injury" (Golisz, 2009) made no recommendation regarding the use of sensory stimulation or coma arousal programs. Furthermore, the National Institute of Neurological Disorders and Stroke's "Coma information page" (NINDS, 2012) did not mention the use of coma stimulation as a therapeutic option.

Cognitive enhancement therapy (CET) is a performance-based, comprehensive, developmental approach to the rehabilitation of social cognitive and neurocognitive deficits. Participants work at recovery through structured group and computer exercises. Cognitive enhancement therapy is designed as a recovery phase intervention for symptomatically stable persons with severe mental illness, who nonetheless remain socially and vocationally disabled. This approach is the culmination of more than 30 years of clinical experience and research in schizophrenia treatment. Overall, CET attempts to increase mental stamina, active information processing, and the spontaneous negotiation of unrehearsed social challenges. It does so with a focus on enhancing perspective taking, social context appraisal, and other components of social cognition.

There are 3 basic components in CET:

1. computer exercises to enhance cognitive skills,
2. a psycho-educational group where interactive work is done through lectures, homework and group exercises. This understanding facilitates a personal process of adjusting to disability and to help participants eventually become more socialized into meaningful adult roles that they identify as goals in their recovery plan, and
3. 1-on-1 coaching.

Gard et al (2009) noted that a burgeoning area of research has focused on motivational deficits in schizophrenia, producing hypotheses about the role that motivation plays in the well-known relationship between neuro-cognition and functional outcome. However, little work has examined the role of motivation in more complex models of outcome that include social cognition, despite the increased understanding of the critical role of social cognition in community functioning in schizophrenia, and despite new basic science findings on the association between social cognitive and reward processing in neural systems in humans. Using path analysis, these researchers directly contrasted whether motivation

1. causally influences known social cognitive deficits in schizophrenia, leading to poor outcome, or
2. mediates the relationship between social cognitive deficits and outcome in this illness.

A total of 91 patients with schizophrenia or schizo-affective disorder completed interview-based measures of motivation and functional outcome as well as standardized measures of neuro-cognition and social cognition in a cross-sectional design. In line with recent research, motivation appears to mediate the relationship between neuro-cognition, social cognition and functional outcome. A model with motivation as a causal factor resulted in poor fit indicating that motivation does not appear to precede neuro-cognition. The authors concluded that findings in the present study indicated that motivation plays a significant and mediating role between neuro-cognition, social cognition, and functional outcome. Potential psychosocial treatment implications were discussed, especially those that emphasize social cognitive and motivational enhancement.

Titov et al (2010)

1. replicated an earlier trial showing that a self-guided Internet treatment for social phobia is efficacious, and
2. examined if the addition of self-guided motivational enhancement strategies improves completion rates and clinical outcomes.

Randomized controlled trial (RCT) of self-guided Internet-based cognitive behavioral treatment (iCBT), or iCBT plus self-guided motivational enhancement strategies (iCBT+MS), was conducted. An intention-to-treat and last observation carried forward model was used for data analyses. The participants consisted of 108 volunteers with social phobia. The iCBT intervention consisted of 2 online lessons about symptoms and treatment of anxiety disorders and 6 lessons about management of social phobia (the Shyness program) with complex automated reminders. The motivational intervention was based on traditional techniques including understanding and exploring ambivalence about change using a cost-benefit analysis, developing and resolving discrepancy between values and symptoms, and enhancing self-efficacy for change. The main outcome measures were the Social Interaction Anxiety Scale and Social Phobia Scale. More iCBT+MS group participants completed the 8 lessons than iCBT group participants (75% versus 56%, respectively), but there were no between-group differences in outcome measures at post-treatment or at 3 month follow up. Large mean within-groups effect sizes (Cohen's d) for the 2 social phobia measures were found for both the iCBT and iCBT+ MS groups (1.1 and 0.95, respectively), which were sustained at 3 month follow-up (1.06 and 1.07, respectively). Both iCBT and iCBT+MS group participants reported that the procedures were highly acceptable. The authors concluded that both self-guided versions of the Shyness program were reliably effective, confirming that people with social phobia may significantly benefit from a highly structured self-guided intervention. Moreover, they stated that the addition of motivational techniques increased completion rates but did not improve clinical outcomes or acceptability.

In a 2-year, randomized-controlled trial with annual structural magnetic resonance imaging and cognitive assessments, Eack and colleagues (2010) examined differential changes in brain morphology in early schizophrenia during cognitive rehabilitation versus supportive therapy. A total of 53 symptomatically stable, but cognitively disabled outpatients in the early course of schizophrenia or schizoaffective disorder were included in this study. Cognitive enhancement therapy is an integrated approach to the remediation of cognitive impairments in schizophrenia that utilizes computer-assisted neurocognitive training and group-based social-cognitive exercises. Enriched supportive therapy is an illness management approach that provides psycho-education and teaches applied coping strategies. Broad areas of frontal and temporal gray matter change were analyzed using longitudinal voxel-based morphometry methods employing mixed-effects models, followed by volumetric analyses of regions demonstrating significant differential changes between treatment groups. Patients receiving CET demonstrated significantly greater preservation of gray matter volume over the course of 2 years in the left hippocampus, para-hippocampal gyrus, and fusiform gyrus, and significantly greater gray matter increases in the left amygdala (all corrected $p < 0.040$), compared with those receiving enriched supportive therapy. Less gray matter loss in the left para-hippocampal and fusiform gyrus, and greater gray matter increases in the left amygdala were significantly related to improved cognition and mediated the beneficial cognitive effects of CET. The authors concluded that CET may offer neurobiologic protective and enhancing effects in early schizophrenia that are associated with improved long-term cognitive outcomes.

Moreover, the authors stated that "Despite the beneficial effects of CET on brain morphology demonstrated in this study, these findings need to be interpreted in the context of a number of important limitations. Although morphometric findings support a neuroprotective effect of CET against the gray matter loss seen during the early course of schizophrenia,6 and in the case of the amygdala, even increase in gray matter, in the absence of functional neuroimaging data the pathophysiological significance of these results for brain function is not clear. Overall structural changes in regional brain volumes were not large, but were reliably detectable, and may reflect functional changes. That we observed significant relations between increased gray matter and cognitive improvement, and that the effects of CET on gray matter change were significant mediators of CET effects on cognition, would suggest that brain functions sub-serving neurocognition and social cognition have been improved. Nonetheless, functional neuroimaging data are needed to better understand the effects of CET on brain function. An integration of morphometric and fMRI studies could be particularly informative in this regard. It is also interesting to note that CET effects on brain regions commonly implicated in neurocognitive dysfunction in schizophrenia were quite modest. For example, no effects were seen in the dorsolateral prefrontal cortex, and only modest effects were observed in the anterior cingulate and hippocampus, which were not associated with neurocognitive change. Although gray matter change in the anterior cingulate and hippocampus might be more strongly related to individual neuropsychological tests, this pattern of findings parallels, to some degree, the cognitive effects observed in this trial of early course patients. In this population, we have observed much stronger effects on social cognition and noted a relative preservation of some general cognitive functions (particularly processing speed) among this sample. The absence of morphometric findings could reflect the better preserved neurocognitive capacity of early course patients. It is also possible that the effects of CET on brain regions implicated in neurocognitive impairment cannot be detected at a morphometric level, but that the primary effects of this approach on frontal brain regions is toward a normalization of functioning. To date, many studies have documented frontal hypofunction in schizophrenia, and if cognitive improvement occurs in the disorder it is also likely to be the result of improved brain function. As a consequence, while this study provides important information on the potential neuroanatomical effects of cognitive rehabilitation in early schizophrenia, future studies are clearly needed to continue to characterize the effects of CET on a variety of other neurobiologic parameters. It is important to remember, however, that significant relations were observed between changes in medial-temporal regions and neurocognition, as well as social cognition, suggesting the relevance of gray matter change in these regions to neurocognitive functioning. However, associations between gray matter and cognitive change were exploratory and not corrected for multiple inference testing, as such these results need to be interpreted with caution until confirmatory replications are available.

This study is also limited by the absence of an appropriately matched group of healthy individuals who could provide data on normative brain development in early adulthood. Although a large body of evidence has accumulated in schizophrenia research indicating a progressive loss of gray matter from the earliest phases of the disorder, healthy individuals also demonstrate some gray matter loss in early adulthood. However, loss appears to be greatest in the frontal cortex, not the subcortical regions demonstrating the most cognitive change in this study, which remain relatively stable or continue to grow after childhood.

In summary, this investigation suggests that CET, a comprehensive cognitive rehabilitation approach, can protect against gray matter loss and may even support gray matter growth in medial-temporal areas of the brain in service of cognitive enhancement among early course schizophrenia patients. Although replication and further neurobiologic characterization is needed, these findings support the potential for cognitive rehabilitative approaches to positively affect the brain in schizophrenia. Further studies are needed to examine the durability of these effects on the brain, as Hogarty and colleagues and Wexler and Bell have both shown that cognitive rehabilitation can continue to confer benefits to schizophrenia patients even after the completion of treatment. Studies of neuronal mechanisms underlying brain change, such as possible effects of cognitive remediation on dopaminergic function,68 brain derived neurotrophic factor, as well as the genomic underpinnings of response to cognitive remediation are also needed".

Jak and colleagues (2013) noted that cognitive enhancement strategies have gained recent popularity and have the potential to benefit clinical and non-clinical populations. As technology advances and the number of cognitively healthy adults seeking methods of improving or preserving cognitive functioning grows, the role of electronic (e.g., computer- and video game-based) cognitive training becomes more relevant and warrants greater scientific scrutiny. This paper served as a critical review of empirical evaluations of publically available electronic cognitive training programs. Many studies have found that electronic training approaches resulted in significant improvements in trained cognitive tasks. Fewer studies have demonstrated improvements in untrained tasks within the trained cognitive domain, non-trained cognitive domains, or on measures of everyday function. Successful cognitive training programs will elicit effects that generalize to untrained, practical tasks for extended periods of time. Unfortunately, many studies of electronic cognitive training programs were hindered by methodological limitations such as lack of an adequate control group, long-term follow-up and ecologically valid outcome measures. Despite these limitations, evidence suggested that computerized cognitive training has the potential to positively impact one's sense of social connectivity and self-efficacy.

UpToDate reviews on "Mindfulness based cognitive therapy as maintenance treatment for unipolar major depression" (Segel, 2013), "Treatment of co-occurring schizophrenia and substance use disorder" (Campbell et al, 2013), and "Psychosocial interventions for schizophrenia" (Bustillo and Weil, 2013) did not mention the use of cognitive enhancement therapy as a management tool.

There is a clinical trial on "Cognitive Enhancement Therapy for Early-Stage Schizophrenia"; however, the recruitment status of this study is unknown because the information has not been verified recently (last verified August 2008). Also, there is currently a clinical trial on "Brain Imaging, Cognitive Enhancement and Early Schizophrenia (BICEPS)" that is not yet open for participant recruitment (last verified March 2012). Furthermore, there is a clinical trial on "Cognitive Enhancement Therapy for Adults with Autism Spectrum Disorders" that is currently recruiting participants (last verified January 2012).

Bahar-Fuchs et al (2013) noted that cognitive impairments, and particularly memory deficits, are a defining feature of the early stages of Alzheimer's disease (AD) and vascular dementia. Interventions that target these cognitive deficits and the associated difficulties with activities of daily living are the subject of ever-growing interest. Cognitive training and cognitive rehabilitation (CR) are specific forms of non-pharmacological intervention to address cognitive and non-cognitive outcomes. These researchers systematically evaluated the evidence for these forms of intervention in people with mild AD or vascular dementia. Randomized controlled trials, published in English, comparing CR or cognitive training interventions with control conditions and reporting relevant outcomes for the person with dementia or the family caregiver (or both), were considered for inclusion. A total of 11 RCTs reporting cognitive training interventions were included in the review. A large number of measures were used in the different studies, and meta-analysis could be conducted for several primary and secondary outcomes of interest. Several outcomes were not measured in any of the studies. Overall estimates of the treatment effect were calculated by using a fixed-effects model, and statistical heterogeneity was measured by using a standard chi-squared statistic. One RCT of CR was identified, allowing the examination of effect sizes, but no meta-analysis could be conducted. Cognitive training was not associated with positive or negative effects in relation to any of the reported outcomes. The overall quality of the trials was low-to-moderate. The single RCT of CR found promising results in relation to some patient and caregiver outcomes and was generally of high quality. The available evidence regarding cognitive training remains limited, and the quality of the evidence needs to improve. However, there is still no indication of any significant benefits from cognitive training. Trial reports indicated that some gains resulting from intervention may not be captured adequately by available standardized outcome measures. The authors concluded that the results of the single RCT of CR showed promise but are preliminary in nature. They stated that further well-designed studies of cognitive training and CR are needed to provide more definitive evidence.

In a Cochrane review, Bowen et al (2013) examined if CR improves functional independence, neglect (as measured using standardized assessments), destination on discharge, falls, balance, depression/anxiety and quality of life in stroke patients with neglect measured immediately post-intervention and at longer-term follow-up; and determined which types of interventions are effective and whether CR is more effective than standard care or an attention control. These investigators searched the Cochrane Stroke Group Trials Register (last searched June 2012), MEDLINE (1966 to June 2011), EMBASE (1980 to June 2011), CINAHL (1983 to June 2011), PsycINFO (1974 to June 2011), UK National Research Register (June 2011). They hand-searched relevant journals (up to 1998), screened reference lists, and tracked citations using SCISEARCH. They included RCTs of CR specifically aimed at spatial neglect. They excluded studies of general stroke rehabilitation and studies with mixed participant groups, unless more than 75% of their samples were stroke patients or separate stroke data were available. Two review authors independently selected studies, extracted data, and assessed study quality. For subgroup analyses, review authors independently categorized the approach underlying the cognitive intervention as either 'top-down' (interventions that encourage awareness of the disability and potential compensatory strategies) or 'bottom-up' (interventions directed at the impairment but not requiring awareness or behavioral change, e.g. wearing prisms or patches). They included 23 RCTs with 628 participants (adding 11 new RCTs involving 322 new participants for this update). Only 11 studies were assessed to have adequate allocation concealment, and only 4 studies to have a low risk of bias in all categories assessed. Most studies measured outcomes using standardized neglect assessments: 15 studies measured effect on activities of daily living (ADL) immediately after the end of the intervention period, but only 6 reported persisting effects on ADL. One study (30 participants) reported discharge destination and 1 study (8 participants) reported the number of falls. Eighteen of the 23 included RCTs compared CR with any control intervention (placebo, attention or no treatment). Meta-analyses demonstrated no statistically significant effect of CR, compared with control, for persisting effects on either ADL (5 studies, 143 participants) or standardized neglect assessments (8 studies, 172 participants), or for immediate effects on ADL (10 studies, 343 participants). In contrast, these investigators found a statistically significant effect in favor of CR compared with control, for immediate effects on standardized neglect assessments (16 studies, 437 participants, standardized mean difference (SMD) 0.35, 95% confidence interval [CI]: 0.09 to 0.62). However, sensitivity analyses including only studies of high methodological quality removed evidence of a significant effect of CR. Additionally, 5 of the 23 included RCTs compared one CR intervention with another. These included 3 studies comparing a visual scanning intervention with another CR intervention, and 2 studies (3 comparison groups) comparing a visual scanning intervention plus another CR intervention with a visual scanning intervention alone. Only 2 small studies reported a measure of functional disability and there was considerable heterogeneity within these subgroups ($I^2 > 40\%$) when they pooled standardized neglect assessment data, limiting the ability to draw generalized conclusions. Subgroup analyses exploring the effect of having an attention control demonstrated some evidence of a statistically significant difference between those comparing rehabilitation with attention control and those with another control or no treatment group, for immediate effects on standardized neglect assessments (test for subgroup differences, p = 0.04). The authors concluded that the effectiveness of CR interventions for reducing the disabling effects of neglect and increasing independence remains unproven. As a consequence, no rehabilitation approach can be supported or refuted based on current evidence from RCTs. However, there is some very limited evidence that CR may have an immediate beneficial effect on tests of neglect. This emerging evidence justifies further clinical trials of CR for neglect. However, future studies need to have appropriate high quality methodological design and reporting, to examine persisting effects of treatment and to include an attention control comparator.

In a Cochrane review, Loetscher and Lincoln (2013) examined if

1. stroke survivors receiving attentional treatment show better outcomes in their attentional functions than those given no treatment or treatment as usual, and
2. stroke survivors receiving attentional treatment techniques have a better functional recovery, in terms of independence in ADL, mood and quality of life, than those given no treatment or treatment as usual.

These investigators searched the Cochrane Stroke Group Trials Register (October 2012), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library October 2012), MEDLINE (1948 to October 2012), EMBASE (1947 to October 2012), CINAHL (1981 to October 2012), PsycINFO (1806 to October 2012), PsycBITE and REHABDATA (searched October 2012) and ongoing trials registers. They screened reference lists and tracked citations using Scopus. They included RCTs of CR for impairments of attention for people with stroke. The primary outcome was measures of global attentional functions, and secondary outcomes were measures of attention domains, functional abilities, mood and quality of life. Two review authors independently selected trials, extracted data and assessed trial quality. They included 6 RCTs with 223 participants. All 6 RCTs compared CR with a usual care control. Meta-analyses demonstrated no statistically significant effect of CR for persisting effects on global measures of attention (2 studies, 99 participants; SMD 0.16, 95% CI: -0.23 to 0.56; p = 0.41), standardized attention assessments (2 studies, 99 participants; p ≥ 0.08) or functional outcomes (2 studies, 99 participants; p ≥ 0.15). In contrast, a statistically significant effect was found in favor of CR when compared with control for immediate effects on measures of divided attention (4 studies, 165 participants; SMD 0.67, 95% CI: 0.35 to 0.98;p < 0.0001) but no significant effects on global attention (2 studies, 53 participants; p = 0.06), other attentional domains (6 studies, 223 participants; p ≥ 0.16) or functional outcomes (3 studies, 109 participants; p ≥ 0.21). Thus, there was limited evidence that CR may improve some aspects of attention in the short-term, but there was insufficient evidence to support or refute the persisting effects of CR on attention, or on functional outcomes in either the short- or long-term. The authors concluded that the effectiveness of CR remains unconfirmed. The results suggested there may be a short-term effect on attentional abilities, but future studies need to assess the persisting effects and measure attentional skills in daily life. Trials also need to have higher methodological quality and better reporting.

In a Cochrane review, Chung et al (2013) examined the effects of CR on executive dysfunction for adults with stroke or other non-progressive acquired brain injuries. They searched the Cochrane Stroke Group Trials Register (August 2012), the Cochrane Central Register of Controlled Trials (The Cochrane Library, August 2012), MEDLINE (1950 to August 2012), EMBASE (1980 to August 2012), CINAHL (1982 to August 2012), PsycINFO (1806 to August 2012), AMED (1985 to August 2012) and 11 additional databases. They also searched reference lists and trials registers, hand-searched journals and conference proceedings, and contacted experts. They included randomized trials in adults after non-progressive acquired brain injury, where the intervention was specifically targeted at improving cognition including separable executive function data (restorative interventions), where the intervention was aimed at training participants in methods to compensate for lost executive function (compensative interventions) or where the intervention involved the training in the use of an adaptive technique for improving independence with ADL (adaptive interventions). The primary outcome was global executive function and the secondary outcomes were specific components of executive function, working memory, ADL, extended ADL, quality of life and participation in vocational activities. They included studies in which the comparison intervention was no treatment, a placebo intervention (i.e., a rehabilitation intervention that should not impact on executive function), standard care or another cognitive rehabilitation intervention. Two review authors independently screened abstracts, extracted data and appraised trials. They undertook an assessment of methodological quality for allocation concealment, blinding of outcome assessors, method of dealing with missing data and other potential sources of bias. A total of 19 studies (907 participants) met the inclusion criteria for this review; these included 13 studies (770 participants) in meta-analyses (417 traumatic brain injury, 304 stroke, 49 other acquired brain injury) reducing to 660 participants once non-included intervention groups were removed from 3 and 4 group studies. These researchers were unable to obtain data from the remaining 6studies. Three studies (134 participants) compared CR with sensorimotor therapy. None reported the primary outcome; data from 1 study was available relating to secondary outcomes including concept formation and ADL. Six studies (333 participants) compared CR with no treatment or placebo. None reported the primary outcome; data from 4 studies demonstrated no statistically significant effect of CR on secondary outcomes. Ten studies (448 participants) compared 2 different CR approaches. Two studies (82 participants) reported the primary outcome; no statistically significant effect was found. Data from 8 studies demonstrated no statistically significant effect on the secondary outcomes. These researchers explored the effect of restorative interventions (10 studies, 468 participants) and compensative interventions (4 studies, 128 participants) and found no statistically significant effect compared with other interventions. The authors concluded that they identified insufficient high-quality evidence to reach any generalized conclusions about the effect of CR on executive function, or other secondary outcome measures. They stated that further high-quality research comparing CR with no intervention, placebo or sensorimotor interventions is recommended.

Farina et al (2015) reviewed the modalities of CR, outcome end-points, and the levels of evidence of efficacy of different interventions. A systematic research in PubMed, Psychinfo, and SCOPUS was performed assessing the articles written in the entire period covered by these databases till December 2013. Articles in English, Spanish or French were evaluated. A manual research evaluated the references of all of the articles. The experimental studies were classified according to the level of evidence of efficacy, using a standardized Italian method (SPREAD, 2007), adopting the criteria reported by Cicerone et al (2000, 2011). A total of 18 papers were classified into 2 reviews, 4 papers dealing with the principles and efficacy of CR in epilepsy, a methodological paper, a single-case report, a multiple-case report, and 9 experimental papers. Most studies involved patients with temporal lobe epilepsy. Different types of CR were used to treat patients with epilepsy. A holistic rehabilitation approach was more useful than selective interventions to treat memory and attention disturbances. The authors concluded that CR may be a useful tool to treat cognitive impairment in patients with epilepsy. However, the modalities of treatment and outcome end-points are important concerns of clinical care and research. They stated that controlled studies are needed to determine the efficacy of rehabilitation in well-defined groups of patients with epilepsy.

Addiction

Rezapour et al (2015) stated that despite extensive evidence for cognitive deficits associated with drug use and multiple publications supporting the effectiveness of cognitive rehabilitation treatment (CRT) services for drug addictions, there are few well-structured tools and organized programs to improve cognitive abilities in substance users. Most published studies on CR for drug dependent patients used rehabilitation tools, which have been previously designed for other types of brain injuries such as schizophrenia or TBI and not specifically designed for drug dependent patients. These studies also suffered from small sample size, lack of follow-up period assessments and/or comprehensive treatment outcome measures. To address these limitations, these researchers developed and investigated the effectiveness of a paper and pencil CR package called NECOREDA (NEuroCOgnitive REhabilitation for Disease of Addiction) to improve neurocognitive deficits associated with drug dependence particularly caused by stimulants (e.g., amphetamine type stimulants and cocaine) and opiates. To evaluate the feasibility of NECOREDA program, these investigators conducted a pilot study with 10 opiate- and methamphetamine-dependent patients for 3 months in outpatient setting. NECOREDA was revised based on qualitative comments received from clients and treatment providers. Final version of NECOREDA was composed of brain training exercises called "Brain Gym" and psycho-educational modules called "Brain Treasures" that was implemented in 16 training sessions interleaved with 16 review and practice sessions. The authors stated that NECOREDA will be evaluated as an add-on intervention to methadone maintenance treatment in a randomized clinical trial among opiate-dependent patients starting from August 2015.

Furthermore, an UpToDate review on "Determining appropriate levels of care for treatment of substance use disorders" (Hartwell and Brady, 2016) does not mention cognitive rehabilitation as a management tool.

Autism Spectrum Disorder

Shahmoradi and Rezayi (2022) stated that emerging virtual technologies and CR methods are 2 new treatment approaches that can be used to strengthen cognitive functions in patients with autism spectrum disorder (ASD). In a systematic review, these investigators examined the effect of using virtual reality-based approaches on cognitive disorders of children and adults with ASD. These researchers identified 688 studies related to this topic and then extracted the effects of interventions on cognitive outcomes. A total of 17 studies met the inclusion criteria, in which 226 persons with ASD had taken place. The sample size in the selected studies ranged from 1 to 56 participants (median of 8, Q1: 3.5, Q3: 15.5); 4 of the studies were case-control studies, 10 were pre-test/post-test studies, and 3 were RCTs. Results of 16 studies showed significant progress in various cognitive indexes, such as task learning, attention, executive functioning, and daily skills in patients with ASD. In most studies, virtual technologies had beneficial effects on reducing cognitive problems, but existing limitations could reduce their effectiveness. These limitations included the cost of virtual reality devices, inappropriate size of software, the weight of devices, potential addiction, intolerance of wearing glasses or headsets by patients with autism (especially in children), and the possibility of eye injury. The authors concluded that applying appropriate virtual-based approaches could improve cognitive indexes in patient with ASD. Moreover, these researchers stated that further studies are needed to examine the long-term effects of these technologies. These investigators noted that the difficulty of comparing studies due to the heterogeneity of the results, as well as the exclusion of published studies other than English language ones were among the drawbacks and challenges of this study.

Bipolar Disorder

Kluwe-Schiavon and colleagues (2015) stated that it has been shown that bipolar disorder (BD) has a direct impact on neurocognitive functioning and behavior. This finding has prompted studies to investigate cognitive enhancement programs as potential treatments for BD, primarily focusing on cognitive reinforcement and daily functioning and not restricted to psycho-education and coping strategies, unlike traditional psychosocial treatments. These investigators presented a systematic review of controlled trials of CR for BD; the main objective was to describe the results of studies of rehabilitation programs for BD and related methodological issues. Electronic database searches (MEDLINE, Web of Science, and Embase) were conducted to identify articles using terms related to BD and CR. The methodological quality of each article was measured using the 5-item Jadad scale. A total of 239 articles were initially identified, but after application of exclusion criteria, only 4 were retained for this review. An average of 17 hours of intervention sessions were conducted, distributed as 0.95 hours per week and 3 of the 4 studies reported better executive function performance after CR interventions. The authors did not find robust evidence to support CR as an effective treatment for BD because of:

1. the variety of intervention designs;
2. the methodological limitations of the studies; and
3. the lack of studies in the field.

Computerized Cognitive Rehabilitation

In a pilot study, Kaldoja and co-workers (2015) evaluated the efficiency and usability of computer-assisted FORAMENRehab program for training specific components of attention in children with mild TBI (mTBI) and partial epilepsy (PE). The second aim was to specify short- and long-term effects of the intervention. A total of 8 children between the ages of 9 to 12 years with attention impairment (3 with PE and 5 with mTBI) and 18 healthy controls participated in this study. FORAMENRehab Attention software, adapted by the authors, was used for intervention. Strict intervention protocol consisting of patients completing 10 sessions over a 6-week period to train 4 components of attention (dividing, focusing, sustaining, and tracking) was designed and applied. Follow-up assessments were conducted after the end of the last training and 1.63 years later. After the intervention, patients' sustained and complex attention improved. Long-term follow-up revealed continuing positive rehabilitation effects; 100% compliance suggested that the used method is attractive for children. The authors concluded that these preliminary results of the pilot study gave reason to presume that the method is effective in attention impairment remediation. However, they stated that more thorough research is needed.

In an exploratory study, Li and colleagues (2015) examined the occurrence of skill generalization to daily living task for individuals with acquired brain injury (ABI) after completion of 8 modules of a commercially available computer-based cognitive retraining (CBCR) program, the Parrot Software. The study investigated changes in individuals' global cognition as measured by the Montreal Cognitive Assessment, and changes in individuals' performance during a medication-box sorting task, a novel instrumental activity of daily living. The medication-box sorting task resembled real life medication management with daily prescribed and over-the-counter medications. A total of 12 individuals with ABI from a community-based program completed the study. Results indicated that CBCR intervention brought about improvement in global cognition, but the improvement did not appear in any particular cognitive domain. Additionally, the gains in global cognition failed to enhance performance in the medication-box sorting task. The authors noted that this exploratory study demonstrated that while CBCR may be a promising intervention for improving global cognition in individuals with ABI, additional intervention might be needed for generalization to occur to a novel daily task. The authors stated that future studies should look for the ultimate therapeutic outcome from CBCR interventions or include interventions that could bridge the gap between CBCR intervention and performance improvement in daily living occupations.

Bogdanova and associates (2016) provided a comprehensive review of the use of computerized treatment as a rehabilitation tool for attention and executive function in adults (aged 18 years or older) who suffered an ABI. Two reviewers independently assessed articles using the methodological quality criteria of Cicerone et al. Data extracted included sample size, diagnosis, intervention information, treatment schedule, assessment methods, and outcome measures. A literature review (PubMed, EMBASE, Ovid, Cochrane, PsychINFO, CINAHL) generated a total of 4,931 publications; 28 studies using computerized cognitive interventions targeting attention and executive functions were included in this review. In 23 studies, significant improvements in attention and executive function subsequent to training were reported; in the remaining 5, promising trends were observed. The authors concluded that preliminary evidence suggested improvements in cognitive function following computerized rehabilitation for ABI populations including TBI and stroke. They stated that further studies are needed to address methodological issues (e.g., inadequate control groups, small sample size) and to inform development of guidelines and standardized protocols.

Leo et al (2016) presented the case of a 30-yearold woman who came to their research institute for an intensive CR cycle following a right parieto-temporal stroke. Because the patient was in the chronic phase, these researchers decided to use 3 different rehabilitative protocols:

1. traditional cognitive training (TCT),
2. computerized cognitive training (CCT), and
3. CCT combined with transcranial direct stimulation (CCT plus) with a 2-week interval separating each session.

Cognitive and language deficits were investigated using an ad-hoc psychometric battery at baseline (T0), post-TCT (T1), post-CCT (T2), and post-CCT plus (T3). The patient showed the best neuropsychological improvement, with regard to attention processes and language domain, after T3. The authors concluded that these findings showed that computerized cognitive training plus transcranial direct stimulation should be considered a promising tool in the treatment of post-stroke.

Svaerke and colleagues (2019) identified studies concerning the effects of computer-based CR (CBCR) on visuospatial neglect (VN) after stroke to summarize the current state of knowledge in this research field and make recommendations for future research. A total of 4 electronic databases were systematically searched. Authors of relevant studies were contacted to detect unpublished data or articles not found by searching databases. Data were extracted from included studies using predefined coding schemes and characteristics and results of individual studies were summarized qualitatively. Studies were included if at least 50% of the included patients had a stroke, if the studies explored the effects of CBCR as a primary intervention for rehabilitation of VN and if they included neuropsychological outcome measures for the presence of VN. A total of 7 studies were included; 6 of the 7 studies suggested positive effects of CBCR on VN after stroke. However, the study that did not find these effects was also the study with the strongest methodological quality. All included studies consisted of small samples, varied greatly in design and had various methodological limitations. The authors concluded that because the existing literature is very sparse and studies have various methodological limitations, it is currently not possible to either support or reject the effects of CBCR on VN after stroke. They stated that future studies should aim to compare CBCR with active and passive control conditions and include larger samples in randomized and blinded designs.

Memory Deficits Associated with Multiple Sclerosis and Stroke

In a Cochrane review, das Nair and colleagues (2016a) examined if individuals with MS who received memory rehabilitation showed

1. better outcomes in their memory functions compared to those given no treatment or receiving a placebo control; and
2. better functional abilities, in terms of ADL, mood, and quality of life (QOL), than those who received no treatment or a placebo.

They searched the Trials Specialized Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group (June 2, 2015) and the following electronic databases: The NIHR Clinical Research Network Portfolio database (NIHR CRN) (from 2010 to June 2015), the Allied and Complementary Medicine Database (AMED) (2010 to June 2015), British Nursing Index (BNI) (2010 to June 2015), PsycINFO (2011 to June 2015), and CAB Abstracts (2010 to June 2015). Start dates for the electronic databases coincided with the last search for the previous review. They also hand-searched relevant journals and reference lists. These researchers selected RCTs or quasi-randomized trials of memory rehabilitation or CR for people with MS in which a memory rehabilitation treatment group was compared to a control group. Selection was conducted independently first and then confirmed through group discussion. They excluded studies that included participants whose memory deficits were the result of conditions other than MS unless they could identify a subgroup of participants with MS with separate results. Three review authors were involved in study selection, quality assessment, and data extraction. They contacted investigators of primary studies for further information where required, and conducted data analysis and synthesis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). They performed a "best evidence" synthesis based on the methodological quality of the primary studies included. These investigators added 7 studies during this update, bringing the total to 15 studies, involving 989 participants. The interventions involved various memory retraining techniques, such as computerized programs and training on internal and external memory aids. Control groups varied in format from assessment-only groups, discussion and games, non-specific cognitive retraining, and attention or visuo-spatial training. The risk of bias of the included studies was generally low, but these investigators found 8 studies to have high risk of bias related to certain aspects of their methodology. They found significant effect of intervention on objective assessments of memory in both the immediate and long-term follow-ups: SMD 0.23 (95% CI: 0.05 to 0.41) and SMD 0.26 (95% CI: 0.03 to 0.49), respectively. They also found significant effect of intervention for QOL in the immediate follow-up (SMD 0.23 (95% CI: 0.05 to 0.41)). These findings showed that the intervention group performed significantly better than the control group. The authors also found a significant difference for ADL in the long-term follow-up (SMD -0.33 (95% CI: -0.63 to -0.03)), showing that the control groups had significantly less difficulty completing ADLs than the intervention groups. They found no significant effects, either immediate or long-term, on subjective reports of memory problems (SMD 0.04 (95% CI: -0.19 to 0.27) and SMD 0.04 (95% CI: -0.19 to 0.27)); on mood (SMD 0.02 (95% CI: -0.16 to 0.20) and SMD -0.01 (95% CI: -0.21 to 0.20)); and on immediate follow-up for ADL (SMD -0.13 (95% CI: -0.60 to 0.33)) and in the long-term for QOL (SMD 0.16 (95% CI: -0.03 to 0.36)). These researchers could not complete a sensitivity analysis of intention-to-treat in comparison with per-protocol analysis, due to insufficient information from the included papers. However, a sensitivity analysis of high-risk versus low-risk studies suggested that while quality of the trials did not affect most outcomes, differences were seen in the objective memory outcomes (both at immediate and long-term) and QOL (immediate) outcome, with studies with higher risk of bias inflating the overall effect size estimates for these outcomes, and the test of overall effect changing from being statistically significant to not significant when studies at high-risk of bias were excluded. This suggested that lower-quality studies may have positively influenced the outcomes. The authors concluded that there is some evidence to support the effectiveness of memory rehabilitation on memory function, as well as on QOL. However, the evidence is limited and does not extend to subjective reports of memory functioning or mood. Furthermore, the objective measures used were not ecologically valid measures, and thus potentially limit generalizability of these findings into daily life. They stated that further robust RCTs of high methodological quality and better quality of reporting, using ecologically valid outcome assessments, are still needed.

In a Cochrane review, das Nair and colleagues (2016b) examined if participants who have received CR for memory problems following a stroke have better outcomes than those given no treatment or a placebo control. The outcomes of interest were subjective and objective assessments of memory function, functional ability, mood, and quality of life. These researchers considered the immediate and long-term outcomes of memory rehabilitation. They used a comprehensive electronic search strategy to identify controlled studies indexed in the Cochrane Stroke Group Trials Register (last searched May 19, 2016) and in the Cochrane Central Register of Controlled Trials (CENTRAL2016, Issue 5), Medline (2005 to March 7, 2016), Embase 2005 to March 7, 2016), CINAHL (2005 to February 5, 2016), AMED (2005 to March 7, 2016), PsycINFO (2005 to March 7, 2016), and 9 other databases and registries. Start dates for the electronic databases coincided with the last search for the previous review. The authors also hand-searched reference lists of primary studies meeting the inclusion criteria and review articles to identify further eligible studies. They selected RCTs in which CR for memory problems was compared to a control condition. They included studies where more than 75% of the participants had experienced a stroke, or if separate data were available from those with stroke in mixed etiology studies. Two review authors independently selected trials for inclusion, which was then confirmed through group discussion. These investigators assessed study risk of bias and extracted data. They contacted the investigators of primary studies for further information where required, and conducted data analysis and synthesis in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. They performed a "best evidence" synthesis based on the risk of bias of the primary studies included. Where there were sufficient numbers of similar outcomes, the authors calculated and reported SMD using meta-analysis. They included 13 trials involving 514 participants. There was a significant effect of treatment on subjective reports of memory in the short-term (SMD 0.36, 95% CI: 0.08 to 0.64, $p = 0.01$, moderate quality of evidence), but not the long-term (SMD 0.31, 95% CI: -0.02 to 0.64, $p = 0.06$, low quality of evidence). The SMD for the subjective reports of memory had small-to-moderate effect sizes. The results did not show any significant effect of memory rehabilitation on performance in objective memory tests, mood, functional abilities, or quality of life. No information was available on adverse events (AEs). The authors concluded that participants who received CR for memory problems following a stroke reported benefits from the intervention on subjective measures of memory in the short-term (i.e., the first assessment point after the intervention, which was a minimum of 4 weeks). This effect was not, however, observed in the longer term (i.e., the second assessment point after the intervention, which was a minimum of 3 months). There was, therefore, limited evidence to support or refute the effectiveness of memory rehabilitation. The evidence was limited due to the poor quality of reporting in many studies, lack of consistency in the choice of outcome measures, and small sample sizes. These researchers stated that there is a need for more robust, well-designed, adequately powered, and better-reported trials of memory rehabilitation using common standardized outcome measures.

Goverover and colleagues (2018) updated the clinical recommendations for cognitive rehabilitation of people with MS, based on a systematic review of the literature from 2007 through 2016. Searches of Medline, PsycINFO, and CINAHL were conducted with a combination of the following terms: attention, awareness, cognition, cognitive, communication, executive, executive function, language, learning, memory, perception, problem solving, reasoning, rehabilitation, remediation, training, processing speed, and working memory. A total of 129 articles were identified and underwent initial screening; 59 articles were selected for inclusion after initial screening; and 19 studies were excluded after further detailed review; 40 studies were fully reviewed and evaluated. Articles were assigned to 1 of 6 categories:

1. attention,
2. learning and memory,
3. processing speed and working memory,
4. executive functioning,
5. metacognition, or
6. non-specified/combined cognitive domains.

Articles were abstracted and levels of evidence were decided using specific criteria. The current review yielded 6 class I studies, 10 class II studies, and 24 class III studies. One intervention in the area of verbal learning and memory received support for a practice standard, 2 computer programs received support as practice guidelines (in the area of attention and multi-cognitive domains), and several studies provided support for 5 practice options in the domains of attention and learning and memory. The authors concluded that substantial progress has been made since the previous review regarding the identification of effective treatments for cognitive impairments in persons with MS. Moreover, they stated that much work remains to be done to optimize rehabilitation potential by applying the most methodologically rigorous research designs to provide class I evidence in support of a given treatment strategy.

Cognitive Rehabilitation in Parkinson's Disease

Alzahrani and Venneri (2018) noted that cognitive impairments are the most common non-motor symptoms in Parkinson's disease (PD). These symptoms have a negative impact on patients' quality of life (QOL) and ADL. These researchers reviewed published articles that examined the efficacy of CR in PD. They reviewed the existing literature on the efficacy of CR in PD and high-lighted the most effective form of intervention to prevent cognitive decline. This review also pointed out any limitations and provided directions for future research. Published articles available in the Web of Science and PubMed databases up to November 2017 were reviewed for possible inclusion. These investigators identified 15 articles that examined the effects of CR in PD and met inclusion criteria. The main outcomes of this review indicated that, although previous studies used different CR methodologies, all studies reported cognitive improvements on at least 1 cognitive domain. Additionally, the most frequent cognitive domains showing improvements were executive functions and attention. The authors concluded that this review reported the outcomes of studies that examined the effectiveness of CR in PD. It also pointed out the drawbacks of the studies indicating the limited availability of follow-up data on the long-term effects of CR. The review also high-lighted the fact that some of the studies did not include a PD group who did not undergo training. Thus, these researchers noted that there is a need for longitudinal studies to examine the potential long-term benefits of cognitive training. In addition, future investigations should determine if any disease characteristics such as disease stage, degree of cognitive impairment and/or the dominant side (right/left) or specific motor symptoms (rigidity/tremor) influence treatment efficacy.

Svaerke and colleagues (2020) stated that deterioration of working memory (WM) is a common cognitive deficit in PD, and severely influences the ability to lead an independent life. Interventions that could delay the impact of WM deficits could positively impact the independence and quality of life (QOL) of patients. These researchers examined the effects of computer-based cognitive rehabilitation (CBCR) on WM in patients with PD. PubMed, Embase, Psycinfo and Cochrane Library were systematically searched. Authors of included studies were contacted to detect unpublished data or articles not found by database-search. Broad selection criteria were applied because literature was expected to be limited. Studies were eligible for inclusion if they examined the effects of CBCR on WM in a sample consisting of at least 50% PD patients, or in which the results of PD patients could be isolated. Studies were further eligible for inclusion in a planned meta-analysis if the effects of the CBCR intervention could be isolated, the CBCR intervention was compared to active or passive control groups consisting solely of PD patients, and the WM outcome measure could be isolated. Only 6 studies were included despite broad inclusion criteria. Study results were heterogeneous, and the risk of bias in study methodology was either unclear or high; 2 studies were eligible for meta-analysis. A meta-analysis was not performed because these studies used different measures of WM that were not rated as equally valid and reliable. The authors concluded that existing literature is sparse and provides insufficient evidence to conclude if CBCR benefits WM in PD patients.

Sanchez-Luengos and colleagues (2021) stated that cognitive deficits influence the QOL of patients with PD. In order to reduce the impact of cognitive impairment in PD, CR programs have been developed. In a systematic review and meta-analysis, these investigators examined the effectiveness of CR in non-demented PD patients; a total of 12 articles were selected according to PRISMA guidelines. The systematic review showed that attention, working memory, verbal memory, executive functions and processing speed were the most frequently improved domains. Meta-analysis results showed moderate effects on global cognitive status (g = 0.55) and working memory (g = 0.50); small significant effects on verbal memory (g = 0.41), overall cognitive functions (g = 0.39) and executive functions (g = 0.30); small non-significant effects on attention (g = 0.36), visual memory (g = 0.29), verbal fluency (g = 0.27) and processing speed (g = 0.24); and no effect on visuo-spatial and visuo-constructive abilities (g = 0.17). Depressive symptoms showed small effect (g = 0.24) and QOL showed no effect (g = -0.07). A meta-regression was carried out to examine moderating variables of overall cognitive function effects, although moderators did not explain the heterogeneity of the improvement following CR. The authors concluded that these findings suggested that CR may be beneficial in improving cognition in non-demented PD patients, although further studies are needed to analyze the effectiveness of CR in patients with PD at the cognitive level and on the instrumental ADL, functionality and QOL. Furthermore, it would be interesting to analyze individual factors such as age, lifestyle, personality and genetic factors, which may be applicable to personalized medicine, in order to design more specific and individualized interventions.

The authors stated that this study had several drawbacks. First, the small number of studies that met the inclusion criteria for this meta-analysis limited the precision of the publication bias. Furthermore, the lack of data or the use of different methods in the analyses limited the possibility of making a comparison between all the studies included in the systematic review. On the one hand, the variability of trained cognitive functions allowed studies divided by different cognitive domains to be compared, although not all the cognitive domains were trained in all the studies and so, in some cases, the comparison would be limited. On the other hand, some of the studies measured the cognitive domains differently. Thus, when the specific cognitive domains were grouped according to the tests used, only studies that reported those tests independently could be included.

The EyeBox Device (Use of Eye Movement Tracking) for the Diagnosis of Traumatic Brain Injury or Concussion

Oculogica, Inc. (New York, NY) is a neuro-diagnostic company founded by Dr. Uzma Samadani. The company developed the EyeBox device that is based on eye-tracking technology. The EyeBox is the first baseline-free, aid that is employed to assist physicians objectively evaluate patients with suspected concussions. The EyeBox is a 4-min test appropriate for individuals aged 5 to 67 years.

Samadani and associates (2015a) developed a technique for eye-tracking that uses temporal rather than spatial calibration, enabling detection of impaired ability to move the pupil relative to normal (neurologically healthy) control volunteers. This study was carried out to show that this technique may detect cranial nerves (CNs) palsies related to brain compression and to provide insight into how the technique may be of value for evaluating neuropathological conditions associated with CN palsy, such as hydrocephalus or acute mass effect. These researchers recorded subjects' eye movements by using an Eyelink 1000 eye tracker sampling at 500-Hz over 200 seconds while the subject viewed a music video playing inside an aperture on a computer monitor. The aperture moved in a rectangular pattern over a fixed time period. This technique was used to examine ocular motility in 157 neurologically healthy control subjects and 12 patients with either clinical CN III or VI palsy confirmed by neuro-ophthalmological examination, or surgically treatable pathological conditions potentially impacting these nerves. These investigators compared the ratio of vertical to horizontal eye movement (height/width defined as aspect ratio) in normal and test subjects. In 157 normal controls, the aspect ratio (height/width) for the left eye had a mean value ± SD of 1.0117 ± 0.0706. For the right eye, the aspect ratio had a mean of 1.0077 ± 0.0679 in these 157 subjects. There was no difference between sexes or ages. A patient with known CN VI palsy had a significantly increased aspect ratio (1.39), whereas 2 patients with known CN III palsy had significantly decreased ratios of 0.19 and 0.06, respectively; 3 patients with surgically treatable pathological conditions impacting CN VI, such as infra-tentorial mass effect or hydrocephalus, had significantly increased ratios (1.84, 1.44, and 1.34, respectively) relative to normal controls, and 6 patients with supra-tentorial mass effect had significantly decreased ratios (0.27, 0.53, 0.62, 0.45, 0.49, and 0.41, respectively). These alterations in eye-tracking all reverted to normal ranges after surgical treatment of underlying pathological conditions in these 9 neurosurgical cases. The authors concluded that this proof-of-concept series of cases suggested that the use of eye-tracking to detect CN palsy while the patient watched television or its equivalent represented a new capacity for this technology. It may provide a new tool for the assessment of multiple central nervous system (CNS) functions that can potentially be useful in the assessment of awake patients with elevated intracranial pressure from hydrocephalus or brain injury.

Samadani and colleagues (2015b) stated that disconjugate eye movements have been associated with traumatic brain injury (TBI) since ancient times. Ocular motility dysfunction may be present in up to 90% of patients with concussion or blast injury. These researchers developed an algorithm for eye tracking in which the Cartesian coordinates of the right and left pupils are tracked over 200 sec and compared to each other as a subject watches a short film clip moving inside an aperture on a computer screen. They prospectively eye-tracked 64 normal healthy non-injured control subjects and compared findings to 75 trauma subjects with either a positive head computed tomography (CT) scan (n = 13), negative head CT (n = 39), or non-head injury (n = 23) to examine if eye tracking would reveal the disconjugate gaze associated with both structural brain injury and concussion. Tracking metrics were then correlated to the clinical concussion measure Sport Concussion Assessment Tool 3 (SCAT3) in trauma patients; 5 out of 5 measures of horizontal disconjugacy were increased in positive and negative head CT patients relative to non-injured control subjects. Only 1 of 5 vertical disconjugacy measures was significantly increased in brain-injured patients relative to controls. Linear regression analysis of all 75 trauma patients demonstrated that 3 metrics for horizontal disconjugacy negatively correlated with SCAT3 symptom severity score and positively correlated with total Standardized Assessment of Concussion score. Abnormal eye-tracking metrics improved over time toward baseline in brain-injured subjects observed in follow-up. The authors concluded that eye-tracking may help quantify the severity of ocular motility disruption associated with concussion and structural brain injury.

The authors stated that this study had several drawbacks. First, in the control subject population, these researchers had relied on self-report for medical and ophthalmic history. Many subjects were hospital employees, research volunteers, colleagues, or friends of the investigative team and may not have been forthcoming regarding their medical history, medications, and drugs used in the day preceding eye-tracking testing. The long-term impact of medications and other agents consumed greater than 1 day before is also unknown. Additionally, not all subjects in all comparison groups were on the same concomitantly administered medications. Because Keppra was the major medication occurring more commonly in one group than the others, it may potentially contribute to abnormal eye movements in the positive head CT group; however, the negative head CT subjects had similar eye movement abnormalities as positive head CT patients, and none of these patients had consumed Keppra. A 2nd drawback arose from the natural incidence of strabismus. In a population of 14,006 consecutive patients examined at a pediatric eye clinic in Rome, 2.72% demonstrated either A- or V-pattern strabismus. Third, in addition to congenital confounders, there may also be conditions leading to acquired disconjugacy, which would yield a false positive with the algorithm. Such disconjugacy may be the result of neurological causes, including hydrocephalus, demyelination, inflammation, infection, degenerative disease, neoplasm/paraneoplastic syndrome, metabolic disease including diabetes, or vascular disruption, such as stroke, hemorrhage, or aneurysm formation. Disconjugacy or vergence disorders may also result from ophthalmologic causes, such as conjunctivitis, ophthalmoplegia, ocular injury, or other thyroid-related orbital dysfunction. Fourth, neither formal optometric nor ophthalmic testing was performed in the trauma setting. These investigators started that future studies will reveal how an evaluation of eye movements (smooth pursuit, dysmetric saccades, and so on) performed by a trained neurological or ophthalmic consultant compares to the eye-tracking device. In addition, cost comparisons of the technology versus an examiner will likely be helpful.

Samadani (2015) noted that recently they published 2 manuscripts describing a novel algorithm for eye-tracking that may be useful for concussion, other forms of TBI and other neuropathologies (Samadani et al, 2015a; Samadani et al, 2015b). Eye-tracking evaluates brain function rather than appearance or electrical activity, and therefore represents a relatively new modality for examination of CNS integrity. The difference between the 2 studies published by the author’s group and nearly all prior eye tracking publications, is that these new papers utilized non-spatially calibrated eye-tracking. Rather than examining what someone chooses to look at, the tracking measures how well the eyes are capable of moving. The author stated that the obvious utility of such technology is detection of concussion, which has been well-established as impacting ocular motility. They demonstrated that eye-tracking could detect and quantitate the severity of abnormal eye movements within a few hours after concussion; the severity of abnormal eye movements correlates with the severity of concussion symptoms using 2 different measures as measured by Spearman correlation; and after concussion eye-tracking initially worsens then improves towards normal within 1 month in most patients (Samadani et al, 2015b). These researchers have not yet determined the shortest possible time between head impact and abnormal eye tracking metrics. The author stated that non-spatially calibrated ocular motility tracking assessment does not require that the subject explicitly consent to being tracked prior to assessment of their CNS functioning, and thus may raise ethical considerations as it can be deployed even remotely via webcam. The potential applications of the algorithm the author has devised include improved diagnosis and detection of diseases ranging from internuclear ophthalmoplegia to strabismus, however its greatest initially recognized potential is as a potential outcome measure or biomarker for brain injury and concussion. The author stated that the ultimate utility of non-spatially calibrated eye tracking will be determined by researchers and clinicians who will, upon replication of these findings, agree that brain injury is more vast than visible on conventional imaging, ultimately validating the fears and concerns of the previously undiagnosed and untreated afflicted. Replication of these findings will also enable the testing of therapeutics and prophylactics for brain injury, perhaps changing the game for many more potential sufferers.

Dr. Uzma Samadani was the principal investigator of a clinical trial entitled "Use of Eye Movement Tracking to Detect Oculomotor Abnormality in Traumatic Brain Injury Patients" that was completed in June 2018 (ClinicalTrials.gov, 2018). However, the results of this clinical trial have not been published.

Mani and co-workers (2018) carried out a review of literature and examined the effect that TBI has on oculomotor functions (OM). These researchers performed a systematic review and meta-analysis from papers that objectively measured saccades and smooth-pursuit eye movements in mild and severe TBI. The overall impact of TBI on OM functions was moderate and significant with an effect size of 0.42 from 181 OM case-control comparisons. The heterogeneity, determined using the random effect model, was found to be significant (Q (180) = 367, $p < 0.0001$, I2 = 51) owing to the variety of OM functions (reflexive saccades, anti-saccades, memory-guided saccades, self-paced saccades and pursuits) measured and varying post-injury periods. The overall effect on OM functions were similar in mild and severe TBI despite differences in combined effect size of various OM functions. OM functions involving complex cognitive skills such as anti-saccades (in mild and severe TBI) and memory-guided saccades (in mild TBI) were the most adversely affected, suggesting that OM deficits may be associated with cognitive deficits in TBI. The authors concluded that TBI often results in long-standing OM deficits. These researchers stated that experimental measures of OM assessment reflect neural integrity and may provide a sensitive and objective biomarker to detect OM deficits following TBI.

Snegireva et al (2018) examined current evidence for the use of eye-tracking technology in sports-related concussion assessment and monitoring. These investigators carried out a systematic literature review following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A search was run using Google Scholar, Microsoft Academic and PubMed for literature published between January 1980 and May 2018. Included were empirical research studies in English where at least 50% of the research subjects were athletes, the subject were individuals with a diagnosis of concussion, and eye movements were measured using an eye-tracking device. This systematic review integrated 21 publications on sports-related concussion and eye-tracking technology, 9 of which also qualified for the meta-analysis. Overall, the literature reported significant findings for variables in each of the 4 classes of eye-tracking measurements (movement, position, count, and latency). Meta-comparison was made for 7 variables for the acute concussions (the difference between the concussed and the control groups was significant for all of them) and 1 variable for the latent concussions (the difference was not significant). The authors concluded that most saccadic and pursuit deficits may be missed during clinical examination, and thus eye-tracking technology may be a useful and sensitive screening and monitoring tool for sports-related concussions. The inconsistencies between the eye movement metrics and methodology still make inferences challenging; however, using tasks that are closely related to brain areas involved in executive functions (such as memory-based saccade or anti-saccade tasks) in the acute injury phase holds promise in differentiating between athletes who have a concussion compared to those who do not.

Yaramothu et al (2019) noted that the Vergence Endurance Test (VET), a quantitative and objective eye movement assessment, was used to differentiate control from concussed subjects. A total of 9 symptomatic concussed (2 men; 30.8 ± 11 years) and 9 asymptomatic control (6 men; 25.1 ± 1.4 years) subjects participated in the VET. Symmetrical disparity vergence step targets were presented with and without visual distractors. A masked data analyst measured vergence latency, peak velocity, response amplitude, settling time, and the percentage of trials that contained blinks. A Binocular Precision Index (BPI) and a Binocular Accuracy Index (BAI) were calculated to quantify the changes that occur in the vergence parameters over the duration of the VET. Convergence and divergence peak velocity, divergence response amplitude, the percentage of trials that contained blinks during the transient portion of the response, and the BAI were significantly ($p < 0.05$) different between the concussed and the control subjects. For these parameters, the BAI and divergence response amplitude yielded the greatest accuracy, 78%, in their ability to discriminate between the groups. The authors concluded that the VET objectively measured the change in vergence performance over time and showed promise as a method to diagnose a concussion. Moreover, these researchers stated that future studies will examine if the VET can be used to evaluate the extent of natural recovery and the effectiveness of therapeutic interventions.

Vakil et al (2019) stated that the facilitation of memory for target stimuli due to the similarity of context in the learning and testing phases is known as the "Context-Effect" (CE). Previous studies reported that TBI affects memory for contextual information when tested directly. However, the indirect effect of contextual information on memory of target (i.e., CE) is preserved. Several studies have demonstrated that CE is composed of multiple, distinct cognitive processes. The present study included 4 context conditions to enable identification of the exact process affected by TBI. In addition, eye movements were monitored to test 3 hypotheses: first, that the TBI group's dwell time on target (DTOT) at encoding would be less than that of controls. Second, that DTOT at encoding would be more highly associated with recognition at test for the control group than for the TBI group. Third, that overall DTOT at encoding on new, as compared to old items ("repetition effect"), would be less pronounced for the TBI group as compared to controls. A total of 24 patients with mild-to-severe TBI and 23 matched controls participated in this study. These researchers presented subjects with photographs of male faces shown wearing distinctive, trial-unique hats (yielding specific Target-Context pairing). Eye movements were recorded throughout the test task. Memory for faces following TBI is impaired compared to that of controls. The magnitude and pattern of CE were the same for both groups. The TBI group had a lower DTOT compared to that of controls. However, the relative length of DTOT in the various conditions was similar in both groups. The authors concluded that behavioral results indicated that although the TBI group had impaired memory for faces, the CE pattern was similar to that of controls. Similarly, in terms of eye movements, although the TBI group focused less on target, relations between the various conditions were similar in both groups.

Murray et al (2020) noted that smooth pursuit eye movements (SPEMs) and saccadic eye movements are both commonly impaired following sport-related concussion (SRC). Typical oculomotor assessments measure individual eye movements in a series of restrictive tests designed to isolate features such as response times. These measures lack ecological validity for athletes because athletes are adept at simple tasks designed for the general population. Yet, because eye movement metrics are sensitive and well-characterized neuroanatomically, it would be valuable to examine if athletes exhibit abnormal eye movements with more challenging tasks. To address this gap in knowledge, these researchers collected eye-tracking data during a sport-like task to gain insight on gaze behavior during active self-motion. SPEMs and saccadic eye movements were recorded during a sport-like visual task within 24 to 48 hours following SRC. A total of 36 Division I student-athletes were divided into SRC and control (CON) groups. All subjects completed 2 blocks of the Wii Fit© soccer heading game (WF) while wearing a monocular infra-red eye tracker. Eye movement classification systems quantified saccadic amplitude (SA), velocity (SV), and count (SC); as well as SPEM velocity (SPV) and amplitude (SPA). Separate Mann-Whitney U tests evaluated SPA and SC and found no significant effects (SPA, $p = 0.11$; SC, $p = 0.10$). A multi-variate analysis of variance (MANOVA) for remaining variables revealed SPV was significantly greater in CON ($p < 0.05$), however, the SRC group had greater SA and SV ($p < 0.05$). The authors concluded that the findings of this study suggested that during a sport-like task, to maintain foveation SRC subjects used larger amplitude, faster saccades, but exhibited slower SPEMs. These researchers stated that measuring oculomotor function during ecologically valid, sport-like tasks may serve as a concussion biomarker and provide insights into eye movement control following SRC.

Horan et al (2020) stated that technological advances provide an opportunity to refine tools that examine CNS performance. These researchers assessed the test-retest reliability and convergent and ecological validity of a newly developed, virtual-reality, concussion assessment tool, "CONVIRT", which uses eye-tracking technology to examine visual processing speed, and manual reaction time (pushing a button on a riding crop) to evaluate attention and decision-making. Subjects ($n = 165$), were evaluated with CONVIRT, which uses virtual reality to give the user the experience of riding a horse during a horse-race. Subjects were also assessed with standard Cogstate computer-based concussion measures in-between 2 completions of the CONVIRT battery. The physiological arousal induced by the test batteries were assessed via measures of heart rate (HR) and HR variability (low-frequency (LF) to high-frequency (HF) ratio). Satisfactory test-retest reliability and convergent validity with Cogstate attention and decision-making subtests and divergent validity in visual processing speed measures were observed. CONVIRT also increased HR and LF/HF ratio, which may better approximate subject arousal levels in their work-place. The authors concluded that CONVIRT may be a reliable and valid tool to examine elements of cognition and CNS disruption. The increased ecological validity may also mean better informed "return-to-play" decisions and stronger industry acceptance due to the real-world meaningfulness of the assessment. However, before this can be achieved, the sensitivity of the CONVIRT battery needs to be demonstrated.

The authors stated that future studies are planned to examine the test-retest reliability over longer time-intervals and to test the sensitivity of this battery in detecting changes in cognitive abilities. Furthermore, in the present study, visual processing speed was measured using the time elapsed to 50% of the total distance to the target stimulus. These researchers have outlined that capturing data from the final 50% of the ocular movement towards the target may include more complex neuronal processes (e.g., deceleration, accuracy adjustments etc.). Their focus was on the speed of saccade and not accuracy, and this aligned with decisions made for other neurocognitive assessment batteries. They stated that in future research, an analysis of the final segments of the gaze-to-target time and measures of vergence may also be useful in assessing CNS performance post-concussion. Finally, these investigators did not evaluate the time lag associated with using the Bluetooth device for measures of simple and choice reaction time in the CONVIRT battery, they will run this experiment in the future.

Furthermore, an UpToDate review on "Sideline evaluation of concussion" (Bloom and Blount, 2020) states that "Additional tools for assessment -- A number of tools are being developed to assist with the evaluation of athletes with a possible concussion. The King-Devick test consists of printed cards with numbers that the athlete reads to assesses saccadic eye movements. According to a 2017 systematic review of critical elements of sideline screening, this test shows promise in small studies as a possible sideline assessment tool. Head impact sensors (helmet sensors, or sensors in mouth guards, headbands, or directly applied to skin) have not been shown to provide helpful information to sideline evaluators about concussion. Some institutions are developing applications for smart phones and hand-held devices for on-field concussion assessment. Further study is needed before recommendations can be made about adopting such tools for sideline evaluation".

Mild Cognitive Impairment and Dementia

Irazoki and colleagues (2020) noted that due to the growing number of older adults with cognitive impairment, it is essential to delay the onset and progression of cognitive decline and promote a healthy lifestyle. The rapid growth of technology has considerably advanced the field of computerized cognitive interventions. Consequently, traditional cognitive interventions are being adapted and new multi-media systems are being developed to encourage health and independent living in the elderly. These investigators identified cognitive stimulation, training and rehabilitation programs aimed at the elderly with mild cognitive impairment (MCI) and dementia. PsycINFO, Medline, CINAHL, Web of Science, PubMed, and CORDIS databases were searched from January 2008 to August 2018; 2 researchers reviewed the potential studies individually for eligibility. Studies of computerized cognitive interventions for individuals with dementia and cognitive impairment were included if they described objectives, users and functioning. They performed a systematic review of the studies, providing a qualitative synthesis of the features and study characteristics of each software. A total of 19 studies met the inclusion criteria, and 11 different cognitive stimulation, training, and rehabilitation programs were identified. The studies found on cognitive intervention software indicated the existence of various technological programs for individuals with MCI and dementia. Overall, the programs were aimed at individuals with different clinical conditions, able to create specific treatments and personalized training, optimized for portable devices, and user-friendly. However, the selected programs differ from each other in terms of objectives, usage mode and characteristics, even if they were used for the same purposes; thus, the information obtained in the review may be relevant to distinguish between programs and select the one that best suits each user. The authors concluded that more information regarding the features and context of use is needed as well as more clinical studies to compare among computerized cognitive programs

The authors stated that this review had several drawbacks. First, studies published longer than 10 years ago were not considered, since they probably studied outdated technologies or programs not functioning anymore. Second, computer-applied software was only examined, excluding researches using other devices such as a smartphone or tablet. In general, the usability of those devices in dementia is lower than the computer and currently, it is advisable to use a computer with big touch screens. Third, the effectiveness of the computerized programs was not analyzed since the objective of the study was not to establish the usefulness of the software. Furthermore, due to the lack of cost-effectiveness information, it was not possible to compare the programs with this respect. Besides, the specific outcome measures used in the studies were not taken into account and the risk of bias of the studies was not evaluated since the aim of this review was not to analyze the potential efficacy of these multi-media resources. Finally, the identified cognitive intervention software was similar but not the same in terms of characteristics such as objectives and function, which made it challenging to compare the programs. It also should be noted that the information obtained from the selected studies was considered as the primary source; however, most the studies offered only an elementary description of cognitive training programs, and in some cases, the characteristics of the technologies were not even reported.

Cafferata and colleagues (2021) stated that cognitive stimulation (CS) is a non-pharmacological intervention often involving group activities and social interaction used to treat cognitive declines in individuals with dementia. In a systematic review and meta-analysis, these researchers examined the effectiveness of CS in producing benefits on cognition (primary outcome) and QOL, ADL, and psychological symptoms (secondary outcomes) across 44 RCTs comprising 45 comparisons including 2,444 participants. A medium-sized effect (g = 0.49) on global cognition was found immediately after the intervention and was supported by decisive Bayesian evidence. Clinical relevance was defined as a reduction of 3 to 4 points on the Alzheimer's Disease Assessment Scale Cognitive subscale; the average attenuation of cognitive decline observed was 2.41 points (after removing 1 outlier); thus, the observed decline was of borderline clinical relevance. Cognitive stimulation was also found to significantly improve memory, ADL, depressive symptoms, and dementia ratings; most of these effects were supported by substantial and strong Bayesian evidence. No significant effects were found for global cognition at 1 to 10 months follow-up assessment for language, QOL, anxiety, and behavior symptoms. However, evidence for the absence of these effects was ambiguous. The authors noted that a review of study bias highlighted that most studies lacked active, double-blinded controls, potentially leading to an over-estimation of the effect, and making it difficult to conclusively attribute the observed improvements to the CS intervention. These researchers stated that although effects are promising, the methodological issues highlighted there is still a need for better controlled studies that provide more compelling evidence.

Cognitive Rehabilitation in Depression

Therond and colleagues (2021) noted that individuals with major depressive disorder often experience cognitive deficits; and CR is an intervention aimed at improving cognition in psychiatric disorders. However, its effectiveness on global and specific domains of cognition in adults with depression requires systematic investigation. Furthermore, given individual differences in treatment outcome, moderators of CR effects in depression need to be identified. These researchers carried out a systematic review and meta-analysis of published controlled trials of CR in adults with depression. They analyzed results from 8 studies to estimate the effectiveness of CR on global cognition and on 6 cognitive domains. These investigators also examined 3 potential moderators, namely session format (individual versus group), treatment duration, and participants' age. Cognitive rehabilitation was found to improve global cognition (g = 0.44), verbal memory (g = 0.60), attention/processing speed (g = 0.41), working memory (g = 0.35), and executive functioning (g = 0.30). No significant improvements emerged for visuo-spatial memory and verbal fluency. In addition, no significant moderating effect of participant's age, session duration or session format were observed. The authors concluded that the findings of this meta-analysis supported the use of CR in improving global cognition in adults with major depressive disorder with a moderate effect size and effectiveness varied between cognitive domains. Moreover, these researchers stated that these conclusions were limited by the small number of studies, the heterogeneity in cognitive measures, and the lack of indicators of everyday functioning.

Cognitive Rehabilitation for Long COVID / COVID "Brain Fog"

In a retrospective, single-center, chart review, Oleena et al (2021) examined the functional impairments of a cohort of patients undergoing inpatient rehabilitation after surviving severe COVID-19 illness to better understand the ongoing needs of this patient population. This study consisted of consecutive patients hospitalized for COVID-19 and admitted to a regional inpatient rehabilitation hospital from April 29 to May 22, 2020. Patient demographics, clinical characteristics and complications from acute hospitalization were examined. Measures of fall risk (Berg Balance Scale), endurance (6 Minute Walk Test [6MWT]), gait speed

(10 Meter Walk Test [10MWT]), mobility (transfer and ambulation independence), cognition, speech and swallowing (American Speech and Hearing Association National Outcomes Measurement System Functional Communication Measures) were evaluated at rehabilitation admission and discharge. The study population included 29 patients (70 % men, 58.6 % white, mean age of 59.5). The mean length of acute hospitalization was 32.2 days with a mean of 18.7 days intubated. Patients spent a mean of 16.7 days in inpatient rehabilitation and 90 % were discharged home. Patients demonstrated significant improvement from admission to discharge in measures of fall risk, endurance, gait speed, mobility, cognition, speech and swallowing, ($p < 0.05$). At discharge, a significant portion of the population continued to exhibit deficits in cognition (attention 37 %; memory 28 %; problem solving 28 %), balance (55 %) and gait speed (97 %). The authors concluded that patients admitted to inpatient rehabilitation following hospitalization with COVID-19 demonstrated deficits in mobility, cognition, speech and swallowing at admission and improved significantly in all of these domains by discharge. However, a significant number of patients exhibited residual deficits at discharge highlighting the post-acute care needs of this patient population.

These researchers stated that study limitations included small sample size (n = 29), single-center, retrospective design and lack of standardized rehabilitation protocol for COVID-19 patients. Moreover, baseline functional status and psychiatric complications were not examined in this study.

Houben and Bonnechere (2022) stated that there is accumulating evidence that patients with severe COVID-19 disease may have symptoms that continue beyond the acute phase, extending into the early chronic phase. This prolonged COVID-19 pathology is often referred to as “Long COVID”. Simultaneously, case investigations have shown that COVID-19 individuals might have a variety of neurological problems. The accurate and accessible assessment of cognitive function in patients post-COVID-19 infection is thus of increasingly high importance for both public and individual health. Little is known regarding the influence of COVID-19 on the general cognitive levels but more importantly, at sub-functions level. These researchers examined the current level of evidence supporting the negative impact of COVID-19 infection on cognitive functions. A total of 27 studies were included in the systematic review representing a total of 94,103 participants (90,317 COVID-19 patients and 3,786 healthy controls). These investigators then carried out a meta-analysis summarizing the results of 5 studies (959 participants, 513 patients) to quantify the impact of COVID-19 on cognitive functions. The overall effect, expressed in SMDs, was -0.41 (95 % CI: -0.55 to -0.27). The authors concluded that the COVID-19 crisis has profoundly changed society’s organization and challenged the different healthcare systems. While re-validation services have been greatly impacted during the different waves (acute management of patients), rehabilitation specialists are now faced with the challenge of managing long-term complications. Among these complications, these investigators have shown in this review important complaints in cognitive functions. Even if most of these disorders diminish with time, on average 6 months after the 1st infection, it is important to develop strategies to improve the situation. There is currently little work that has been carried out focusing on the rehabilitation of cognitive functions; however, the current evidence suggests that the best option would be a combination of physical rehabilitation exercises combined with cognitive training. The latter can be performed using computerized solutions. In the future, it is important to think about the best way to integrate cognitive stimulations within physical rehabilitation since cognitive disorders are frequently associated with many pathologies requiring rehabilitation, not only COVID-19 as have been discussed in this paper, but also for example stroke, multiple sclerosis, and Parkinson’s disease.

Stanford Medicine’s article on “Brain fog after COVID-19 has similarities to ‘chemo brain” (Digitale, 2022) noted that researchers found that damage to the brain’s white matter following COVID-19 resembles that observed after cancer chemotherapy, raising hope for treatments to help both conditions. Michelle Monje, professor of Immunology and of Molecular, Cellular and Developmental Biology at Yale University, stated that “The overlap between what happens in COVID-19’s cognitive aftermath and chemo brain, as it’s colloquially known, could be good news for patients because it may speed research on treatments. The exciting message is that because the pathophysiology is so similar, the last couple of decades in cancer therapy-related research can guide us to treatments that may help COVID brain fog … While there are many similarities to cognitive impairment after cancer, there are probably differences, too. We need to test any potential therapies explicitly for COVID”.

Bertuccelli et al (2022) stated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a worldwide public health issue. Almost 2 years into the pandemic, the persistence of symptoms following the acute phase is a well-recognized phenomenon. These investigators carried out a scoping review to map cognitive domain impairments, their frequency, and associated psycho-affective disorders in individuals with a previous COVID-19 infection. They searched PubMed/Medline, Scopus, and PsycInfo to identify relevant reports published between December 1, 2019 and February 21, 2022. These researchers followed the PRISMA extension for scoping review guidelines. A total of 3 independent reviewers selected and charted 25 records out of 922. Memory, attention, and executive functions appeared to be the most affected domains. Delayed recall and learning were the most impaired domains of memory. Among the executive functions, abstraction, inhibition, set shifting, as well as sustained and selective attention were most commonly impaired. Language and visuo-spatial abilities were rarely affected, although this finding might be biased by the scarcity of reports. Neurological and respiratory conditions were often reported in association with cognitive deficits. Results on psycho-affective conditions were inconclusive due to the low frequency of reported data. Admission to an intensive care unit (ICU) is not related to cognitive deficits. This review highlighted a potential effect of a previous post-COVID-19 infection on a pattern of memory, attention, and executive functions impairments. These investigators stated that these findings need to be confirmed on larger cohorts with comprehensive neuropsychological batteries and correlated to neurophysiological and neurobiological substrates. The authors stated that despite rising evidence, a clear picture of the cognitive alterations following COVID-19 infection is missing. Characterizing the post-COVID-19 pattern of cognitive impairments and their frequency will contribute to a better understanding of its pathophysiology. The final aim is to set up appropriate care and rehabilitation pathways.

National Institute for Health and Clinical Excellence (NICE)'s guideline on long COVID (Venkatesan, 2022) does not mention the use of cognitive rehabilitation.

Furthermore, an UpToDate's “Patient education: Recovery after COVID-19 (The Basics) “written by the doctors and editors at UpToDate” (January 4, 2023) as well as UpToDate reviews on “COVID-19: Evaluation and management of adults following acute viral illness (long COVID)” (Mikkelsen and Abramoff, 2022) and “Geriatric rehabilitation interventions” (Hoenig and Cary, 2022) do not mention cognitive rehabilitation as a management / therapeutic option.

A clinical trial of cognitive rehabilitation for post-COVID syndrome is currently underway (Hagen, et al., 2022).

Combined Motor and Cognitive Rehabilitation for Patients with Mild Cognitive Impairment

Kiper et al (2022) noted that mild cognitive impairment (MCI), a neurodegenerative disease leading to Alzheimer's disease (AD) or dementia, is often associated with physical complaints. Combined physical and cognitive training (PCT) has been employed to examine their effects on cognitive function; however, its impact on motor functions and activities of daily living (ADL) has not been explored yet. The combination of physical and cognitive training may be a valuable non-pharmacological intervention that could preserve motor function and QOL. These investigators examined if combined PCT is effective at improving motor performance in patients with an MCI. They carried out a systematic electronic literature search and a meta-analysis were performed. The following criteria were compulsory for inclusion in the study: RCT design; combined PCT compared to motor training alone or no intervention; motor outcomes as a study's endpoint. A total of 9 studies met the inclusion criteria. Results showed that PCT significantly enhanced balance compared to motor training alone (SMD 0.56; 95 % CI: 0.07 to 1.06; I2 = 59 %; 160 participants), whereas a significant improvement was found for mobility in the PCT group when compared to no intervention (MD -1.80; 95 % CI: -2.70 to -0.90; I2 = 0 %; 81 participants). However, there was no evidence that individuals with MCI experienced an increase in gait speed and QOL at the end of their practice sessions. The authors concluded that further investigation with larger samples and a longer period of monitoring after intervention should be undertaken.

The authors stated that this review had several drawbacks. First , only a small number of studies (n = 5) were included for the meta-analysis. This could impact the analysis and conclusion of the effect or lack thereof of the intervention on MCI participants. Second, the low quality of reporting in some studies, which made it impossible to include some studies in the analyses. Third, these researchers included 3 studies by the same authors, and it was not possible to detect whether the population analyzed in those studies was the same. These investigators could neither confirm nor exclude those studies a priori, so they have all been reported.

Transcranial Electrical Stimulation for Facilitation of Post-Stroke Cognitive Rehabilitation

Khan et al (2022) stated that non-invasive brain stimulation methods have been widely employed in research settings to manipulate and understand the functioning of the human brain. In the past 20 years, transcranial electrical stimulation (tES) has opened new doors for the treatment of impairments caused by various neurological disorders. However, tES studies have shown inconsistent results in post-stroke cognitive rehabilitation, and there is no consensus on the effectiveness of tES devices in improving cognitive skills following the onset of stroke. In a systematic review and meta-analysis, these investigators examined the effectiveness of tES in improving post-stroke global cognition, attention, working memory, executive functions, visual neglect, and verbal fluency. In addition, these researchers provided a pathway to an effective use of stimulation paradigms in future studies. They followed the PRISMA guidelines; RCTs were systematically searched in 4 different databases, including Medline, Embase, PubMed, and PsychInfo. Studies using any tES methods published in English were considered for inclusion; SMD for each cognitive domain was used as the primary outcome measure. The meta-analysis included 19 studies evaluating at least 1 of the 6 cognitive domains. A total of 5 RCTs examining global cognition, 3 assessing visual neglect, 5 evaluating working memory, 3 assessing attention, and 9 studies focusing on aphasia were included for meta-analysis. As informed by the quantitative analysis of the included studies, the results favored the efficacy of tES in acute improvement in aphasic deficits (SMD = 0.34, CI: 0.02 to 0.67, p = 0.04) and attention deficits (SMD = 0.59, CI: -0.05 to 1.22, p = 0.07), however, no improvement was observed in any other cognitive domains. The authors concluded that the findings of this review favored the effectiveness of tES in an improvement in aphasia and attentive deficits in stroke patients in acute, subacute, and chronic stages. However, the outcome of tES could not be generalized across cognitive domains. The difference in the stimulation montages and parameters, diverse cognitive batteries, and variable number of training sessions may have contributed to the inconsistency in the outcome. These researchers suggested that in future longitudinal studies (with refined experimental designs and standardized stimulation protocols) are needed to determine if tES can actually improve functional ability in stroke patients with cognitive deficits.

Non-Invasive Brain Stimulation for Cognitive Rehabilitation Following Traumatic Brain Injury

Alashram et al (2023) stated that TBI can cause numerous cognitive deficits. These deficits are associated with disability and reduction in QOL. Non-invasive brain stimulation (NIBS) provides excitatory or inhibitory stimuli to the cerebral cortex. In a systematic review, these investigators examined the effectiveness of NIBS (i.e., transcranial magnetic stimulation [rTMS] and transcranial direct current stimulation [tDCS]) on cognitive functions in patients with TBI. PubMed, SCOPUS, PEDro, CINAHL, Medline, REHABDATA, and Web of Science were searched from inception to May 2021. The risk of bias in the RCTs was assessed using the Cochrane Collaboration's instrument. The Physiotherapy Evidence Database (PEDro) scale was employed to examine the risk of bias in the non-RCTs. A total of 10 studies met the inclusion criteria – 6 studies used rTMS, and 4 used tDCS as cognitive rehabilitation interventions. The results showed heterogenous evidence for the effects of rTMS and tDCS on cognitive function outcomes in individuals with TBI. The authors concluded that the evidence for the effects of NIBS on cognition following TBI was limited; tDCS and rTMS were safe and well-tolerated interventions post-TBI. However, the optimal stimulation sites and stimulation parameters remain unknown. These researchers stated that combining NIBS with traditional rehabilitation interventions may contribute to greater enhancements in cognitive functions post-TBI.

Virtual Reality Therapy for the Rehabilitation of Acquired Cognitive Disorders

Wiley et al (2022) noted that virtual reality (VR) are user-computer interface platforms that implement real-time simulation of an activity or environment, allowing user interaction via multiple sensory modalities. VR therapy may be an effective intervention for improving cognitive function following stroke. In a systematic review and meta-analysis, these investigators examined the effectiveness of exercise-based VR therapy on cognition post-stroke. They searched electronic databases for terms related to "stroke", "virtual reality", "exercise", and "cognition". Studies were included if they were RCTs; included VR-based interventions; included individuals with stroke; and included outcome measures related to cognitive function. Data from included studies were synthesized qualitatively and where possible, random effects meta-analyses were carried out. A total of 8 studies entailing 196 subjects were included in the review, of which 5 were included in meta-analyses (n = 124 subjects). Studies varied in terms of type (combination of VR therapy and conventional therapy, combination of VR therapy and computer-based cognitive training, VR therapy alone) and duration of interventions (20 to 180 mins), sample size (n = 12 to 42), length of the interventions (4 to 8 weeks), and cognitive outcomes examined. VR therapy was not more effective than control for improving global cognition (n = 5, SMD = 0.24, 95 % CI: -0.30 to 0.78, p = 0.38), memory (n = 2 studies, SMD = 0.00, 95 % CI: -0.58 to 0.59, p = 0.99), attention (n = 2 studies, MD = 8.90, 95 % CI: -27.89 to 45.70, p = 0.64) or language (n = 2 studies, SMD = 0.56, 95 % CI: -0.08 to 1.21, p = 0.09). The authors concluded that VR therapy was not superior to control interventions in improving cognition in individuals with stroke. Moreover, these investigators stated that future research should include high-quality and adequately powered studies examining the impact of VR therapy on cognition post-stroke. These researchers stated that VR therapy is a promising new form of technology that has been shown to increase patient satisfaction towards stroke rehabilitation. VR therapy has the added benefits of providing instant feedback, and the difficulty can be easily modified, underscoring the user-friendliness of this form of rehabilitation. These investigators stated that VR therapy has the potential to improve various motor, cognitive, and physical deficits following stroke.

In a narrative review, Catania et al (2023) examined the use of VR technology in cognitive rehabilitation for individuals with neurological conditions, such as stroke, traumatic brain injury, and neurodegenerative diseases. The introduction highlighted the challenges posed by cognitive impairments and the limitations of traditional rehabilitation methods. VR is presented as a transformative tool that immerses individuals in interactive environments, offering promising opportunities for enhancing cognitive functions and improving QOL. These investigators discussed the foundational principles of VR, its applications across different clinical conditions and cognitive domains, and examined empirical evidence supporting its effectiveness. In addition, they discussed the advantages, limitations, challenges, as well as ethical considerations in the use of VR for cognitive rehabilitation. The authors concluded by exploring future developments, including advancements in VR technology, the integration of augmented reality (AR) as well as artificial intelligence (AI), and the importance of standardized assessment tools for the objective evaluation of rehabilitation outcomes. These researchers stated that the incorporation of AI into VR-based cognitive rehabilitation is on the horizon. AI algorithms can customize interventions based on real-time user performance and adapt to individual progress, offering tailored exercises that maximize cognitive gains. Natural language processing and speech recognition AI can facilitate language therapy, while machine-learning (ML) models can analyze user data to provide therapists with actionable insights, streamlining treatment planning. Additionally, AI can contribute to the gamification of cognitive exercises, making them more engaging and enjoyable for users. To harness the full potential of VR-based cognitive rehabilitation, standardized assessment tools that are specifically designed for VR environments are essential. These tools should measure progress across cognitive domains effectively, allowing for objective and comparable evaluations of rehabilitation outcomes. By developing standardized assessments that align with the immersive and dynamic nature of VR, researchers and clinicians can more accurately track cognitive improvements, enabling evidence-based interventions and enhancing the credibility of VR-based cognitive rehabilitation as a therapeutic approach.

Dabrowska et al (2023) stated that the consequences of stroke have a significant impact on self-sufficiency and health-related QOL (HR-QOL). VR-based rehabilitation has the potential to impact these modalities; however, information on timing, volume, and intensity is not yet available. In a RCT, these researchers examined the impact of conventional rehabilitation combined with VR on self-care and domains of HR-QOL in patients 6 months or less post-stroke. The intervention group completed a total of 270 mins of conventional VR + rehabilitation sessions. The control group underwent conventional rehabilitation only. Primary assessments with the WHO disability assessment schedule 2.0 (WHODAS 2) questionnaire were carried out before rehabilitation (T0), after completion of the intervention (T1), and at the 4-week follow-up (T2); secondary outcomes included self-sufficiency and balance assessments. A total of 50 patients completed the study (mean age of 61.2 ± 9.0 years, time since stroke 114.3 ± 39.4 days). There were no statistically significant differences between the groups in WHODAS 2, self-sufficiency, and balance scores (p > 0.05). The authors concluded that the use of VR did not result in significantly different changes compared to conventional therapy. Patients experienced improvements in self-sufficiency and QOL; however, these improvements were similar to the changes observed with conventional therapy. These researchers stated that more RCTs are needed to examine the effectiveness of VR training on the QOL and self-sufficiency in post-stroke patients.

The authors stated that this study had several drawbacks. First, some patients found VR tasks easy to perform after a certain period and would need incorporation of more challenging tasks into their therapy. Second, the small sample size (n = 50), which became even smaller due to the patients' illness and the positivity of COVID-19, may also have affected the study results. Third, the time since the stroke was not the same in all patients. The appropriate timing of physical activity is a topic of ongoing debate. Fourth, some patients preferred to remain temporarily at home after the stroke and postponed subsequent rehabilitation. This is a natural reaction of the patient who is forced to react to the change in his/her life situation, and his/her reaction depends on many factors, the degree of impairment of physical and mental functions, life experiences, personality, and attitude. Even spare capacity in subsequent rehabilitation facilities plays a role in early rehabilitation.

Sokołowska (2024) stated that dynamic technological development and its enormous impact on modern societies are posing new challenges for 21st-century neuroscience. A special place is occupied by technologies based on VR. The author conducted a review on VR and its influence on brain health. This review was carried out according to the PRISMA guidelines across electronic databases (such as Web of Science Core Collection; PubMed; and Scopus, Taylor & Francis Online and Wiley Online Library) to identify beneficial effects and applications, as well as adverse impacts, especially on brain health in human neuroscience. More than half of these studies were published within the past 5 years and represented state-of-the-art approaches and results (e.g., 54.7 % in Web of Sciences and 63.4 % in PubMed), with review papers accounting for approximately 16 %. The results showed that in addition to proposed novel devices and systems, various methods or procedures for testing, validation and standardization were presented (about 1 % of articles). Also included were virtual developers and experts, (bio)(neuro)informatics specialists, neuroscientists, and medical professionals. The author concluded that VR environments allow for expanding the field of research on perception and cognitive and motor imagery, both in healthy and patient populations. In this context, research on neuroplasticity phenomena, including mirror neuron networks and the effects of applied virtual (mirror) tasks and training, is of interest in virtual prevention and neuro-geriatrics, especially in neurotherapy and neurorehabilitation in basic/clinical and digital neuroscience.

The author noted that the data obtained to-date, both from experimental and modeling studies and from (clinical) observations, indicated the vast and important potential of digital worlds; however, their use can have both beneficial and unfavorable effects, including digital ethical aspects that require further research. This investigator stated that current VR research on human health (and disease) has shown that digital technologies are attractive and stimulate the rapid development of contemporary civilization and the exploration of human brain capabilities; and are promising, motivating, easy to personalize and control, and relatively safe for rebuilding/remodeling motor and cognitive functions in brain health and/or disorders.

Tortora et al (2024) noted that VR has been gaining increasing attention as a potential ecological and effective intervention system for treating mild cognitive impairment (MCI); however, it remains unclear the efficacy and effectiveness of VR-based CRT (VR-CRT) in comparison with CRT alone. These investigators carried out a systematic review on PubMed, Scopus, PsycInfo, and Web Of Science to examine the available evidence published between 2003 and April 2023. Only studies that adopted CRT as control group and that included some measure of at least 1 domain among overall cognitive function, executive function as well as functional status were included. Subjects needed to be older adults aged 65 years or over with a diagnosis of MCI. The risk of bias and the quality of evidence were assessed using the Version 2 of the Cochrane risk-of-bias tool for randomized trials. Initially, 6,503 records were considered and screened after removing duplicates (n = 1,321). Subsequently, 81 full texts were assessed for eligibility. A total of 4 studies met the inclusion criteria; however, 2 of them were merged as they were describing different outcomes of the same research project. Consequently, 3 overall studies with a total of 130 subjects were included in the final analysis. Due to the high heterogeneity in the methodology and outcome measures employed, it was not possible to carry out a meta-analysis. Included studies used semi-immersive (k = 2) and full-immersive (k = 1) VR systems in their research. Two articles examined overall cognitive function via the MoCA together with specific tests for executive functions (n = 69), while 1 study adopted a comprehensive neuropsychological battery to examine both cognitive function and executive function (n = 61). Finally, 1 study examined functional status via instrumental ADL (n = 34). However, the limited number of studies, the small sample size, as well as the potential issues with the quality and methodology of these studies that emerged from the risk of bias assessment may raise doubts regarding the reliability of these findings. Nevertheless, although scarce, results of the present review suggested that VR-CRT may be paramount in treating MCI for its additional ecological and adaptive advantages, as all of the studies highlighted that it was at least as effective as conventional CRT for all the outcome measures; thus, more rigorous research that compares VR-CRT and CRT is needed to examine the degree to which VR-CRT is effective with older adults with MCI and the potential role of immersion to influence its effectiveness. The authors concluded that these these preliminary findings highlighted the need for the development of standardized VR protocols, as the integration of such technology into clinical practice may aid in improving the QOL and cognitive outcomes for this growing demographic.

Appendix

Documentation Requirements

Aetna requires that cognitive therapy and other rehabilitation be provided in accordance with an ongoing, written plan of care created by the therapist. The purpose of the written plan of care is to assist in determining medical necessity and should include the following:

The written plan of care should be sufficient to determine the medical necessity of treatment, including:

- The diagnosis along with the date of onset of the condition;
- A reasonable estimate of when the goals will be reached;
- Long-term and short-term goals that are specific, quantitative and objective;
- Cognitive therapy evaluation;
- The frequency and duration of treatment; *and*
- The specific techniques to be used in treatment.

The plan of care should be ongoing, (i.e., updated as the patient's condition changes), and treatment should demonstrate reasonable expectation of improvement. Cognitive therapy is considered medically necessary only if there is a reasonable expectation that cognitive therapy will achieve measurable improvement in the patient's condition in a reasonable and predictable period of time.

The therapist should re-evaluate the patient regularly (this is typically done on a monthly basis) and document the progress toward the goals of cognitive therapy in the patient's clinical record. The treatment goals and subsequent documentation of treatment results should specifically demonstrate that cognitive therapy services are contributing to such improvement.

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Policy History

- Last Review 04/09/2025

  Effective: 03/17/1998

  Next Review: 03/13/2025

- Review History

- Definitions

Additional Information

- Clinical Policy Bulletin Notes