

ERABI

EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

6. Cognition Interventions Post Acquired Brain Injury

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Abbreviations

ABI	Acquired Brain Injury
APT	Attention Process Training
CES	Cranial Electrotherapy Stimulation
GH	Growth Hormone
Met	Methionine Allele
PASAT	Paced Auditory Serial Addition Task
PDA	Personal Digital Assistant
PTA	Post Traumatic Amnesia
RCT	Randomized Controlled Trial
TBI	Traumatic Brain Injury
TPM	Time Pressure Management
Val	Valine Allele

Key Points

Although attention training programs in general improve attention scores, the level of structure in these programs does not appear to influence the success of the intervention.

Dual-task training has been shown to improve measures of attention to the extent that the ABI population does not significantly differ from healthy controls, however it is undetermined if the strength of these effects compared to non-dual-task training are greater.

Computer-based interventions are no more effective than no intervention in improving measures of attention and concentration post ABI.

Repetitive virtual reality tasks which include repetition are effective in improving attention and concentration in ABI populations.

Goal management training is effective in assisting those who sustain an ABI learning to manage life goals through improved attention.

Therapies which focus on emotional regulation or mindfulness do not appear to be effective at improving attention post ABI.

In order to determine if attentional training is effective in improving attention post-ABI standardized protocols must be developed to allow between study comparisons.

Tasks that involve mathematical skills may be effective at improving attention post-ABI.

Cognitive rehabilitation therapy is not likely to remediate attentional deficits in ABI populations.

Transcranial direct current stimulation may be effective in remediating attentional deficits when combined with computer assisted training in ABI populations.

Donepezil can help improve attention in individuals with ABI.

The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear.

Methylphenidate is effective in improving reaction time for working memory.

Response to methylphenidate may depend on genotype.

Bromocriptine might improve executive function, but not memory, attention, or reading ability in patients post TBI.

Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy.

Rivastigmine may not be effective in treating attention deficits post-ABI.

Pager and voice-organizer programs may improve a patient's ability to complete tasks post TBI.

Personal digital assistant (PDA) devices are superior to paper-based interventions at improving memory and task completion post TBI; specially when introduced using systematic instructions and in combination with occupational therapy. Patients who have used previous memory aids might benefit from this intervention the most.

Text message prompts sent to a patient's smartphone, when used alone or in combination with other memory-improvement therapies, likely improve task completion post TBI. However, risk exists of device dependency exists.

A television assisted prompting (TAP) program may be superior to other methods of memory prompting in patients post TBI.

Automated prompting systems, such as Guide (audio-verbal interactive micro-prompting system) and a computerized tracking system, can reduce the amount of prompts needed from support staff to patients to complete tasks post TBI.

Calendars may be effective tools for improving memory and task completion post ABI.

The use of a diary may help to improve memory and task completion post ABI, but more so if diary training is combined with self-instructional training.

Virtual reality programs may enhance the recovery of memory, learning, but there is currently limited evidence supporting the use of virtual reality programs.

Memory-retraining programs appear effective, particularly for functional recovery although performance on specific tests of memory may or may not change.

Specific computer-based softwares seem to be effective for improving memory post-ABI.

Computer-based interventions may be as effective as therapist administered interventions.

Emotional self-regulation therapy may be effective for improving specific elements of memory.

Recall and recognition of words can be enhanced by using a spaced learning condition.

Cranial electrotherapy stimulation is likely not effective at enhancing memory and recall abilities following TBI.

Donepezil likely improves attention and memory following TBI.

There is conflicting evidence that methylphenidate administration post TBI improves attention, memory, concentration and processing speed.

Response to methylphenidate likely varies depending on genotype at the catechol-O-methyltransferase (COMT) gene.

Sertraline has not been shown to improve learning, or memory within the first 12 months post TBI, and may be associated with side effects.

Amantadine might not be effective at improving learning and memory deficits post TBI.

Pramiracetam might improve memory in males post TBI; however, additional studies are required.

Physostigmine likely improves long-term memory in men with TBI.

Bromocriptine may improve dual task performance and motivational deficits but its effect on memory is controversial. More research is needed before the benefits of using bromocriptine to enhance learning and memory deficits are required.

Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy.

The administration of recombinant human Growth Hormone (rhGH) is likely not different than placebo at improving executive functioning, memory, or learning in patients post TBI; however certain aspects of patient quality of life may be improved.

The administration of recombinant human Growth Hormone (rhGH) might be superior at improving intelligence and cognition in patients with a growth hormone deficiency, versus those who do not, post TBI. Molecular markers of growth however may not be different post treatment between groups.

Rivastigmine may not be effective in treating memory deficits post-ABI.

Targeted hypnosis may improve memory, attention, and cognitive function in patients post TBI or stroke; however, only as long as the intervention is being administered.

Attention improvement interventions may be superior to non-specific cognitive or education programs at improving memory and attention in patients post TBI.

A comprehensive cognitive treatment strategy is likely superior to a computerized training package at improving task initiation and completion in patients post TBI; this intervention may also improve cerebral blood flow.

It is unclear whether virtual-reality training is superior to conventional training at improving cognitive and executive function outcomes post TBI. Conflicting evidence exists, and further studies are required.

Computer or smartphone software programs (BrainHQ, Parrot Software, ProSolv app) may not be superior to common interventions at improving memory, attention, and problem-solving skills in patients post TBI.

Goal management training may be superior to motor skills training at improving every day skills (meal preparation), but not intelligence or neuropsychological outcomes in patients post TBI.

It is unclear whether goal oriented interventions delivered in a group setting are more successful than educational interventions at improving cognitive and executive function post ABI. However, no detrimental effects have been found with the intervention.

Emotional regulation interventions delivered in a group setting may improve executive function in patients post TBI; however, it is unclear if it is superior at doing so compared to conventional cognitive remediation.

It is unclear whether cognitive interventions (such as the Metacognitive Strategy Instruction program) improve language ability, and executive/ cognitive function in patients post TBI.

Remedial occupational therapy is likely superior to adaptive occupational therapy at improving general cognitive functioning in patients post TBI.

Low intensity outpatient cognitive rehabilitation might improve goal attainment and cognitive function in patients post ABI.

Donepezil might improve attention, learning and short-term memory following TBI; however, side effects may occur from its use.

The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear. Further studies with larger populations are required.

Sertraline has not been shown to improve cognitive functioning within the first 12 months post TBI, and may be associated with side effects.

Amantadine might not be effective at improving attention and memory deficits post TBI. Its impact on executive functioning should be studied further.

Bromocriptine may improve some executive cognitive functions such as dual task performance and motivational deficits. More research is needed before the benefits of using bromocriptine to enhance cognitive functioning are known.

The administration of recombinant human Growth Hormone (rhGH) is likely not different than placebo at improving executive functioning, memory, or learning in patients post TBI; however certain aspects of patient quality of life may be improved.

The administration of recombinant human Growth Hormone (rhGH) might be superior at improving intelligence and cognition in patients with a growth hormone deficiency, versus those who do not, post TBI. Molecular markers of growth however may not be different post treatment between groups.

Rivastigmine may not be effective in treating memory deficits post-ABI.

6. Cognition Interventions Post Acquired Brain Injury

6.1 Introduction

Cognitive dysfunction is a common symptom of acquired brain injury (ABI) which can negatively affect many areas of cognition such as attention, memory, executive function, learning, and social cognition. Each of these cognitive functions represents a unique area of cognition which allows individuals to execute activities of daily living. Cognitive impairment can be caused not only by the initial trauma, but also by secondary inflammation or insult. Compared to mild traumatic brain injury (TBI), moderate/severe TBI is associated with more severe and persistent cognitive deficits, with about 65% of patients reporting long-term cognitive problems (Rabinowitz & Levin, 2014). The effects of TBI on overall cognitive functioning vary depending on the time post injury (Schretlen & Shapiro, 2003). Even with good medical prognosis, cognitive ability remains one of the best predictors of successful return to work and independent living (Brain Injury Medicine, pp 990). With the diverse nature of the brain there are a multitude of ways that each trauma can impact cognition. As a result, there are a variety of interventions available to clinicians to help rehabilitate cognitive function post ABI. In Ontario, the mean direct per-patient medical costs in the first follow-up year after ABI was \$32 132 for TBI and \$38 018 for non-traumatic brain injury. (Chen et al., 2012).

The broadest categories of cognitive interventions can be classified as pharmacological and non-pharmacological. Pharmacological interventions use medication in an attempt to remediate cognitive deficits. These types of medications usually moderate neurotransmitters in the brain which regulate cognitive functions. By influencing the concentration and absorption of either excitatory or inhibitory neurotransmitters these medications are able to affect memory, attention, and social behaviours (Brain Injury Medicine, pp 1205). Non-pharmacological interventions span a broader spectrum and can include anything from physical exercise to memory programs with assistive technology. However, there are multiple challenges when evaluating the effectiveness of cognitive interventions. First, there is no consensus regarding a definition of attention; currently, it is used as a general construct. Attention can be further broken down into sub types (sustained, divided, focused, selective, vigilance, speed of information processing), however this is not always reflected in the literature. Second, researchers and clinicians may use different measures when reporting outcomes, making comparisons between interventions difficult. Third, a study may use the same outcome measures repeatedly, thereby confounding practice and treatment effects (e.g., Paced Auditory Serial Attention Task (PASAT)). Finally, studies may not consider or account for the rate of spontaneous recovery following brain injury (i.e., would participants naturally show recovery of function in the absence of treatment?). For these reasons, assessing the efficacy of interventions for cognitive rehabilitation is more challenging compared to other modules due to the heterogeneous presentation and assessment of cognitive deficits..

This module reviews the available evidence related to interventions for cognitive rehabilitation following ABI. Studies that specifically deal with cognitive-communication deficits are discussed in module 7.

6.2 Rehabilitation of Attention, Concentration, and Information Processing Speed

Although there is no specific agreement on the definition of attention, it is usually measured using externally directed tests, such as instructing participants to focus their attention on a sequence of stimuli or attenuating to a particular stimulus.

In general, TBI populations demonstrate significant deficits compared to control populations. Dymowski et al. (2015) showed that mild to severe TBI participants performed significantly worse on speed of information processing tasks compared to a healthy control group. Dockree et al. (2006) and Hasegawa and Hoshiyama (2009) found that TBI patients made significantly more errors than their non-TBI counterparts on dual task experiments for sustained attention. However, a case series by Foley et al. (2010) found that level of injury severity as measured by the Glasgow Coma Scale or PTA did not play a role in who performed poorly on the dual task assignment given to participants. They found that only 27% of TBI study participants performed below the cut-off for normal performance.

Two studies assessing the reaction times of individuals demonstrated that those with a TBI were found to have slower reaction times than individuals who had not sustained a TBI (Azouvi et al., 2004; Stuss et al., 1989). Results of the visual analogue scale also indicated that mental effort was higher for those with a TBI than for the controls. The results of this study confirmed what previous studies had found: those with a TBI have greater difficulty when dealing with two simultaneous tasks (Azouvi et al., 2004).

In order to better understand the mechanism by which cognitive interventions can improve attention, concentration, and information processing, there needs to be a consensus as to the definition of specific cognitive processes, such as attention.

6.2.1 Non-Pharmacological Interventions

6.2.1.1 Drill and Practice

The following studies examined the influence of “drill & practice” exercises (either computerized and/or paper-and-pencil) on attentional functioning. Drill and practice training aims to improve attention through repetitive training of specific tasks involving attention.

Table 6.1 The Effect of Drill and Practice on Attention Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Novack et al. (1996) USA RCT PEDro=5 N=44</p>	<p>Population: Severe TBI; <i>Focused Stimulation Group (n=22):</i> Mean Age=28.7yr; Mean Time Post Injury=5.9wk. <i>Unstructured Stimulation Group (n=22):</i> Mean Age=26.4yr; Mean Time Post Injury=6.4wk</p> <p>Intervention: Participants were randomly placed into a focused or unstructured stimulation group. Patients in the focused group received hierarchical attentional learning training (30min, 5x/wk). Skills were not taught in a hierarchical or sequential fashion in the unstructured group.</p> <p>Outcome Measure: Digit Span and Mental Control subtests of Wechsler Memory Scale-Revised (WMS-R), computer-based simple and choice reaction time tests. <i>Secondary outcome</i></p>	<ol style="list-style-type: none"> 1. Analysis of primary outcome measures revealed no significant differences between the focused and unstructured stimulation groups, both at baseline and discharge. 2. There was a significant time effect with participants performing significantly better at the time of discharge than on admission (p<0.0001). 3. There were no significant differences between the groups with respect to any secondary outcome measures studied.

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<i>measures:</i> Logical Memory I & II, Sentence Repetition, Judgment of Line Orientation, Trail Making A & B, Arithmetic subtest Wide Range Achievement Test-Revised, Visual imperceptions.	
Lindelov et al. (2016) Denmark PCT N _{Initial} =78, N _{Final} =35	Population: ABI Group (n=17): Mean Age=56.1yr; Gender: Male=13, Female=4; Mean Time Post Injury=57d. Healthy Group (n=18): Mean Age=56.1yr; Gender: Male=8, Female=10. Treatment: ABI and healthy participants were randomized and analyzed separately. Experimental group participants received 20 sessions of N-back training (N-back), where participants press a key when presented stimulus is identical to the stimulus N back in the sequence. Control group participants received 20 sessions of visual search training (VS), where participants press a key if a target symbol is present in an NxN array of symbols. Outcome Measure: Raven’s Advanced Progressive Matrices (RAPM), Wechsler Adult Intelligence Scale-IV (WAIS-IV), Working Memory Index (WMI Index, digit span, arithmetic, letter-number sequencing), Operation Span Test (OSPAN), WAIS-IV Processing Speed Index (PSI index, search, coding), Stroop Test.	<ol style="list-style-type: none"> Both ABI and healthy groups showed significant improvement post-intervention on the assigned training tasks (Bayes factor >> 1000). The standardized mean difference was 0.45 for ABI N-back, 6.11 for healthy N-back, 1.06 for ABI VS, and 3.34 for Healthy VS. The healthy group showed greater improvement than the ABI group (Bayes factor >> 1000). No significant differences in improvements between N-back and VS treatments (time x treatment interaction) were found in ABI or healthy groups for WMI-digit span, WMI-arithmetic, WMI-letter-number sequencing, WMI index, PSI-search, PSI-coding, PSI index, RAPM, OSPAN, or Stroop. No significant differences in improvement between healthy and ABI groups (group x time x test interaction) were found for WMI-digit span, WMI-arithmetic, WMI-letter-number sequencing, WMI index, PSI-search, PSI-coding, PSI index, RAPM, OSPAN, or Stroop.
Park et al. (1999) Canada Case-Control N=46	Population: TBI=23; Age matched controls=23. Intervention: Attention process training program of 20 two hour sessions for a total of 40 hr. Outcome Measure: Paced Auditory Serial Addition Task (PASAT); Consonant Trigrams; Beck Depression Inventory (BDI).	<ol style="list-style-type: none"> No statistically significant improvements on the BDI from pre- to post-treatment for the TBI group. TBI (p<0.01) and control (p<0.001) groups improved significantly in PASAT before/after tests. Performance declined with increases in delay (p<0.001), and study position (p<0.001) on the Consonant trigrams.

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Park et al. (1999) examined whether “attention processing training (APT)” had a beneficial effect on attention measures (PASAT, Consonant Trigrams) in a severe TBI group (tested pre and post training approximately 7 months apart). They compared their results to a “convenience” sample of controls, given the same measures one week apart without training. Results suggested that APT did not have a significantly beneficial effect as performance improved on all measures across both groups (indicating practice effects and possibly spontaneous recovery). Similarly, two trials did not find significant differences between groups for attentional, functional, and/or cognitive skills assessed (Lindelov et al., 2016; Novack et al., 1996). Novack et al. (1996)

compared focused hierarchical attentional learning with an unstructured non-sequential, non-hierarchical intervention, while Lindelov et al. (2016) compared N-back training with visual search training. Overall there is weak evidence in support of training programs as an effective rehabilitation intervention for attention.

Conclusion

There is level 2 evidence that training programs designed to improve attention in general may be effective compared to unstructured stimulation in ABI populations.

There is level 3 evidence that attention processing training may improve attention compared to visual search training in ABI populations.

Although attention training programs in general improve attention scores, the level of structure in these programs does not appear to influence the success of the intervention.

6.2.1.2 Dual-Task Training

The following studies examined the effect of “dual-task” training on speed of processing. Dual-task training involves dividing attention between two stimuli in order to complete two tasks concurrently and successfully, such as walking while speaking.

Table 6.2 The Effect of Dual-Task Training on Speed of Processing Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Couillet et al. (2010) France RCT PEDro=5 N=12</p>	<p>Population: severe TBI; Gender: Male=9, Female=3. <i>Group 1 (n=5):</i> Mean Age=23.8yr; Mean GCS=4.8; Mean Time Post Injury=6.3mo. <i>Group 2 (n=7):</i> Mean Age=26.7yr; Mean GCS=4.8; Mean Time Post Injury=16.1mo. Intervention: Randomized AB versus BA design, where “A” represents the control phase and “B” represents the treatment (dual-task training) phase. In the dual-task phase, patients were trained to conduct two concurrent tasks simultaneously. Group 1 started with the control phase (AB) and Group 2 (BA) with the treatment phase. Each phase lasted 6 wk (4, 1 hr sessions/wk). Outcome Measure: Test Battery for Attentional Performance (TAP: divided attention and flexibility subtests), Go-no go and Digit Span, Trail Making Test, Stroop Test, Brown-Peterson Paradigm, Rating Scale of Attentional Behaviour.</p>	<ol style="list-style-type: none"> 1. Following training, there was a significant improvement in the 2 tasks that targeted divided attention (TAP-divided attention, Go-no go and Digit Span: p<0.0001 for both). 2. The two groups differed significantly at 6 wk with those in the BA design doing better on TAP reaction times (p<0.01), the digit span dual-task (p<0.001), and the Rating Scale of Attentional Behaviour (p<0.01). 3. There was a significant differences between groups at 6 wks on the Stroop test (p<0.001) and the flexibility subtest of the TAP (p<0.001), but not the Trail Making Test or the Brown-Peterson task. 4. Experimental training had no significant effects on non-target measures.

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

One RCT with a TBI population showed that attention and information processing outcomes could be improved within the dual task paradigm (Couillet et al., 2010; Sacco et al., 2016). Couillet et al. (2010) found that dual-task training significantly improved attentional behaviour and reaction time compared to a non-specific cognitive program.

Conclusion

There is level 2 evidence that dual task training may be effective in improving attention task performance in ABI populations compared to non-specific training.

Dual-task training has been shown to improve measures of attention to the extent that the ABI population does not significantly differ from healthy controls, however it is undetermined if the strength of these effects compared to non-dual-task training are greater.

6.2.1.3 Computer-Based Interventions

An increase in available technology has allowed for the development for more computer-based interventions designed to improve attention, concentration, and information processing. Common treatment modalities include computer cognitive training programs and virtual reality sessions. Virtual reality is discussed in further detail in 6.3.1.1.3 where its effects on learning and memory are presented.

Table 6.3 The Effect of Computer-Based Interventions on Reaction Time Post ABI

Author/Year/ Country/Study Design	Methods	Results
Dirette et al. (1999) USA RCT PEDro=4 N=30	Population: TBI: Mean age=38yr; Gender: male-22, female-8; Time since injury range=2-12 months. Intervention: Randomly assigned to remedial (without instruction, n=15) and compensatory strategy (verbalization, chunking and pacing) intervention (n=15) groups receiving a 45-minute session once a week for 4 weeks. Outcome Measure: Pre and Post-test on the Paced Auditory Serial Addition Task (PASAT).	1. Pre/post and weekly tasks significantly improved in both groups (p<0.01). 2. No significant improvement due to intervention (p>0.05).
Grealy et al. (1999) Scotland RCT PEDro=1 N=13	Population: TBI patients: Age Range: 19-64; Gender: male=8, female=5. Intervention: Crossover design: patients were allocated to 4-week interventions of receiving a single bout of Virtual reality (VR) exercise or a no-exercise control condition. Outcome Measure: Tests measuring attention, information processing, learning, memory, and reaction and movement times.	1. Intervention group (n=13) performed significantly better than control group (n=320) on digit symbol (p<0.01), verbal (p>0.01) and visual (p<0.05) learning tasks. 2. Reaction (p<0.01) and movement (p<0.05) times improved significantly after a single VR session.
Dahdah et al. (2017) USA	Population: CVA=6, TBI=5, Tumor=2, Anoxia brain injury=2; Mean Age=40.3yr; Gender: Male=12, Female=3.	1. No statistically significant performance differences were found from baseline to conclusion of the study for the VR

<p>Pre-Post N_{Initial}=21, N_{Final}=15</p>	<p>Treatment: Participants received the virtual reality (VR) intervention sessions (apartment and classroom) twice per week for a 4wk period. Sessions 1 and 8 included all types of distractors, sessions 2 and 3 included no distracting stimuli, sessions 4 and 5 included only auditory distracting stimuli, and sessions 6 and 7 included only visual distracting stimuli.</p> <p>Outcome Measure: Woodcock-Johnson, 3rd edition (WJ-III pair cancellation subtest), Delis-Kaplan Executive Function System (D-KEFS Color-Word Interference subtest), Automated Neuropsychological Assessment Metrics (ANAM Go/No-Go and unimodal Stroop subtests), VR Stroop task (apartment and classroom).</p>	<p>apartment Stroop or D-KEFS Stroop test.</p> <ol style="list-style-type: none"> For the VR classroom, participants' shortest response time on the word-reading condition was significantly reduced by session 8 (p=0.0383). All other VR classroom Stroop variables did not show significant differences. No significant differences from session 1 to session 8 were found for all pair cancellation subtest scores. From session 1 to 8, the ANAM Stroop word-reading percentage of items with a correct response (p=0.0293), ANAM Stroop word-reading number of correct responses per minute (p=0.0321), and ANAM Go/No-Go number of impulsive/bad responses (p=0.0408) significantly increased. All other ANAM variables did not show significant differences.
<p>O'Neil-Pirozzi and Hsu (2016) PCT N_{Initial}=14, N_{Final}=12</p>	<p>Population: TBI=4, CVA=2, Brain tumour=1; Severity: moderate/severe. <i>Experimental Group (n=7):</i> Mean Age=51.3yr; Gender: Male=5, Female=2; Mean Time Post Injury=20.9yr; Etiology: TBI=5, CVA=2. <i>Control Group (n=7):</i> Mean Age=46.9yr; Gender: Male=7; Mean Time Post Injury=25.0yr.</p> <p>Treatment: Experimental group participants received BrainHQ, a commercially available online computerized cognitive exercise program (Attention, Brain Speed, Memory, People Skills, Intelligence, and Navigation) for 5 mo, 5d/wk. Control group participants did not have a private computer and received no intervention.</p> <p>Outcome Measure: Number/percentage of sessions completed, Number/percentage of sessions initiated by participants, Number/percentage of sessions completed independently by participants, Mean amount of external cures provided for session completion, Wisconsin Card Sorting Test (WCST), Hopkins Verbal Learning Test-Revised (HVLt-R immediate, delayed), Controlled Oral Word Association Test-FAS (COWAT), Trail Making Test (TMT A and B accuracy and speed), Satisfaction with Life Scale (SWLS), Semi-structured interview questions.</p>	<ol style="list-style-type: none"> Of the five experimental group participants that completed the study, they completed an average 87% of sessions, initiated an average 25% of sessions, and independently completed an average 7% of sessions. Two participants needed minimum external cues, two participants needed moderate external cures, and one participant needed maximum external cues. Comparing 3mo prior to intervention with 1wk prior to intervention, there were no significant differences within either group for WCST, HVLt-R, COWAT, TMT A or B, or SWLS. There were no significant differences between groups at 1wk prior to intervention (baseline) for WCST, HVLt-R, COWAT, TMT A or B, or SWLS. Compared to baseline, experimental group showed significant improvement post-intervention for HVLt-immediate (p=0.0255) and SWLS (p=0.0075). There were no significant improvements for WCST, HVLt-delayed, or TMT A or B. Compared to baseline, control group did not show significant differences post-intervention for WCST, HVLt, TMT A or B, or SWL. Compared to control group, experimental group showed significantly higher post-intervention improvements on HVLt-immediate (p=0.0068) and COWAT (p=0.0310). No significant differences between groups

		<p>were found for changes in WCST, HVLTD, TMT A or B, or SWL..</p> <p>7. Of the experimental group participants who completed the study, 60% reported improved everyday thinking abilities, 60% reported improved memory, and 20% reported improved attention, organization, and/or problem solving skills, but 60% reported they would not continue with exercise program post-study completion.</p>
<p>Li et al. (2015) USA Pre-Post N_i=13, N_f=12</p>	<p>Population: Stroke=5, TBI=5, Brain tumor=2; Mean Age=61yr; Gender: Male=10, Female=2. Treatment: Participants received the computer-based cognitive retraining program, Parrot Software. The following eight modules were each completed in separate 1h sessions: Visual Instructions, Attention Perception and Discrimination, Concentration, and Visual Attention Training, Remembering Written Directions, Remembering Visual Patterns, Remembering Written Letters, and Remembering Written Numbers. Outcome Measure: Montreal Cognitive Assessment (MoCA overall, attention, memory), Medication-box sorting task.</p>	<ol style="list-style-type: none"> 1. Compared to baseline, there was a significant mean increase in overall MoCA of 3.25 (p=0.03) post-intervention. However, the attention and memory subscales did not show significant differences. 2. There were no significant differences before and after intervention for the medication-box sorting task. 3. Participants with previous computer-based cognitive retraining experience had significantly more MoCA improvement than those without (p<0.01). 4. Age, education level, or type of ABI diagnosis did not have any significant effects on MoCA or medication-box scores.
<p>Gerber et al. (2014) USA Pre-Post N=19</p>	<p>Population: TBI; Mean Age=50.4yr; Gender: Male=11, Female=8; Mean Time Post Injury=10yr; GCS=4-14; Severity: Severe=9, Moderate=1, Mild=7. Intervention: Participants completed a series of virtual reality tasks in a standardized order utilizing a hepatic stylus; 1) Participants were asked to clear a workbench and mount tools on an upright pegboard (TOOL), then 2) spell as many 3-letter words as possible from a set of letter tiles (SPELL), then 3) prepare a virtual peanut butter and jelly sandwich (SAND), and finally 4) hammer in two nails and tighten two screws through tool use (TUSE). TOOL, SAND and TUSE tasks had a time limit of 5 minutes while SPELL task had a time limit of 2 minutes. Participants had 3 chances to perform each task (Baseline, 2nd, Final). Outcome Measure: Self-reported measures (engagement and frustration), Boredom Propensity Scale (BPS), Purdue Pegboard Test (PPT), and Neurobehavioural Symptom Inventory (NSI).</p>	<ol style="list-style-type: none"> 1. All of the participants reported a high level of engagement during the interactions. 2. Thirty percent of participants reported a high level of frustration, but were able to complete the tasks with short breaks. 3. From baseline to final, TOOL mean time decreased by 60s, TUSE mean time decreased by 68s, SAND mean time decreased by 72s and SPELL means increased by 2.7 words. 4. PPT correlated with TOOL (p=0.016) and TUSE (p=0.014) time during the final trial. 5. SPELL correlated with the BPS (p=0.08) during the baseline and NSI (p=0.05) during the final trial.
<p>Dvorkin et al. (2013) USA</p>	<p>Population: TBI; Mean Age=37.8yr; Gender: Male=17, Female=4; Mean Time Post Injury=10.3wk.</p>	<ol style="list-style-type: none"> 1. The interactive virtual environment was well tolerated by 18 of the 21 patients, 3 participants could not complete the 6

<p>Pre-Post N=21</p>	<p>Intervention: Participants completed a virtual reality task and were instructed to hold the handle of a robot, moving the handle towards targets that appeared in the virtual environment. Patients reached to as many targets as they could within 4 minutes (1 block). Participants completed 6 blocks per day for 2 consecutive days. On each day, each pair of blocks included one haptic condition that affected the robotic handle and was either; 1) no haptic feedback (no force condition), 2) a break-through force, similar to popping a balloon (break-through condition) or 3) a gentle pulse of force (nudge condition). Outcome Measure: Tolerance, attention (pauses, pause duration), number of targets reached, and Agitated Behaviour Scale (ABS).</p>	<p>blocks in each visit due to fatigue or frustration.</p> <ol style="list-style-type: none"> 2. In 15 participants ABS was reduced on the second visit. 3. Attention loss was reported before and during arm movements, however on the second visit patients exhibited significantly less pauses ($p<0.0001$) and shorter pause duration ($p=0.007$). 4. Patients were able to reach more targets on the second visit compared to the first visit ($p<0.0001$). 5. During the first visit, participants reached significantly less targets in the break-through and no force conditions compared to the nudge condition ($p<0.02$); the break-through and no force conditions were not significantly different. 6. During the second visit, participants reached significantly more targets in the nudge and no force conditions compared to the break-through condition ($p<0.002$); the nudge and no force conditions were not significantly different. 7. Break-through trials were significantly longer than the no force and nudge conditions on both the first and second day ($p<0.0001$). 8. Participants acquired more targets during the second visit compared to the first ($p=0.0003$) and acquired more targets with each block ($p<0.0001$).
<p>Li et al. (2013) USA Pre-Post N=11</p>	<p>Population: ABI; Mean Age=49.45yr; Mean Time Post Injury=21.27yr. Intervention: All participants completed eight 60 minute sessions using the attention and memory sub programs of the computer-based cognitive retraining Parrot Software. The participants focused on one of the eight subprograms during each session with each subprogram containing 10 lessons with increasing difficulty. Assessments were conducted before and after intervention. Outcome Measure: The cognitive assessment (attention & memory).</p>	<ol style="list-style-type: none"> 1. There was a significant improvement in attention cognitive assessment scores from pre to post intervention (mean change=2.091; $p<0.005$). 2. There was a significant improvement in memory cognitive assessment score from pre to post intervention (mean change=1.73; $p<0.05$).
<p>Zickefoose et al. (2013) USA Pre-Post N=4</p>	<p>Population: TBI; Mean Age=42.75yr; Gender: Male=4, Female=0; Mean Time Post Injury=17.5yr; Severity: Severe=4, Moderate=0. Intervention: Participants engaged in computer-based brain games over the course of two 1-month treatment phases. Participants received Attention Process Training-3 (APT-3) or Lumosity™ in phase 1, and then received the alternate treatment in phase 2. Both phases consisted of twenty</p>	<ol style="list-style-type: none"> 1. All four participants demonstrated significant progress in reaching new levels of difficulty on all tasks over the course of both treatments ($p<0.01$). 2. NAB analysis showed that one participant demonstrated significant improvement on one sub-test, while two participants demonstrated non-significant improvement on one or more sub-tests. Improvements

	<p>30-minute sessions. Outcomes were assessed at baseline and after each phase. Outcome Measures: Test of Everyday Attention (TEA); Neurological Assessment Battery (NAB)–Numbers and Letters Test Parts B, C, and D; Perceptual rating scale (PRS).</p>	<p>occurred during phase 1, regardless of treatment.</p> <ol style="list-style-type: none"> 3. TEA analysis showed that one participant demonstrated improvement on several sub-tests during both treatments, while the scores of the other three participants were inconsistent for either treatment. 4. On the PRS, two participants showed strong enjoyment and willingness to continue APT-3, while the other two participants showed an equally strong rejection of ATP-3. 5. On the PRS, all four participants showed strong enjoyment of Lumosity™, while only two participants showed a strong willingness to continue.
<p>Chen et al. (1997) USA Case-Control N=40</p>	<p>Population: Age=18+years; Gender: male=27, female=13; Condition: TBI. Intervention: Divided retrospectively into computer-assisted rehabilitation (CACR) and tradition therapy groups Outcome Measure: Neurophysiological test scores (WAIS-R; WMS).</p>	<ol style="list-style-type: none"> 1. Both groups made significant post-treatment gains on the neurophysiological test scores ($p<0.05$), with the CACR group making significant gains on 15 measures ($p<0.05$) and the comparison group making significant gains on seven measures ($p<0.005$). 2. However, no significant difference was found between groups on their post-treatment gains.

PEdro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Chen et al. (1997) studied the effect of computer assisted cognitive rehabilitation versus traditional therapy methods. While measures of attention significantly improved in both groups after treatment, no significant differences were observed between groups (Chen et al., 1997). Other studies with brand name computer-assisted cognitive rehabilitation showed less favourable results. A small pre-post study of Luminosity showed improvements in attention for a minority of participants, however this improvement did not significantly differ from those who received Attention Process Training-3 (Zickefoose et al., 2013). Parrot software showed mixed results with a pilot study reporting significant attention improvement post-intervention (Li et al., 2013), but a subsequent study reported no significant changes on measures related to attention (Li et al., 2015). BrainHQ did not significantly improve attention outcomes over time or compared to no intervention (O'Neil-Pirozzi & Hsu, 2016). The lack of evidence supporting the efficacy of computer-based cognitive rehabilitation may be due to different programs and strategies used to train participants. An RCT by Drette et al. (1999) found no significant differences in improvements between participants taught specific compensatory strategies and those that simply completed the computer tasks without instruction of compensatory strategies. However, both groups significantly improved over time, with those that used the compensatory strategies (whether taught or spontaneously acquired) performing better than those that did not (Drette et al., 1999).

Repetition of tasks in virtual reality improved performance, both in terms of speed and accuracy (Dvorkin et al., 2013; Gerber et al., 2014). Gentle nudges corrected behaviour better than break-

through or no feedback (Dvorkin et al., 2013). However, repetition of the Stroop test in different virtual reality environments showed limited improvement in performance on those specific tests (Dahdah et al., 2017). A virtual reality exercise program demonstrated significant benefits in reaction times but not attention after intervention; more high quality research is needed to confirm the efficacy of virtual reality exercise (Grealy et al., 1999).

Conclusions

There is level 2 evidence that neither general nor name brand computer-based rehabilitation intervention may improve attention outcomes compared to usual care in ABI populations.

There is level 4 evidence that attention performance can be improved in ABI populations through repetition of tasks, either through computer-based or virtual reality environments.

Computer-based interventions are no more effective than no intervention in improving measures of attention and concentration post ABI.

Repetitive virtual reality tasks which include repetition are effective in improving attention and concentration in ABI populations.

6.2.1.4 Attention Training Programs

With regards to cognitive rehabilitation, much of therapy is patient goal directed with both long and short term goals often identified (Carswell et al., 2004). The ability to manage goals is often emphasized as a component of brain injury community reintegration programs and is integral in the completion of instrumental activities of daily living. The execution of these goals relies on an individual having the ability to maintain attention on a given task.

Cicerone et al. (2005) recommended strategy training for persons with TBI for improving deficits of attention. It should be noted, however, that there was insufficient evidence to distinguish the effectiveness of specific attention training during acute stage rehabilitation from improvements made from spontaneous recovery or from more general cognitive interventions (Cicerone et al., 2005).

Table 6.4 The Effect of Attention Training Programs on Attention and Concentration Post ABI

Author/Year/ Country/Study Design	Methods	Results
Dundon et al. (2015) Ireland RCT PEDro=3 N=26	Population: TBI; Mean Age=38.96yr; Gender: Male=19, Female=7. Treatment: Participants were assessed during a dichotic listening task (DLT) presented at 6 levels of distraction difficulty, and randomly received either adaptive training (AT, n=9), non-adaptive training (NAT, n=8), or no training (NT, n=9) between sessions	1. For the DLT, there was a significant main effect of group (F=3.99, p=0.035), such that the AT group showed poorer performance than the NAT group (p=0.019) and the NT group (p=0.031). 2. For the DLT, there was a significant interaction between group and time (F=4.38, p=0.026), such that

	<p>(Study 2). Outcomes were assessed before and after training. Outcome Measures: DLT performance; Test of Everyday Attention (TEA).</p>	<p>improved performance was seen in the AT ($p=0.036$) and NAT ($p=0.0025$) groups over time, but not in the NT group ($p=0.34$).</p> <ol style="list-style-type: none"> On the TEA, there was a significant main effect of group ($F=2.45$, $p=0.13$), such that the NT group showed better performance than the AT group ($p<0.001$) and the NAT group ($p=0.036$). On the TEA, there was a significant main effect of time ($p=0.022$), such that performance improved in all groups.
<p>Cantor et al. (2014) USA RCT PEDro=7 N=98</p>	<p>Population: TBI; Mean Age=45.3yr; Gender: Male=37, Female=61; Mean Time Post Injury=12.6yr; Severity: Mild=49, Moderate=19, Severe=30. Intervention: Participants were randomly assigned to either immediate start (IS; $n=49$) or waitlist control (WL; $n=49$) groups. Participants received group sessions of emotional regulation (2 sessions, 45min) and an individual problem solving session of attention training (1 session, 60min) per day (3 days/wk for 12 weeks). Group sizes were generally 4-6 participants. Outcome Measure: Attention Rating and Monitoring Scale (ARMS), Behavioural Assessment of the Dysexecutive Syndrome, Difficulties in Emotion Regulation Scale (DERS), Executive Function Composite from Factor Analysis (EF index), Problem Solving Inventory (PSI), and Frontal System Behavioural Scale (FrSBe).</p>	<ol style="list-style-type: none"> There was a significant treatment effect for the EF index favoring the IS group ($p=0.008$). There was no significant difference between groups in the DERS of ARMS. Secondary analysis revealed a significant treatment effects for the FeSBe scale ($p=0.049$) and the PSI ($p=0.016$). There were no other significant treatment effects. Variance of depression, age, severity and time since injury did not change treatment effects.
<p>McHugh and Wood (2013) Ireland RCT PEDro=5 N=24</p>	<p>Population: TBI. <i>Mindfulness Group (N=12):</i> Mean Age=28.45yr; Mean Time Post Injury=785.5d; Mean GCS=8.5. <i>Control group (N=12):</i> Mean Age=30.5yr; Mean Time Post Injury=664.7d; Mean GCS=7.42. Intervention: Patients were randomly assigned to the control group or mindfulness group (focused attention). The mindfulness group received instructions (mindfulness induction) prior to completing experimental tasks. Participants then completed a memory load task (remembering the location of symbols) and an over-selectivity task and test. Outcome Measure: Minimal Attention Awareness Scale (MAAS), Trail making test A and B (test of visual attention and task switching) and the Wechsler Test of Adult Intelligence.</p>	<ol style="list-style-type: none"> There was a significant decrease in stimulus over-selectivity after the mindfulness training compared to the control group ($p<0.05$, $t(22)=1.74$).

<p>Chen et al. (2011) USA RCT PEDro=5 N=12</p>	<p>Population: TBI=9, Other=3: Mean Age=48yr; Gender: Male=5, Female=7; Time Post-Injury Range=6mo-6yr. Intervention: Participants were randomized to receive either the goals training intervention (n=7) or education intervention (n=5) for 5 wk, after which they switched to the other condition for another 5 wk. The goals training was spread over 5 wk and involved: group, individual and home-based training. The education program was a 5 wk didactic educational instruction regarding brain injury. Outcome Measures: Letter number sequencing, Wechsler Adult Intelligence Scale-III, Auditory consonant trigrams, Digit Vigilance Test, Design and Verbal Fluency Switching, Trails B, Stroop Inhibition, Hopkins Verbal Learning Test, Brief Visual Memory Test Revised, Trails A test, Visual Attention Task.</p>	<ol style="list-style-type: none"> 1. On the domain of attention and executive functions, all participants in the goal training intervention showed an increase from pre to post goals training; while only 7/12 in the education intervention showed an increase from pre to post education ($p<0.0001$). 2. For learning and memory performance scores increased an average of 0.70 units after participation in goals training than after participation in education intervention ($p=0.02$). 11/12 participants improved in the goals training group while 4/12 improved in the education group ($p=0.009$). 3. Tests of motor speed of processing showed no significant differences between the two interventions with a non-significant trend for greater improvements in goal-training compared to education ($p=0.07$).
<p>Novakovic-Agopian et al. (2011) USA RCT Crossover PEDro=5 N=16</p>	<p>Population: TBI=11, Stroke=3, Other=2: Mean Age=50.4yr; Gender: Male=7, Female=9; Time Post Injury Range=1-23yr. Intervention: Participants were randomized to 5 wk interventions consisting of a goals training program (n=8) or an educational instruction group (n=8). Goal training focused on mindfulness-based attentional regulation and goal management strategies for participant-defined goals. Educational training was didactic instructional sessions about brain injury. At the end of 5wk, participants were switched to the other intervention. All participants were assessed at baseline, Week 5 and again at Week 10. Outcome Measure: Auditory Consonant Trigrams, Letter Number Sequencing (working memory); Digit Vigilance Test (sustained attention); Stroop Inhibition Delis-Kaplan Executive Function System (Inhibition); Trails B, Design Fluency-switching (mental flexibility), Hopkins Verbal Learning Test-Revised, Brief Visual Memory Test-Revised.</p>	<ol style="list-style-type: none"> 1. At the end of wk 5 participants in the goals-edu group showed significant improvement on measures of attention and executive function from baseline ($p<0.0001$), while the edu-goals group showed no change or minimal change ($p>0.05$). 2. The goals-edu group had significantly greater improvements than the edu-goals group on the following at wk 5: working memory (<i>Mean</i> 1.12 vs -0.12, $p<0.0001$); mental flexibility (<i>Mean</i> 0.64 vs 0.04, $p=0.009$); inhibition (<i>Mean</i> 0.62 vs 0.04, $p=0.005$); sustained attention (<i>Mean</i> 0.96 vs 0.27, $p=0.01$); learning (<i>Mean</i>=0.51 vs 0.08, $p=0.02$); and delayed recall (<i>Mean</i> 0.39 vs -0.27, $p=0.01$). 3. At wk 10, the edu-goals group significantly improved compared to wk 5 on: attention and executive function (0.79 vs 0.03, $p<0.0001$); working memory (1.31 vs -0.12, $p<0.0008$); mental flexibility (0.66 vs 0.04, $p<0.0008$); inhibition (0.50 vs 0.04, $p=0.01$); sustained attention (0.44 vs 0.27, $p=0.01$); memory (0.609 vs -0.10, $p=0.02$); learning (0.66 vs 0.08, $p=0.05$); and delayed recall (0.55 vs -0.27, $p=0.02$). 4. Those in the goals-edu group who had completed the training session were able to maintain their gains and there were significant improvements in attention and executive function ($p<0.04$) and working memory ($p<0.02$).

<p>McMillan et al. (2002) UK RCT PEDro=5 N=130</p>	<p>Population: TBI; <i>Attentional Control Training (ACT; n=44)</i>: Mean Age=34.6yr; Gender: Male=35, Female=9; Median GCS=9. <i>Physical Exercise (PE) Group (n=38)</i>: Mean Age=31.4yr; Gender: Male=30, Female=8; Median GCS=10. <i>Control Group (n=48)</i>: Mean Age=36.2yr; Gender: Male=36, Female=12; Median GCS=9 Treatment: Patients were assigned to 1 of 3 groups. The ACT group received supervised practice (5, 45min session over 4wk) and were given an ACT audiotape to practice daily with. The PE group had the same amount of therapist contact but the audiotape was based on physical training. The control group had no therapist contact. Assessments were done pre- and post-training, and 6 and 12mo. Outcome Measure: Test of Everyday Attention, Adult Memory and Information Processing Battery, Paced Auditory Serial Addition Test, Trail Making Test, Sunderland Memory Questionnaire, Cognitive Failures Questionnaire.</p>	<ol style="list-style-type: none"> 1. Results showed no significant differences in outcome measures among the 3 training groups at any of the assessment points. 2. The exception to the above finding was the results of the Cognitive Failure Questionnaire where patients in both treatment groups (ACT and PE) had significantly greater reduction in self-reported cognitive failures compared to the control group at 12 mo follow-up (p<0.05).
<p>Levine et al. (2000) Canada UK RCT PEDro=4 N=30</p>	<p>Population: TBI: <i>Goal Management Training (GMT) Group (n=15)</i>: Mean Age=29.0yr; Gender: Male=5, Female=10; Mean GCS=10.7; Mean Time Post Injury=3.7yr. <i>Motor Skill Training (MST) Group (n=15)</i>: Mean Age=30.8yr; Gender: Male=9, Female=6; Mean GCS=10.8; Mean Time Post Injury=3.8yr. Intervention: Patients were randomized into the GMT or MST group. The GMT was comprised of five steps: 1) orienting and alerting to task, 2) goal selection, 3) partitioning goals into sub-goals, 4) encoding and retention of sub-goals, and 5) monitoring. The MST was training that was unrelated to goal management: reading and tracing mirror-reversed text and designs. Participants were tested on everyday paper and pencil tasks that focused on holding goals in mind, sub-goal analysis and monitoring. Outcome Measure: Goal Neglect (Everyday paper and pencil tasks), Stroop Interference Procedure, Trail Making A and B, Wechsler Adult Intelligence Scale Revised (WAIS-R).</p>	<p>Everyday paper and pencil Task</p> <ol style="list-style-type: none"> 1. The GMT group compared to the MST group had significantly greater accuracy on the everyday paper and pencil tasks post-training (p<0.05). 2. The MST group also had significantly more errors during the everyday paper and pencil tasks (p<0.01). 3. The GMT group significantly reduced their errors from pre-post training during the everyday paper and pencil tasks (p<0.01). 4. The GMT also devoted significantly more time to proofreading and the room-layout tasks than the MST group from pre to post-training (p<0.05). <p>Neuropsychological Tasks</p> <ol style="list-style-type: none"> 1. The GMT group was generally slower on timed neuropsychological tests: Stroop Interference Procedure, Trail Making Part A and B (p<0.05 and p<0.06, respectively). 2. No significant differences between groups for the WAIS-R (p>0.05).
<p>Sohlberg et al. (2000) USA RCT PEDro=8 N=14</p>	<p>Population: TBI=11, ABI=1, Other=2. <i>Attention Process Training (APT) Group (n=7)</i>: Mean Age=33.1yr; Mean Time Post Injury=7.5yr; <i>Control Group (n=7)</i>: Mean Age=38.1yr; Mean Time Post Injury=1.6yr. Intervention: Patients were randomized to receive either the APT training (treatment) or the brain injury education and supportive listening (control), in a cross over design.</p>	<ol style="list-style-type: none"> 1. Those in the APT group reported significantly more changes than the control group (0.91 and 0.58 respectively, p<0.05). 2. The effect of type of change was significant (p<0.0001); a greater number of memory/ attention changes were reported for the APT group,

	<p>APT was 24hr over 10wk and the control group received 10hr over 10wk. All subjects worked directly with a therapist and assessed pre and post intervention. Outcome Measure: Trail Making Test, Paced Auditory Serial Addition Task (PASAT), Gordon Diagnostic Vigilance and Distraction, Controlled Oral Word Association Task (COWAT), Stroop Task, Attention Questionnaire.</p>	<p>whereas more psychological changes were reported for the control.</p> <ol style="list-style-type: none"> Changes in PASAT scores corresponded with perceived cognitive improvement in the interview; changes in PASAT scores were greater for those who reported >2 cognitive changes (p<0.05). Results of the PASAT, Stroop Task, Trail Making Test B, and COWAT also found that those with higher levels of vigilance had improved scores (p<0.01). For the aforementioned tasks, there were also specific improvements in performance associated with APT that were greater than those associated with brain injury education (p<0.05).
<p>Fasotti et al. (2000) Netherlands RCT PEDro=5 N=22</p>	<p>Population: TBI; <i>Experimental Group (n=12):</i> Mean Age=26.1yr; Gender: Male=8, Female=4; Mean Time Post Injury=9.8mo. <i>Control group (n=10):</i> Mean Age=30.1yr; Gender: Male=7, Female=3; Mean Time Post Injury=8.3mo. Intervention: Patients in the experimental group received Time Pressure Management (TPM) training (1hr, 2-3x/wk, 2-3wk). TPM training used videotaped short stories. The program was designed to increase awareness of errors and deficits, encourage the acceptance and acquisition of the TPM strategy, and emphasize strategy application and maintenance. The control group received concentration training (30min, 2-5hr/wk, 3-4hr). Mean training was 7.4hr and 6.9hr for the TPM and control groups, respectively. Patients were assessed 2wk prior to training, post-training, and at 6mo follow-up. Outcome Measure: Waterbed (WB) and Harvard Graphics (HG) tasks, Rey's 15-word test, Rivermead Behavioural Memory Test, Auditory Concentration Test, Paced Auditory Serial Addition Task, Visual Choice Reaction Time Task.</p>	<ol style="list-style-type: none"> Training improved performances in both HG and WB tasks, but differences were not significant relative to control. Scores on 2 of 3 standardized memory variables and all 3 attention variables increased significantly in the TPM group (p<0.05), whereas no memory variables and 1 of 3 attention variables increased significantly for the control group. Follow-up (6 mo) data for 10 from the TPM group and 9 from the control group indicated that there was a significant time effect (p<0.05) but no significant group time interaction (p=0.23); this suggests that there still was a significant improvement after 6 mo but that this improvement could not be attributed specifically to the treatment or control training.
<p>Hellgren et al. (2015) Sweden Case Series N=48</p>	<p>Population: Cerebral infarction=23%, TBI=21%, Infection=19%, Intracerebral hemorrhage=13%, Subarachnoid hemorrhage=10%, Brain tumor=8%, Other=6%; Mean Age=43.7yr; Gender: Male=30, Female=18; Mean Time Post Injury=51.2mo. Treatment: Participants received a working memory training program (Cogmed) consisting of various visuospatial and verbal working memory tasks. There were 4-5 sessions/wk for 5-7wk, consisting of 45-60min of intense exercise with one break. Occupational therapist coaches were present during every session and provided</p>	<ol style="list-style-type: none"> At 20wk post-training, there were significant improvements in PASAT (p<0.001), Listening Span (p<0.001), Forward block repetition (p<0.001), Backward block repetition (p<0.001), COPM performance (p<0.001), COPM satisfaction (p<0.001), EQ-5D index (p=0.009), and EQ-VAS (p<0.001) compared to baseline. Compared to baseline, all participants significantly improved their WM Index at 20wk follow-up (p<0.001). No significant differences in treatment effect were found for all outcomes in terms of sex or time post-injury, except

	<p>weekly feedback in addition to continuous feedback from the computer program.</p> <p>Outcome Measure: Paced Auditory Serial Attention Test (PASAT 2.4), Forward and backward block repetition, Listening Span Task, Canadian Occupational Performance Measure (COPM performance and satisfaction), EuroQol descriptive (EQ-5D Index), EuroQol visual analogue scale (EQ-VAS), Working Memory Index (WM Index).</p>	<p>for ≤18 mo since injury exhibiting more improvement than >18mo in terms of WM index difference (p<0.05), COPM performance improvement (p<0.05), and COPM satisfaction improvement (p<0.05).</p>
<p>Serino et al. (2007) Italy Case Series N=9</p>	<p>Population: TBI: Age range=16-57 yr; Gender: male=6, female=3; Time since injury=6-78 months.</p> <p>Intervention: A long sequence of numbers is presented and patients were asked to add each new number to the number preceding it and say the sum out loud. Two additional tests (the Months tasks and the Word tasks) were also administered in a similar way. The GST and the WMT were each 4 sessions/week, for 4 weeks. To vary tasks and their level of difficulty, in the interstimulus interval was varied.</p> <p>Outcome Measure: Working memory training (WMT); Paced Auditory Serial Addition Test (PASAT); Months task</p>	<ol style="list-style-type: none"> 1. Study results indicate the greatest improvement in performance occurred from the intermediate to the final sessions (p<0.0005) after the WMT. 2. Improvement from the initial to intermediate sessions did not show any significant improvement in working memory (p<0.46) after GST. 3. Working memory (p<0.05), divided attention (p<0.05), executive function (p<0.05), and long term memory (p<0.05) for subjects were significantly improved in the final session compared to the intermediate session. 4. The same was not noted on the speed processing and sustained attention tasks (p>0.05). Working memory training tasks were also found to improve scores on various psychosocial outcomes.
<p>Boman et al. (2004) Sweden Pre-Post N=10</p>	<p>Population: TBI: Mean age=47.5yr; Gender: male=5, female=5; Time Post injury=9-40 months.</p> <p>Intervention: Each participated in an individual cognitive training session for 1 hr/3x a week for 3 weeks at home or work. The program included attention process training (APT), generalization for training and teaching of compensatory strategies for self-selected cognitive problems. Identification of cognitive problems in everyday life was also part of the compensatory strategy.</p> <p>Outcome Measure: Digit Span Test; Claeson-Dahl test; Rivermead Behavioural Memory test (RBMT); Assessment of Motor and Process Skills; European Brain Injury Questionnaire.</p>	<ol style="list-style-type: none"> 1. For the following: sustained attention, selective attention and alternating attention significant changes (p<0.05, P<0.05, p<0.01 respectively) were noted in the scores of the APT test and Digit Span task between the pre to post training session and the 3 mo follow up. 2. Score increases (p<0.05) on the RBMT were found at the 3 mo follow up compared to the RBMT scores at the pretest. 3. When looking at changes in the RBMT score pre to post training, changes were not found. 4. No significant changes were found (pre to post and pre to 3 month follow up) when looking at the scores on the Claeson-Dahl Memory
<p>Laatsch et al. (1999) USA Case series N=5</p>	<p>Population: TBI; Age Range=18-65yr; Time Post-Injury=2-48 months;</p> <p>Intervention: Cognitive rehabilitation therapy (CRT) programme in a longitudinal protocol involving a resting SPECT and neuropsychological evaluation are pre-treatment, post-treatment and post non-treatment intervals.</p> <p>Outcome Measure: Neuropsychological</p>	<ol style="list-style-type: none"> 1. NP measures: WAIS-R, WMS-R, CVLT, RCFT, SCWT, WCST or ACT, SPECT image. 2. SPECT data revealed significant increases in cerebral blood flow during the treatment period (p<0.05). 3. CRT was found to be effective in improving both NP and everyday functioning. All patients were able to

	measures.	be more productive in their lives following treatment.
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Discussion

Levine et al. (2000) completed an RCT comparing a group of patients taking goal management training strategies to a control group who were exposed to only motor skills training. The treatment group improved on paper and pencil everyday tasks as well as meal preparation, which the authors used as an example of a task heavily reliant on self-regulation. A recent RCT (Dundon et al., 2015) examined the effect of adaptive training on dichotic listening tasks and attention, interestingly the adaptive training group had significantly higher scores on the listening task compared to non-adaptive training group, however, the non-adaptive training group surpassed the adaptive training group in test of everyday attention scores.

Emotional regulation was also examined as a potential intervention for the remediation of attention post-ABI (Cantor et al., 2014). However, this treatment was not seen to be effective in the recovery of attention, other significant effects on executive functioning from this study are discussed further in section 6.4.1.1. Another study which focused specifically on mindfulness (McHugh and Wood, 2013) found that mindful focused training significantly improved participant’s ability to correctly select stimuli compared to controls.

Fasotti et al. (2000) assessed the effectiveness of time pressure management (TPM) training compared to concentration training in patients with slowed processing speed as a result of traumatic brain injury. Though both groups showed improvements on information intake task performance, no significant differences between groups were observed even though specific time pressure management strategies were learned by the experimental group (Fasotti et al., 2000).

Taking focused training a step further, many studies examined the effects goal training or cognitive training (Boman et al., 2004; Chen et al., 2012; Laatsch et al., 1999; Novakovic-Agopian et al., 2011; Sohlberg et al., 2000). Physiologically cognitive rehabilitation therapy resulted in an increase in cerebral blood flow during treatment in the experimental group (Laatsch et al., 1999), as well as the experimental group reporting greater improvements in productivity. Levine et al. (2000) completed an RCT comparing a group of patients taking goal management training strategies, to a control group who were exposed to only motor skills training. The treatment group improved on paper and pencil everyday tasks as well as meal preparation, which the authors used as an example of a task heavily reliant on self-regulation. A pre-post study (Boman et al., 2004) found that cognitive training for three weeks significantly improved attention task scores compared to pre-test scores. One study did demonstrate that cognitive training (although beneficial) may not be more beneficial than other interventions such as educational training with respect to processing speed (Chen et al., 2011). In this study both groups significantly improved in attention directed goal completion. Another study comparing the effects of attentional training with another intervention (in this case physical exercise), found that there was no significant difference between groups post-intervention, but there was a within subjects effect such that both groups reported significantly less cognitive failures (McMillan et al., 2002). Novakovic-Agopian et al. (2011), found similar results in an RCT crossover where participants were assigned to received goal-training followed by education or the reverse. The goal training

first group saw a significant improvement in sustained attention compared to the education-first group, additionally the goal training first group maintained their gains over 10 weeks. When it comes to attention process training, that was also shown to have greater results in attention remediation compared to education (Sohlberg et al., 2000). One study examined the effects of a memory training program on attention, to positive results. Hellgren et al. (2015), found that a memory training program was successful in improving attentional scores on the Paced-Auditory Serial Attention Test, as well as further enhancing memory in general which is discussed later on in the chapter.

The inconsistencies between studies may be due to a lack of standardized goal management training or attention process training protocols. The lack of a consensus on the definition of certain cognitive processes appears to be reflected in the interventions used to attempt to rehabilitate these deficits. Unfortunately, this decreases the ability to compare studies on a more specific level, however, general conclusions can still be made that specific training programs which intend to increase attentional capacity are effective, to what extent they are more beneficial than other training programs needs to be addressed in the future through comparative methodologies. Only one study (Serino et al., 2007) described the specific task which was successful in improving attention. This cognitive task involved mental addition in combination with two other standardized tasks and was an effective strategy for improving attention.

Conclusions

There is level 2 evidence that adaptive training is no more effective than non-adaptive training in remediating attention in ABI populations.

There is level 1b evidence that emotional regulation therapy is not effective in treating attentional disorders compared to waitlist controls in ABI populations.

There is level 2 evidence that mindfulness training compared to no intervention may improve an individual's ability to correctly reject inappropriate stimuli post ABI.

There is level 2 evidence to suggest goal management training, when compared to education, may be effective at improving attention in post-ABI individuals. .

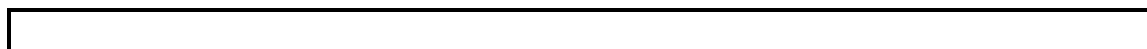
There is level 2 evidence that goal management training is more effective in remediating task completion times than motor skill training, however is not more effective in treating attention deficits, in post-ABI individuals.

There is conflicting (level 2) evidence that attentional control or processing training may not significantly improve attention in post-ABI individuals compared to control training.

There is level 4 evidence that summation tasks may be effective at improving attention in individuals post ABI.

There is level 4 evidence that a working memory training program may remediate attention in post-ABI individuals.

There is level 4 evidence that cognitive rehabilitation therapy may not be effective for improving attention post-ABI.



Goal management training is effective in assisting those who sustain an ABI learning to manage life goals through improved attention.

Therapies which focus on emotional regulation or mindfulness do not appear to be effective at improving attention post ABI.

In order to determine if attentional training is effective in improving attention post-ABI standardized protocols must be developed to allow between study comparisons.

Tasks that involve mathematical skills may be effective at improving attention post-ABI.

Cognitive rehabilitation therapy is not likely to remediate attentional deficits in ABI populations.

6.2.1.5 Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) is a technique that painlessly delivers electrical currents to specific regions of the brain. These electrical currents modulate neuronal activity through electrodes placed over the head at different regions. To our knowledge only one recent study has examined the effects of tDCS on cognitive functioning post-ABI.

Table 6.5 The Effect of Transcranial Direct Current Stimulation on Attention Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Sacco et al. (2016) Italy RCT PEDro=4 N=32</p>	<p>Population: TBI. Mean Time Post Injury=8.73yr; Severity: Severe=32, Moderate=0, Mild=0. <i>Treatment Group (TG, n=16):</i> Mean Age=37.7; Gender: Male=12, Female=4. <i>Control Group (CG, n=16):</i> Mean Age=35.2; Gender: Male=14, Female=2.</p> <p>Intervention: Participants were randomized to receive transcranial direct current stimulation (tDCS, TG) or sham tDCS (CG) with computer-assisted training (2/d, 5d). Outcomes were assessed at baseline (T0), before treatment (T1), after treatment (T2), and 1-month follow-up (T3).</p> <p>Outcome Measures: Test for the Examination of Attention, Divided Attention subtest (DA); Repeatable Battery for the Assessment of Neurological Status (RBANS).</p>	<ol style="list-style-type: none"> 1. For DA, the TG performed significantly better at T2 compared to T0 and T1, with faster reaction times (p=0.004) and fewer omission errors (p<0.0001). 2. For DA, the CG did not perform better at T2 compared to T0 and T1. 3. For DA, there was a significant interaction between time (T0/T1 vs T2) and group (TG vs CG), for both reaction time (p=0.05) and omission errors (p=0.03). 5. On RBANS, the TG showed a non-significant improvement in performance on attention task (p=0.057), but no improvement on visual-spatial abilities, semantic fluency, working memory, and long-term memory.

Discussion

Only one RCT to our knowledge has examined the effects of transcranial direct current stimulation (tDCS) on attention in a post-ABI population. Sacco et al. (2016) found that the addition of transcranial direct current stimulation to computer-assisted training was superior to sham stimulation for improving divided attention. However more high level studies are needed in order to fully examine the potential benefits of adding tDCS to standard attentional therapies.

There is level 2 evidence that transcranial direct current stimulation compared to sham stimulation may improve divided attention in individuals post ABI.

Transcranial direct current stimulation may be effective in remediating attentional deficits when combined with computer assisted training in ABI populations.

6.2.2 Pharmacological Interventions

6.2.2.1 Donepezil

Originally developed for improving cognitive function and memory in people with Alzheimer’s disease, donepezil is an acetylcholinesterase inhibitor (Cacabelos, 2007). Donepezil has been found to be effective at delaying cognitive impairment in people with Alzheimer’s disease (Takeda et al., 2006). Since evidence suggests that cholinergic dysfunction may contribute to persistent cognitive deficits for people after traumatic brain injury, improvements in attention, memory, and other aspects of cognition related to the acetylcholine system are expected when cholinergic function is reduced (Arciniegas, 2003).

Table 6.6 The Effect of Donepezil on Memory and Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Zhang et al. (2004) USA RCT PEDro=7 N=18</p>	<p>Population: TBI; <i>Group A</i> (n=9): Mean Age=33yr; Gender: Male=6, Female=3; Mean GCS=9.3; Mean Time Post Injury=4.6mo; <i>Group B</i> (n=9): Mean Age=31yr; Gender: Male=7, Female=2; Mean GCS=8.9; Mean Time Post Injury=3.9. Intervention: In a randomized crossover trial, <i>Group A</i> received oral donepezil for the first 10wk, followed by a washout period of 4wk, then followed by 10wk of placebo. <i>Group B</i> received the treatments in the opposite order. Donepezil was administered at 5mg/d for the first 2wk, and at 10mg/d for the remaining 8wk. Outcome Measure: Auditory (All) and Visual (VII) subtests of Wechsler Memory Scale-III, and the Paced Auditory Serial Addition Test (PASAT).</p>	<ol style="list-style-type: none"> At week 10, <i>Group A</i> achieved significantly better scores in All (95.4±4.5 versus 73.6±4.5; p=0.002), VII (93.5±3.0 versus 64.9±3.0; p<0.001), and in the PASAT (p≤0.001) compared to <i>Group B</i>. This increase in scores in <i>Group A</i> were sustained after washout and placebo treatment (week 24), leading to no significant differences in All (105.9±4.5 versus 102.4±4.5; p=0.588), VII (91.3±3.0 versus 94.9±3.0; p=0.397), and PASAT (p>0.1) compared to <i>Group B</i> at study end. Within-group comparisons showed that patients in both <i>Group A</i> and <i>Group B</i> improved significantly in All and VII (p<0.05), as well as in PASAT (p<0.001), after receiving donepezil.
<p>Khateb et al. (2005) Switzerland Pre-Post N_{initial}=15, N_{final}=10</p>	<p>Population: TBI; Mean age=43yr; Gender: Male=8, Female=7; Mean Time Post Injury=42mo. Intervention: Patients were administered donepezil 5 mg/day for 1mo, followed by 10 mg/day for 2mos. Outcome Measure: Stroop test, Trail Making Test (TMT), Rey Auditory Verbal Memory Test (RAVMT) and Test for Attentional Performance (TAP).</p>	<ol style="list-style-type: none"> 4 of 15 participants stopped due to side effects within the first week (e.g., nausea, sleep disorders, anxiety, dizziness, etc.). Changes on the neuropsychological evaluation show modest improvement, the comparison of the global score of all questionnaires before and after therapy was marginally significant (p=0.058). A significant improvement in executive function was only found for the Stroop Colour naming test (87.3±22.9 to 79.5±19.1, p=0.03); for learning and memory the

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
		RAVMT-learning (47.7±6.9 to 53.5±5.0, p=0.05); and for attention, the errors subsection of divided attention (5.8±3.3 to 2.9±2.7, p=0.03).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

Khateb et al. (2005) found only modest improvement on the various neuropsychological tests used to measure attention. In an RCT, Zhang et al. (2004) demonstrated that donepezil was associated with significantly more improvement in tasks of sustained attention compared to placebo. These improvements were sustained even after the washout period, resulting in non-significant differences between groups after crossover.

Conclusion

There is level 1b evidence that donepezil may improve attention compared to placebo post ABI.

Donepezil can help improve attention in individuals with ABI.

6.2.2.2 Methylphenidate

Methylphenidate is a stimulant whose exact mechanism is unknown (Napolitano et al., 2005). One theory is that methylphenidate acts on the presynaptic nerve to prevent the reabsorption of serotonin and norepinephrine, thereby increasing their concentrations within the synaptic cleft. This in turn leads to increased neurotransmission of serotonin and norepinephrine (Kim et al., 2006). In healthy individuals, methylphenidate has been found to improve memory but not other cognitive functions such as attention, mood, or executive function (Repantis et al., 2010). Methylphenidate is extensively used as a treatment for attention deficit disorder, as well as narcolepsy (Glenn, 1998). No serious side effects have been observed in clinical trials, though there is a lack of evidence for long term safety (Godfrey, 2009).

Table 6.7 The Effect of Methylphenidate on Attention, Concentration, and Processing Speed Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Dymowski et al. (2017) Australia RCT PEDro=9 N _{Initial} =11, N _{Final} =10	Population: TBI. <i>Methylphenidate Group (n=6):</i> Mean Age=35 yr; Gender: Male=4, Female=2; Mean Time Post Injury=366 d; Mean Worst GCS=4.83. <i>Placebo Group (n=4):</i> Mean Age=32.5 yr; Gender: Male=2, Female=2; Mean Time Post Injury=183.5 d; Mean Worst GCS=4.50. Treatment: Participants were randomly assigned to receive either methylphenidate (0.6	1. After applying Bonferroni corrections, no significant differences between groups from baseline to 7 wk, baseline to 8 wk, or baseline to 9 mo were observed for SDMT, TMT A, TMT B, Hayling A, Hayling B, Hayling error, DS Forward, DS Backward, DS Sequencing, DS Total, 2&7 ASRS, 2&7

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>mg/kg/d rounded to the nearest 5mg with maximum daily dose of 60 mg) or placebo (lactose). Outcomes relating to processing speed, complex attentional functioning, and everyday attentional behaviour were assessed at baseline, 7 wk (on-drug), 8 wk (off-drug), and 9mo follow-up.</p> <p>Outcome Measure: Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT) A and B; Hayling (A, B, error), Digit Span (DS-Forward, Backward, Sequencing, Total), Ruff 2&7 Selective Attention Test Automatic Speed Raw Score (2&7 ASRS), Ruff 2&7 Selective Attention Test Controlled Speed Raw Score (2&7 CSRS), Simple Selective Attention Task Reaction Time (SSAT RT), Complex Selective Attention Task Reaction Time (CSAT RT), N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, Rating Scale of Attentional Behaviour Significant Other (RSAB SO).</p>	<p>CSRS, SSAT RT, CSAT RT, N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, or RSAB SO.</p>
<p>Zhang and Wang (2017) China RCT PEDro=10 N_{Initial}=36, N_{Final}=33</p>	<p>Population: TBI; Severity: mild to moderate. <i>Methylphenidate Group (n=18):</i> Mean Age=36.3 yr; Gender: Male=13, Female=5. <i>Placebo Group (n=18):</i> Mean Age=34.9 yr; Gender: Male=14, Female=4.</p> <p>Treatment: Participants were randomly assigned to receive methylphenidate (flexibly titrated from 5 mg/d at the beginning, then gradually increased by 2.5 mg/d until reaching 20 mg/d) or placebo for 30 wk.</p> <p>Outcome Measure: Mental Fatigue Scale (MFS), Choice Reaction Time (CRT), Compensatory Tracking Task (CTT), Mental Arithmetic Test (MAT), Digit Symbol Substitution Test (DSST), Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAMD).</p>	<ol style="list-style-type: none"> 1. At baseline, there were no significant differences between groups in terms of demographics, MFS, CRT, CTT, MAT, DSST, MMSE, BDI, or HAMD. 2. Post-intervention, the experimental group had significantly lower scores compared to control group for MFS (p=0.005), CRT (p<0.001), CTT (p<0.001), BDI (p=0.040), and HAMD (p=0.005). 3. Post-intervention, the experimental group had significantly higher scores compared to control group for MAT (p=0.020), DSST (p<0.001), MMSE (p<0.001).
<p>Willmott et al. (2013) Australia RCT PEDro=10 N=32</p>	<p>Population: TBI; Gender: Male=21, Female=11; Mean Time Post Injury=68 d; <i>TBI Val/Val Group (n=11):</i> Mean Age=22.64 yr; Mean GCS=4.67; <i>TBI Val/Met Group (n=14):</i> Mean Age=28.57 yr; Mean GCS=5.38; <i>TBI Met/Met Group (n=7):</i> Mean Age=30.57 yr; Mean GCS=6.83.</p> <p>Intervention: Participants with TBI, in a crossover design, received 0.3 mg/kg methylphenidate (2 x/d) for 6 sessions in total (spanning 2 wk), alternating between treatment and placebo for every other session. Results were compared against those from healthy controls (n=40). Groups were stratified by the presence of the Val158Met gene.</p> <p>Outcome Measures: Ruff 2 & 7 Selective Attention Test – automatic (2 & 7 ASRS) and controlled (2 & 7 CSRS), Selective Attention</p>	<ol style="list-style-type: none"> 1. At baseline, there were no significant differences across various genotypes on attentional performance. 2. Participants with TBI and Met/Met alleles performed significantly poorer on the SDMT (p<0.0005), 2 & 7 ASRS (p=0.001), 2 & 7 CSRS (p<0.0005), DC RT (p=0.005), and SI RT (p=0.002), when compared to controls. Analyses with participants with TBI and Val/Val alleles showed even worse outcomes, demonstrating poorer performance on 7/8 outcome measures. 3. Following methylphenidate treatment one significant drug and genotype interaction was seen between Met/Met carriers and performance on

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	Task, Four Choice Reaction Time Task (4CRT) – dissimilar compatible (DC) and similar incompatible (SI), Symbol Digit Modalities Test (SDMT), Letter Number Sequencing Task, Wechsler Test of Adult Reading.	the SDMT (F=4.257; p=0.024), suggesting Met/Met carriers were more responsive to methylphenidate than either the others.
<p>Kim et al. (2012) USA RCT PEDro=7 N=23</p>	<p>Population: Moderate/Severe TBI; Mean Age=34.2 yr; Gender: Male=18, Female=5; Mean Time Post Injury=51.1 mo. Intervention: In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate followed by placebo, or the reverse and were assessed after each. Outcome Measure: Visual sustained attention task (VSAT), Two-back task.</p>	<ol style="list-style-type: none"> 1. Relative to placebo, both accuracy (1.62±1.03 versus 2.23±1.07; p<0.005) and mean reaction time (827.47±291.17s versus 752.03±356.87s; p<0.050) in the VSAT were improved significantly on MPH. 2. Relative to placebo, mean reaction time (929.31±192.92s versus 835.02±136.12s; p<0.050), but not accuracy, in the two-back task was improved significantly when on MPH.
<p>Willmott & Ponsford (2009) RCT PEDro=10 N=40</p>	<p>Population: TBI; Mean Age=26.93 yr; Gender: Male=28, Female=12; Time since injury=68.38 d. Intervention: Patients received either methylphenidate (0.3 mg/kg 2 x/d, rounded to the nearest 2.5 mg) or a placebo. Patients were seen for 6 sessions across 2 week period. Patients then crossed-over. Outcome Measure: Ruff 2 and 7 Selective Attention Test, Selective Attention Task, Four Choice Reaction Time Task, Sustained Attention to Response Task, Symbol Digit Modalities Test, Letter Number Sequencing Task, Wechsler Test of Adult Reading.</p>	<ol style="list-style-type: none"> 1. Methylphenidate significantly increased speed of information processing on the Symbol Digit Modalities Test (p=0.020); Ruff 2 and 7 Test-Automatic Condition (p=0.003); Simple Selective Attention Task (p=0.001); Dissimilar compatible (p=0.003), and Similar Compatible (p=0.002).
<p>Kim et al. (2006) Korea RCT PEDro=6 N=18</p>	<p>Population: TBI; <i>Methylphenidate Group (n=9):</i> Mean Age=30.1 yr; Gender: Male=9, Female=0; Mean Time Post Injury=1.6 yr; <i>Placebo Group (n=9):</i> Mean Age=38.3 yr; Gender: Male=7, Female=2; Mean Time Post Injury=3.6 yr. Intervention: Patients were randomly allocated to receive either 20 mg methylphenidate or the placebo. Assessments were done at baseline (T1), 2 hr post treatment (T2), and 2 d later (T3). Outcome Measure: Visual sustained attention task (VSAT), Two-back task.</p>	<ol style="list-style-type: none"> 1. At T1 there were no significant differences in mean reaction time or in accuracy between the two groups. 2. For those in the treatment group, the mean reaction time of the two-back task improved significantly compared to those in the placebo group from T1 to T2 (13.74±13.22% versus 4.02±9.48%; p<0.05). 3. No significant difference in improvement as seen with accuracy of the two-back task (p=0.07), nor with the VSAT.
<p>Whyte et al. (2004) USA RCT PEDro=8 N=34</p>	<p>Population: TBI; Mean Age=37 yr; Gender: Male=29, Female=5; GCS<12; Median Time Post Injury=3.2 yr. Intervention: Participants received 0.3 mg/kg/dose methylphenidate for 3 wk, 2x/d, and placebo for 3 wk, for a total of 6 wk, with conditions alternating weekly. Washout lasted a day, after which time the groups crossed over. Outcome Measure: Attention Tasks.</p>	<ol style="list-style-type: none"> 1. Methylphenidate showed significant improvements in information processing speed (p<0.001), work task attentiveness (p=0.010), and caregiver attention ratings (p=0.010), pre-post. 2. No treatment-related improvements were observed in susceptibility to distraction, and divided or sustained attention.

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Plenger et al. (1996) USA RCT PEDro=5 N=23</p>	<p>Population: TBI; Gender: Male=17, Female=6; <i>Placebo Group (n=13)</i>: Mean Age=26.6 yr; Mean GCS=8.1; <i>Methylphenidate Group (n=10)</i>: Mean Age=31.4 yr; Mean GCS=9.3. Intervention: Patients were randomly allocated to receive either methylphenidate or placebo. Methylphenidate was administered at 30 mg/kg, 2x/d, for 30 d. Outcome Measure: Disability Rating Scale (DRS), Continuous Performance Test (CPT), 2 & 7 Test (2 & 7), Paced Auditory Serial Addition Test (PASAT), Digit Span & Attention/ Concentration from Wechsler Memory Scale-Revised (Attn/Conc from WMS-R).</p>	<ol style="list-style-type: none"> At 30 d follow-up (n=15), significant differences were obtained on DRS, suggesting better outcome for the methylphenidate group. This difference however was not seen at 90 d follow-up (n=11). Significant differences were found on the attention-concentration domain at the 30 d follow-up, as indicated by CPT, PASAT, 2 & 7, and Attn/Conc from WMS-R (p<0.030). The treatment group performed better in these measures compared to the placebo group.
<p>Speech et al. (1993) USA RCT PEDro=7 N=12</p>	<p>Population: TBI; Mean Age=27.6 yr; Gender: Male=5, Female=7; Mean Time Post Injury=48.5 mo. Intervention: In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate, 2 x/d, for 1 wk, followed by 1 wk of placebo, or receive the treatment in the reverse order. Outcome Measure: Gordon Diagnostic System, Digit Symbol and Digit Span subtests of the Wechsler Adult Intelligence Scale-Revised, Stroop Interference Task, Sternberg High Speed Scanning Task, Selective Reminding Test, Serial Digit Test, Katz Adjustment Scale.</p>	<ol style="list-style-type: none"> No significant differences were found between methylphenidate and placebo condition in any of the outcome measures studied.
<p>Pavlovskaysa et al. (2007) Pre-Post Israel N=6</p>	<p>Population: TBI; Age Range=18-47 yr; Gender: Male=4, Female=2; GCS ≥8. Intervention: Participants were administered 5 to 10 mg of methylphenidate (MHP) over a 2 week period. Participants were evaluated before, during and after the administration of methylphenidate. Outcome Measure: Performance on the Visual Spatial Attention Task Analyzing Rightward and Leftward Shifts of Attention.</p>	<ol style="list-style-type: none"> Prior to treatment, patients were found to have great difficulty in shifting attention between hemifields. There was a significant improvement in the asymmetry with MHP (p<0.001). The right side performance was significantly better on average than the left side (0.77 versus 0.59; p<0.050). Performance was significantly better for ipsilateral valid cueing (p<0.010) than for invalid cross-trials (p<0.001). The difference between ipsi- and cross-cueing for left side target performance is significant for each of the stages (p<0.001).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In an RCT, Whyte et al. (2004) indicated that speed of processing, attentiveness during individual work tasks and caregiver ratings of attention were all significantly improved with methylphenidate treatment. No treatment related improvement was seen in divided or sustained attention, or in susceptibility to distraction. Similarly, Plenger et al. (1996) and Pavlovskaysa (2007) found that methylphenidate significantly improved attention and

concentration, and visuo-spatial attention, respectively

Speech et al. (1993) conducted a double blind placebo controlled trial evaluating the effects of methylphenidate following closed head injury. In contrast to the results noted by Whyte et al. (2004) and Plenger et al. (1996), methylphenidate did not demonstrate significant differences compared to placebo on measures of attention, information processing speed, or learning. Kim et al. (2006) examined the effects of a single-dose treatment of methylphenidate and, although a trend was found in favour of improved working and visuospatial memory for the treatment group, these results did not reach significance. Recently, Kim et al. (2012) found that reaction time improved significantly while on the methylphenidate. This is in line with Willmott and Ponsford (2009) who found that administering methylphenidate to a group of patients during inpatient rehabilitation, did significantly improve the speed of information processing. Conflicting results continue to be reported, as two high-quality RCTs reached different conclusions regarding methylphenidate use. While Dymowski et al. (2017) noted no improvements in any measures of attention and mental processing, Zhang and Wang (2017) noted improvements in reaction time, arithmetic tests, and even mental health outcomes after intervention by methylphenidate.

In a recent RCT conducted by Willmott et al. (2013), the authors hypothesized that an individuals' response to methylphenidate depends on their genotype. More specifically, that individuals possessing the methionine (Met) allele at the catechol-O-methyltransferase (COMT) gene would confer greater response to methylphenidate compared to those with the valine (Val) allele. While both Met/Met and Val/Val carriers performed more poorly in various attentional tasks compared to healthy controls, Met/Met carriers did show greater improvements in strategic control in attention than Val/Val carriers. As well, the authors were able to identify one significant drug and genetic interaction between Met/Met carriers and performance on the Symbol Digit Modalities Test (SDMT). These findings suggest Met/Met carriers may in fact be more responsive to methylphenidate than individuals with the Val genotype. However, further studies are needed to draw firm conclusions.

Conclusions

There is conflicting level 1b evidence regarding the effectiveness of methylphenidate following brain injury for the improvement of attention and concentration in individuals post ABI.

There is level 1a evidence that methylphenidate improves reaction time of working memory compared to placebo in individuals post ABI.

The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear.

Methylphenidate is effective in improving reaction time for working memory.

Response to methylphenidate may depend on genotype.

6.2.2.3 Bromocriptine

Bromocriptine is a dopaminergic agonist which exerts its effects primarily through the binding of D₂ receptors (Whyte et al., 2008). It has been suggested that dopamine is an important neurotransmitter for prefrontal function (McDowell et al., 1998). In a study looking at the effects of bromocriptine on rats, Kline et al. (2002) noted that the animals showed improvement in working memory and spatial learning; however, this improvement was not seen in motor abilities. Two studies have been identified investigating the use of bromocriptine as an adequate treatment for the recovery of cognitive impairments following brain injury.

Table 6.8 The Effect of Bromocriptine on Attention Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
Whyte et al. (2008) USA RCT PEDro=7 N=12	<p>Population: Moderate/ Severe TBI; Mean Age=35.75 yr; Gender: Male=8, Female=4; Median Time Post Injury=3.3 yr.</p> <p>Intervention: In a crossover design, participants were randomly assigned to receive bromocriptine (1.25 mg 2x/d titrated to 5mg 2x/d over a 1 wk), followed by placebo or the reverse order. Each lasted 4 wk with a 1 wk washout period.</p> <p>Outcome Measure: Attention Tasks.</p>	<ol style="list-style-type: none"> 1. Though some improvements were observed in certain subtests of attentional tasks (e.g. speed decline, decline in responding, test of everyday attention), they were not significant. 2. Overall results suggest bromocriptine had little effect on attention.
McDowell et al. (1998) USA RCT PEDro=4 N=24	<p>Population: TBI; Median Age=32.5 yr; Gender: Male=20, Female=4; GCS Range=3-8; Time Post injury Range=27d-300 mo.</p> <p>Intervention: In a crossover design, participants were randomly assigned to receive 2.5 mg bromocriptine followed by placebo, or the reverse order.</p> <p>Outcome Measure: Dual-task paradigm (counting and digit span), Stroop Test, spatial delayed-response task, Wisconsin Card Sorting Test (WCST), reading span test, Trail Making Test (TMT), controlled oral word association test (COWAT), Control tasks.</p>	<ol style="list-style-type: none"> 1. Following bromocriptine treatment there were significant improvements on the dual-task counting (p=0.028), dual-task digit span (p=0.016), TMT (p=0.013), Stroop Test (p=0.05), COWAT (p=0.02), and WCST (p=0.041). 2. Bromocriptine had no significant effects on working memory (e.g. spatial delayed-response task and reading span test; p=0.978), or on control tasks (p=0.095).

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The question of whether bromocriptine improves cognitive function in patients with ABI was explored in two RCTs (McDowell et al., 1998; Whyte et al., 2008). In an earlier investigation, low-dose bromocriptine (2.5 mg daily) improved functioning on tests of executive control including a dual task, Trail Making Test, the Stroop test, the Wisconsin Card Sorting Test and the controlled oral word association test (McDowell et al., 1998). However, bromocriptine did not significantly influence working memory tasks. Further, a study by Whyte et al. (2008) found that bromocriptine had little effect on attention. It was noted that several participants did experience moderate to severe drug effects and withdrew or were withdrawn from the study.

Although McDowell et al. (1998) demonstrated some benefits following administration of bromocriptine, there was only a single administration of bromocriptine and the dose was considerably lower than that given by Whyte et al. (2008). Spontaneous recovery may have been a factor leading to the improved abilities in individuals receiving a single dose (2.5 mg

daily) of the medication; however, study results did not answer this question. Results from Whyte et al. (2008) noted that the placebo group demonstrated better (although not significant) trends in improvement on the various tasks administered..

Conclusions

There is level 1b evidence that bromocriptine compared to placebo does not improve performance on attention tasks in patients post TBI.

There is level 2 evidence that bromocriptine improves attention, compared to placebo post ABI.

Bromocriptine might improve executive function, but not memory, attention, or reading ability in patients post TBI.

6.2.2.4 Cerebrolysin

As explained by Alvarez et al. (2003), “Cerebrolysin (EBEWE Pharma, Unterach, Austria) is a peptide preparation obtained by standardized enzymatic breakdown of purified brain proteins, and comprises 25% low-molecular weight peptides and free amino acids” (pg. 272). Cerebrolysin has been demonstrated to have neuroprotective and neurotrophic effects, and has been linked to increased cognitive performance in an elderly population.

Table 6.9 The Effect of Cerebrolysin on Attention Post ABI

Author/Year/ Country/Study Design/N	Methods	Outcomes
Alvarez et al. (2003) Spain Pre-Post N=20	<p>Population: TBI; Mean Age=30.1 yr; Gender: Male=15, Female=5; Mean GCS=6.1; Time Post Injury Range=23-1107 d.</p> <p>Intervention: Patients with TBI received a total of 20 intravenous infusions of cerebrolysin solution (30 mL/infusion) over 4 wk. Assessments were made at baseline, during treatment, and after the 4 wk treatment period.</p> <p>Outcome Measure: Syndrome Kurztest (SKT), Electroencephalogram (EEG)/brain mapping recordings, Glasgow Outcome Scale (GOS).</p>	<ol style="list-style-type: none"> 1. Compared to baseline, patients with TBI showed a significant decrease in slow bioelectrical activity frequencies (delta: $p < 0.010$; theta: $p < 0.050$), and a significant increase in fast frequencies (beta: $p < 0.010$) after receiving cerebrolysin, suggesting improvement in brain bioelectrical activity. 2. Significant improvements in SKT performance was noted from pre to post treatment (15.9 ± 2.4 versus 12.0 ± 2.1; $p < 0.010$). 3. GOS scores significantly improved from pre to post treatment (3.7 ± 0.3 versus 3.95 ± 0.3; $p < 0.050$).

Discussion

In an open-label trial of 20 patients with TBI Alvarez et al. (2003) found that cerebrolysin was associated with improved brain bioelectrical activity, as evidenced by a significant increase in fast beta frequencies. A brief neuropsychological battery (Syndrome Kurztest) consisting of nine subtests was administered to evaluate memory and attentional functions in patients undergoing treatment with cerebrolysin. There was an overall significant improvement in performance post treatment, suggesting patients experienced cognitive benefits from cerebrolysin treatment.

Improvements were also seen in terms of neurological recovery, as measured by the Glasgow Outcome Scale (Alvarez et al., 2003). Together these findings suggest that cerebrolysin may represent an effective neuroprotective therapy with tangible cognitive benefits for individuals living with an ABI. However, controlled trials are necessary to further explore the efficacy of this drug.

Conclusions

There is level 4 evidence that cerebrolysin may improve attention scores post ABI.

Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy.

6.2.2.5 Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors prevent the enzyme acetylcholinesterase from breaking down acetylcholine. This increases the concentration of acetylcholine in synapses. Acetylcholine has been most strongly linked with the hippocampus and memory deficits, however it is also implicated in attentional processing.

Table 6.10 The Effect of Rivastigmine on Attention and Processing Speed Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Silver et al. (2006) USA RCT PEDro=9 N=123</p>	<p>Population: TBI. <i>Rivastigmine</i> (n=80): Mean Age=37 yr; Gender: Male=53, Female=27. <i>Placebo</i> (n=77): Mean Age=37.1 yr; Gender: Male=53, Female=24. Intervention: Participants were randomized to receive either rivastigmine (3-6 mg/d) or placebo. At the end of the first 4 wk, rivastigmine doses were increased to 3.0 mg, 2x/d. If necessary doses were decreased to 1.5 mg or 4.5 mg 2x/d. Outcome Measure: Trails A and B, Hopkins verbal learning test (HVLt), Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing (CANTAB RVIP A).</p>	<ol style="list-style-type: none"> Results of the CANTAB RVIP A' and HVLt found no significant differences between the placebo group and the treatment group. Rivastigmine was found to be well tolerated and safe.
<p>Silver et al. (2009) USA Pre-Post N=127</p>	<p>Population: TBI. <i>Ex-Rivastigmine</i> (n=65): Mean Age=36.9 yr; Gender: Male=43, Female=22; Time Post Injury=73.5 mo. <i>Ex-placebo</i> (n=62): Mean Age=38 yr; Gender: Male=42, Female=20; Time Post Injury=100.1 mo. Intervention: Participants were randomized to receive rivastigmine injections (1.5 mg 2x/d to a max of 12 mg/d) or placebo injection.</p>	<ol style="list-style-type: none"> The mean final dose of rivastigmine was 7.9 mg/day. 40% of patients were responders on CANTAB RVIP A' or HVLt score at week 38. At the end of the study period all (n=98) were seen to improve of the CANTAB RVIP A' (p<0.001), the HVLt (P<0.001), and the Trails A and B (p<0.001).

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	Outcome Measure: Trails A and B, Hopkins verbal learning test (HVLTL),Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).	

Discussion

In two studies rivastigmine was administered to patients who had sustained a moderate to severe TBI (Silver et al., 2006; Silver et al., 2009). Results from both studies indicate that rivastigmine improved cognitive function and memory impairment, although results were not significant. In Silver’s (2009) follow-up open-label cohort study to their original RCT, participants (n=98) showed significant improvement on the CANTAB RVIP A’, the HVLTL and the trail A and B scales at the end of 38 week study period; however when further sub-analysis was performed depending on what group the patient previously belonged to, those in the ex-rivastigmine group to those in the ex-placebo group, the improvements were not significant.

Conclusions

There is level 1b evidence that Rivastigmine compared to placebo may not be effective for improving concentration or attention in individuals post

Rivastigmine may not be effective in treating attention deficits post-ABI.

6.3 Rehabilitation of Learning and Memory Deficits

Memory impairment is one of the most common symptoms following brain injury and it is estimated that time and cost of care would be reduced if effective treatments were found to improve memory (Walker et al., 1991). When evaluating intervention strategies to improve memory performance following brain injury, the literature indicates that there are two main approaches to rehabilitation: restoration/retraining of memory, and compensation of deficits. Compensation includes “training strategies or techniques that aim to circumvent any difficulty that arises as a result of the memory impairment.” (McLean et al., 1991). Compensatory techniques include internal aids, which are “mnemonic strategies that restructure information that is to be learned.” (McLean et al., 1991). (McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)(McLean et al., 1991)On the other hand, various interventions have focused on the remediation of memory deficits in individuals with TBI, ranging from interventions that include assistive technology to visual imagery. Several studies were identified examining interventions to improve learning and memory following ABI. Studies were categorized into the following groupings: assistive technology (external aids, computer assisted training and virtual reality and cognitive functioning), internal strategies used during learning to enhance recall, memory interventions and cranial electrotherapy stimulation and memory.

Cicerone et al. (2000) reviewed 42 studies examining the effectiveness of various interventions to improve memory impairment following stroke and TBI. In 2005 and again in 2011, Cicerone and colleagues updated their original review (2005; 2011). It should be noted that studies were not included in our review if the population did not comprise of more than 50% brain-injured patients, or if the sample size (n) was less than 3. As well only those studies dealing with moderate-to-severe brain-injured individuals were included in this review.

Cappa and colleagues (2005) reviewed various strategies used to improve memory deficits without the use of electronic devices, external aids were judged to be “possibly effective.” Specific learning strategies (e.g. errorless learning) were found to be “probably effective” depending upon the task used, the type of memory involved and the severity of impairment.

6.3.1 Non-Pharmacological Interventions

6.3.1.1 Assistive Devices

Assistive devices for aiding learning and memory can include anything from physical or external devices to internal memory strategies. The following section discusses a variety of aids which can be used to support individuals with memory or learning deficits as a result of an ABI.

6.3.1.1.1 External Technology Aids

External aids, of which there are active or high tech (computers, personal digital assistants (PDAs), and mobile phones) devices and passive or low tech/no tech (calendars, diaries, lists, timetables and dictaphones) devices, have been shown to assist memory (McDonald et al., 2011). As active aids become more readily available, there is a greater need to study their effectiveness in helping those with an ABI deal with prospective memory impairments. Included here are studies which examined how external aids, both active and passive, could be used to enhance memory following brain injury.

Cicerone et al. (2000) recommended that the use of memory notebooks or other external aids “may be considered for persons with moderate to severe memory impairments after TBI (and) should directly apply to functional activities, rather than as an attempt to improve memory function per se.”

Table 6.11 The Effect of External Aids on Memory Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Gracey et al. (2017) UK RCT PEDro=6 N_{Initial}=74, N_{Final}=59</p>	<p>Population: CVA=23, Infection=3, TBI=33, Tumor=10, Missing=1. <i>Control First (n=34):</i> Mean Age=50.18 yr; Gender: Male=23, Female=11; Mean Time Post Injury=8.62 yr. <i>Assisted Intention Monitoring (AIM, n=36):</i> Mean Age=46.36 yr; Gender: males=23, females=13; Mean Time Post Injury=4.89 yr. Treatment: Participants were randomized to receive AIM or control first. In the AIM-first group, participants received goal management training followed by text messages for improving achievement of everyday intentions. Control-first group</p>	<ol style="list-style-type: none"> 1. Participants achieved a greater proportion of intentions during the AIM intervention relative to control (p=0.040). 2. Participants achieved a greater proportion of goal attainment (without the phone call task) during the AIM intervention relative to control (p=0.033). 3. No significant Group x Time interaction effect was found for the POMS MD or Hotel Test. 4. When only comparing group differences at post-intervention phase 1, intention to treat analysis showed no significant

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>received brain injury information, Tetris game, and non-informational text messages. After 3 wk, participants were crossed over with AIM-first group receiving usual care and control-first group receiving AIM.</p> <p>Outcome Measure: Mean daily proportion of intentions achieved, Achievement of all goals excluding the phone call task, Profile of Mood States total mood disturbance (POMS MD), Hotel Task, Verbal Fluency.</p>	<p>difference between groups for proportion of intentions achieved or achievement of goals excluding the phone task.</p>
<p>O’Neill et al. (2017) UK RCT PEDro=7 N_{Initial}=27, N_{Final}=24</p>	<p>Population: TBI=16, Subarachnoid hemorrhage=3, Other=5; Mean Age=45.14 yr; Gender: Male=22, Female=2; Mean Time Post Injury=5.53 yr; Severity: severe.</p> <p>Treatment: Participants were randomly assigned to experimental (n=10) or control group (n=14), and assessed before (baseline), during, and after intervention (return to baseline). Experimental group participants received Guide, an audio-verbal interactive micro-prompting software designed to emulate the verbal prompts and questions provided by carers or support workers. Control group participants received rehabilitation as usual.</p> <p>Outcome Measure: Morning Checklist (number of support worker prompts, number of safety critical and general errors, deviations from and repetitions of the necessary sequence), Satisfaction score (5-point scale).</p>	<ol style="list-style-type: none"> 1. Compared to baseline, there was a significantly greater reduction in the intervention group than the control group during (p<0.010) and after (p<0.010) the intervention for the number of prompts needed. 2. There were no significant differences between groups across the three phases in terms of number of errors, sequence errors, or satisfaction scores.
<p>Lannin et al. (2014) Australia RCT PEDro=8 N=42</p>	<p>Population: TBI; Mean Age=33.5 yr; Gender: Male=26, Female=16; Mean Time Post Injury=9.2 yr.</p> <p>Intervention: Participants were randomly allocated to either the experimental group (EG; n=21), who received 8 weeks of training in the use of a personal digital assistant (PDA) with an occupational therapist, or the control group (CG; n=21) who received 8 weeks of traditional occupational therapy. Training sessions for the EG focused on PDA training for application and organization into everyday life.</p> <p>Outcome Measure: Goal Attainment Scale (GAS), Memory Functioning Questionnaire (MFQ) and Memory Compensation Questionnaire (MCQ).</p>	<ol style="list-style-type: none"> 1. There was a significant difference between EG and CG groups in the functional memory failures subset of the GAS (p=0.0001); however, the total GAS score was not significant between groups (p=0.165). 2. The caregiver report on the frequency of forgetting and retrospective memory subset of the MFQ were significant between groups (p=0.021, p=0.042 respectively); however, seriousness of forgetting and mnemonic usage subset of the MFQ were not significant between groups (p=0.455, p=0.301 respectively) 3. Internal strategies subset of the MCQ was significant between groups (p=0.021); however, external strategies subset of the MCQ was not significant between groups (p=0.580).
<p>Powell et al. (2012) USA RCT PEDro=7</p>	<p>Population: TBI=23, ABI=6; Mean Age=42.31 yr; Gender: Male=17, Female=12; Mean Time Post Injury=13.59 yr.</p>	<ol style="list-style-type: none"> 1. Those receiving systematic instruction performed significantly more (p<0.01) correct tasks at the 30 d follow-up

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
N=29	<p>Intervention: Patients were assigned to either the systematic instruction group (n=15) or the conventional group (control; n=14). The systematic group was based on direct instruction and mastery, rather than exploratory learning (e.g., errorless learning). The control group received conventional, trial and error learning (e.g., errorful learning). Participant’s sessions targeted selected skills on a personal digital assistant (PDA; Palm Tungsten E2). All participants received 12 sessions (45 min, 2-3 x/wk for 4-6 wk).</p> <p>Outcome Measure: Assessment of PDA skills, California Verbal Learning Test II-Short Form, Wechsler Memory Scale III (Logical Memory, Visual Reproduction), Controlled word Association Test, Trail Making A and B.</p>	<p>compared to participants receiving the conventional instruction.</p> <ol style="list-style-type: none"> Those receiving systematic instruction also performed the correct tasks more quickly (16 sec) than the conventional instruction group (41.15 vs 57.73 sec, p=0.050). Fluency scores (ability to follow through with a task) were also found to be higher in those in systematic instruction group compared to those in the conventional instruction group at 30 d follow-up (p=0.050). There was no statistically significant main effect on treatment condition for content generalization. Overall systematic instruction resulted in better environmental generalization compared to trial and error learning (p<0.050) at post-test, but not 30d follow-up.
<p>Dowds et al. (2011) USA RCT PEDro=5 N=36</p>	<p>Population: TBI patients: Mean age: 42.1 yr (Age Range: 16-66 yr); Gender: male=17, female=19;</p> <p>Intervention: Participants were trained on how to use two Personal Digital Assistant devices (Palm OS and Microsoft OS device) to assist them in organizing activities that needed to be completed throughout the week.</p> <p>Participants were randomly assigned to four memory aid conditions (Palm OS, Microsoft OS, Combined Baseline, or paper organizer) in a crossover fashion.</p> <p>Outcome Measure: Timely completion rates.</p>	<ol style="list-style-type: none"> When using the PDAs the individuals had a higher task completion rate than when they used paper memory aids (Palm OS: p<0.005; Microsoft OS: p<0.001). Results also indicated that those using the Palm OS PDA had a higher completion rate than those using the Microsoft OS PDA (p<0.0005).
<p>Lemoncello et al. (2011) USA RCT PEDro=5 N=23</p>	<p>Population: Group A (n=12): Mean age=47.17 yr, Mean time post-injury=9 yr; Group B (n=11): Mean age=47.55 yr, Mean time post-injury=12.45 yr.</p> <p>Intervention: Patients were randomly assigned to group A or group B. In group A participants were assigned to use the Television Assisted Prompting (TAP) system, which gave them personalized task reminders through their television, in the crossover phase participants used their own typical practice (TYP) strategies of remembering what tasks they had to complete. In group B participants started with the TYP phase, and then at crossover used the TAP system.</p> <p>Outcome Measure: Task completion.</p>	<ol style="list-style-type: none"> No significant differences were found between groups A or B; therefore data from the two groups was collapsed. Task completion was significantly better when participants used the TAP condition (72%) versus the TYP condition (43%). In the TAP condition participants completed significantly more experimental tasks compared to either preferred (p=0.01) or non-preferred tasks (p=0.01).
<p>Wilson et al. (2001) UK RCT</p>	<p>Population: Mean Age: 38.57 yr; Gender: Male=105, female=38; Mean Time Post-</p>	<ol style="list-style-type: none"> During the last 2 weeks of the 7-week treatment period, the participants using the pager were significantly more

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
PEDro=4 N=143	<p>Injury: 4.9 yr; Condition: TBI=63 (44.1%), Stroke=36 (25.2%), Other ABI=44 (30.7%).</p> <p>Intervention: After a 2 week baseline patients were randomized into two groups: Group A received a pager first and Group B was put on a waiting list. After 7 weeks of treatment patients switched conditions. Measures were taken during the last 2 weeks of each treatment period/ Patients chose their own tasks in which they wanted to be reminded.</p> <p>Outcome Measure: Patients' Ability to Successfully Carry out Everyday Tasks.</p>	successful in achieving target behaviors than the waiting list group (p<0.001).
<p>Evald et al. (2015) Denmark Pre-Post N=13</p>	<p>Population: TBI; Mean Age=41.5 yr; Gender: Male=11, Female=2; Mean Time Post Injury=11 yr; Mean GCS=6.6.</p> <p>Intervention: Participants underwent memory training using smartphones (1 individual and 5 group sessions, 1.5 hr/session, 1 session/wk, for 6 weeks). In the individual session participants were instructed on smartphone setup. During the group sessions participants were instructed on compensatory memory strategies using appointment, tasks and contacts applications. Each group session was completed in 4 steps; 1) introduction to the memory strategy, 2) demonstration of the application, 3) exercises with examples and 4) homework instructions.</p> <p>Outcome Measure: Self-reported measures of overview, memory, stress and fatigue.</p>	<ol style="list-style-type: none"> 1. 5 of the 13 participants reported memory improvements following smartphone use, while the remaining reported no change. 2. 3 of the 13 participants reported stress improvements following smartphone use while the remaining reported no change. 3. 1 of the 13 participants reported fatigue improvements following smartphone use while the remaining reported no change. 4. 9 of the 13 participants reported a positive overview of smartphone use while the remaining reported no change. 5. There were no negative events reported.
<p>Gentry et al. (2008) Canada Pre-Post N=23</p>	<p>Population: TBI patients: Age Range 18-66 yr; Gender: Male=16, Female=7; Time Post-Injury=1-34 yr.</p> <p>Intervention: Participants were each given a PDA and trained in how to use by an occupational therapist (OT).</p> <p>Outcome Measure: Craig Handicap Assessment and Rating Technique Revised (CHART); Canadian Occupational Performance Measure (COPM).</p>	<ol style="list-style-type: none"> 1. On the COPM, improvements were noted when looking at post training performance and post training satisfaction (p<0.001). 2. Scores on the CHART-R self-assessment rating scale showed improvement as well post-training (p<0.001). 3. Significant improvement was seen on the scores of the cognitive independence, mobility, and occupation subsections of the test (p<0.001).
<p>Fish et al. (2007) UK Case Series N=20</p>	<p>Population: Age Range: 19-60 yr; Gender: Male=15, Female=5; Condition: TBI=14, Other=6.</p> <p>Intervention: Participants were trained to associate the text message 'STOP' with a cue for participants to stop and think about what needed to be done, what they were doing etc. Participants were asked to make telephone calls at specific times of the day for a 3-week period. Over the 3-week period on 5 randomly selected days a text message "STOP" was sent to participants.</p>	<ol style="list-style-type: none"> 1. During the first week 15% of the participants failed to make the calls. 2. The effect of cueing on participants had a significant impact on the number of calls made (p<0.001). 3. Participants made 87.6% of calls when cued but only 71.2% of calls when they were not cued. 4. Of note there was a positive relationship between the number of calls made (completed) and the time in which they were made (within 5 minutes of the target)

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	Outcome Measure: Completion of task.	time).
Hart et al. (2002) USA Pre-Post N=10	Population: TBI: Mean Age: 31.5 yr; Gender: male=8, female=2. Intervention: Individualised current therapy goals were randomly assigned to a portable voice organizer (n=3) or not having an organizer (n=3), 2-5 days per week. Outcome Measure: Recall of goals.	1. Recorded goals were recalled significantly better than unrecorded goals (p<0.010).
Burke et al. (2001) USA Pre-Post N=5	Population: Mean Age: 50 yr; Condition: TBI=3, SAH=2. Intervention: Assessing patient’s ability to use a patient locator and minder (PLAM) system to assist in their adherence to therapy schedules. Patients were prompted by hospital staff about appointment times when necessary. Outcome Measure: Number of human prompts necessary to direct a patient to a therapy destination.	1. Average number of human prompts declined significantly using the PLAM system by more than 50% (p<0.001) and the number of sessions requiring no prompting increased from 7 to 44% (p<0.005). 2. Patients arrived on average 1.3 minutes earlier using PLAM – a 6.1 minute improvement over baseline.
Wright et al. (2001a) UK Pre-Post N=12	Population: Mean Age: 39 yr; Gender: male=10, female=2; Mean Time Post-Injury 3 yr; Condition: TBI=9, Subarachnoid Hemorrhage=2. Intervention: Two different computer aid formats for 2 months (with a one month gap between machines). Outcome Measure: Attitudes, Usage, Relation to Psychometric Factors.	1. Appointment diary was used more than any other aid. 2. High users made more new diary entries (p<0.060) suggesting a conceptual understanding of how to use memory aids in everyday living was a prerequisite for benefiting from them.
Wright et al. (2001b) UK Pre-Post N=12	Population: Mean Age: 34 yr; Gender: male=6, female=6; Mean Time Post-Injury=6 yr. Intervention: Two-month comparative study of Casio and HP electronic organizers (one month break between brands). Outcome Measure: Frequency of use.	1. No significant correlations between any single psychometric measure and organizer entries. 2. People accustomed to using memory aids (any type) made more use of pocket computers (p<0.070). 3. Low frequency users were put off organizers when it had a physical keyboard (p<0.010). 4. High frequency users used the keyboard more (p<0.070).
Kim et al. (2000) USA Case Series N=12	Population: Age Range: 22-67 yr; Gender: male=8, female=4; Condition: TBI=11, CVA=1; Intervention: Supervised usage trial of a palmtop computer that included scheduling software capable of generating audible reminder cues. Outcome Measure: Survey of subjects’ use of computer as an aid.	1. Nine subjects (75%) reported that the palmtop computer had been a useful tool. 2. Seven of these 9 patients expressed that they continued to use the computer following the completion of the study. 3. All patients recommended that the computer continue to be used in outpatient brain injury rehabilitation.
van den Broek et al. (2000) UK Case Series N=5	Population: Age Range: 25-56 yr; Gender: male=4, female=1; Time Post Injury: 19-54 mo; Condition: TBI=1, ABI=4. Intervention: Evaluate the effectiveness of the external aid “the Voice Organizer” for a	1. All patients benefited from the introduction of the Voice Organizer as measured using the message-passing task and the Positive and Negative Affect Schedule (PANAS).

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	period of 3-weeks. Messages could be dictated into the organizer and verbal reminders were repeated at specified times throughout the day. Outcome Measure: Positive and Negative Affect Schedule (PANAS)	
Wilson et al. (1997) UK Pre-Post N=15	Population: Gender: male=11, female=4; Condition: TBI=10, Stroke=1; ABI=4. Intervention: Evaluation of a NeuroPage, a portable paging system. Patients assessed at baseline and after treatment. Outcome Measure: Task completion.	1. There was a significant improvement in task completion between the baseline and treatment phase of each subject ($p < 0.050$). 2. Mean success at baseline was 37.08%, during treatment (85.56%) and post-treatment (74.46%).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Many studies have been conducted looking at the effectiveness of various active reminders used for those with memory impairment. Wilson et al. (1997) found that a portable paging system, NeuroPage, could reduce everyday memory problems and improve task completion. A crossover RCT also demonstrated that the pager system significantly increased participants' ability to carry out daily tasks, and successful task achievement was more efficient after the pager intervention was introduced (Wilson et al., 2005; Wilson et al., 2001). However, the need for a centralized system to send reminders reduces the feasibility of pagers since many people may be able to achieve the same results using other electronic reminder systems.

Voice organizers have also been shown to improve goal execution. In a study by Kim et al. (2000), 12 TBI patients were given palmtop computers programmed with scheduling software capable of generating audible reminder cues. Patient feedback suggested that the use of the palmtop computer was beneficial for their rehabilitation, and over half of the patients continued to use the device even after the conclusion of the study. In addition, one case series (van den Broek et al., 2000) and one RCT (Hart et al., 2002) found that voice organizers helped to improve recall of previously identified goals.

With advances in technology, more sophisticated organizers integrating these tools into personal digital assistants (PDAs) have also been studied. Patients accustomed to using memory aids were more likely to make use of computerized organizers (Wright et al., 2001b). Dowds et al. (2011) found that two different PDAs improved task completion rates compared to a paper-based schedule book, while Lannin et al. (2014) found that the use of a PDA in addition to conventional occupational therapy significantly reduced memory failures and forgetting. However, the variety of available electronic organizers and learning curve for use prevent clear conclusions across studies. An RCT by Powell et al. (2012) demonstrated the importance of systematic instruction, as they compared direct instructions to conventional, trial and error patient learning on a PDA. Those receiving systematic instruction were superior in the number and speed of correct PDA tasks compared to conventional trial and error learning group. No differences were found between groups based on PDA input (physical vs touch-screen keyboard), provided the three core memory aides of appointment diary, notebook, and to-do list were maintained (Wright et al., 2001a).

Smartphones represent a relatively new area of accessible technology and provide the user with many benefits. Smartphones are already designed to send notifications about their use, as well as multiple companies design apps for each phone brand interface allowing individuals to keep their current devices and still access helpful applications. The most common advantages to smartphones are reminders/alarms and ability to combine a calendar, tasks list, contacts, mail, and phone on one device. Disadvantages included the reduction of battery life and risk of dependency on the assistive device, however these are minor inconveniences in comparison to the reported improvement in memory in some patients (Evald, 2015). The increasing availability of smartphones also creates the ability to enhance current therapies with text messages. A case series by Fish et al. (2007) demonstrated that participants could be trained to associate a text message with stopping and thinking about what needed to be done, with participants more likely to remember the instruction to call the investigators when texted the message “STOP”. Gracey et al. (2017) also found that goal management training could be supplemented with text messages for improving achievement of everyday intentions, with individuals who received text prompt more likely to succeed in their goals compared to those not receiving prompts. This effect was not observable once the texts had stopped to both groups.

External memory aids can also be incorporated into an individual’s home or work environment. Lemoncello et al. (2011) developed a television assisted prompting (TAP) system that provided reminders of events to be completed through the television screen. This crossover RCT found that compared to traditional methods (paper planner, cell phones or computers), participants using the TAP system completed significantly more tasks (Lemoncello et al., 2011).

These external aids can also be adapted for use in an inpatient settings. O’Neill et al. (2017) developed an audio-verbal interactive micro-prompting system, Guide, designed to emulate the verbal prompts and questions provided by caregivers or support workers. The number of support workers prompts needed during their morning routine was reduced, even though there were no significant differences between groups in terms of the number of errors and satisfaction scores (O’Neill et al., 2017). An acute rehabilitation unit also showed efficacy for a computerized tracking system designed to locate patients and send reminders when patients moved in the wrong direction for appointments (Burke et al., 2001). By reducing the number of staff prompts needed, these systems can increase patient independence and help free up support personnel for other tasks.

Conclusions

There is level 4 evidence that the NeuroPage system may increase a patient’s ability and efficiency to complete tasks post TBI.

There is level 4 evidence that voice organizer programs are effective at improving recall of goals, and are found to be effective by patients post TBI.

There is level 2 evidence that personal digital assistants (PDAs) are superior to a paper-based schedule book at improving task completion rates post TBI.

There is level 1b evidence that the use of a personal digital assistant (PDA) in combination with conventional occupational therapy is superior to occupational therapy alone at improving memory in patients post TBI.

There is level 1b evidence that use of a personal digital assistant (PDA) after receiving systematic instructions is superior to PDA trial and error learning at improving the number and speed of correct tasks post TBI.

There is level 4 evidence that conventional or touch-screen personal digital assistant (PDA) use are similar at improving memory post TBI.

There is level 1b evidence that reminder text messages sent to patients through their smartphones, whether alone or in combination with goal management training, may improve goal completion post TBI.

There is level 2 evidence that a television assisted prompting (TAP) system is superior to traditional methods of memory prompting (paper planners, cell phones, computers) at improving the amount of completed tasks post TBI.

There is level 1b evidence that the audio-verbal interactive micro-prompting system, Guide, can reduce the amount of support-staff prompts needed for the patient to complete a task post TBI.

There is level 4 evidence that a computerized tracking system that sends reminders to patients when they are moving in the wrong direction reduces the amount of support-staff prompts needed for patients to complete a task post TBI.

Pager and voice-organizer programs may improve a patient's ability to complete tasks post TBI.

Personal digital assistant (PDA) devices are superior to paper-based interventions at improving memory and task completion post TBI; specially when introduced using systematic instructions and in combination with occupational therapy. Patients who have used previous memory aids might benefit from this intervention the most.

Text message prompts sent to a patient's smartphone, when used alone or in combination with other memory-improvement therapies, likely improve task completion post TBI. However, risk exists of device dependency exists.

A television assisted prompting (TAP) program may be superior to other methods of memory prompting in patients post TBI.

Automated prompting systems, such as Guide (audio-verbal interactive micro-prompting system) and a computerized tracking system, can reduce the amount of prompts needed from support staff to patients to complete tasks post TBI.

6.3.1.1.2 External Passive Technology or Non-Technology Aids

A specific intervention for improving general cognitive functioning is computer-assisted training. The use of computer-assisted cognitive retraining has multiple potential benefits within the rehabilitation setting following brain injury. Computer retraining allows for flexibility in retraining procedures, increased individuality of therapy programs, and also decreases the amount of direct time a therapist is with the patient. It also has the potential of continuing cognitive retraining within the community setting. Furthermore, as presented at the NIH Consensus Development Panel (1999) computer-assisted strategies are used to improve neuropsychological processes, including attention, memory and executive skills.

In recent years, clinicians have recommended the use of computers as an efficacious tool in cognitive rehabilitation. A systematic review identified 23 studies that demonstrated computerized cognitive interventions were effective for improvement of attention and executive functions (Bogdanova et al., 2016).

Table 6.12 The Effect of Passive Devices on Memory and Task Completion Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>McDonald et al. (2011) UK RCT PEDro=5 N=12</p>	<p>Population: Mean Age: 47yr; Gender: male=6, female=6; Condition: TBI=4, Stroke=4, Other ABI=3. Intervention: One of two groups (Group A or Group B). All were asked to complete weekly monitoring forms indicating what activities they would like to complete within the next 15 weeks. Those assigned to Group A (the Google calendar group) were shown how to use the calendar to remind them of upcoming activities. They were discouraged from using other reminder strategies during the next 5 weeks. Group B was the standard diary group. At the end of the 5 weeks, group B began using the Google calendar while Group A began using the standard diary. Outcome Measure: Task completion.</p>	<ol style="list-style-type: none"> Overall the use of memory aids assisted individuals in completing tasks as opposed to no memory aids. Memory performance was greater using the google calendar compared to the standard diary (p<0.001). During the Google Calendar intervention phase, there was 40.6% increase in completing their prospective intention compared to the standard diary phase. Overall 82% of targets were reached using Google calendar but only 55% using the standard diary.
<p>Ownsworth & McFarland (1999) Australia RCT PEDro=3 N=20</p>	<p>Population: Mean Age: 43.1 yr; Gender: male=19, female=1; Condition: TBI=15, Stroke=1, Other ABI=4; Injury etiology: traffic accident (n=12), sport injury (n=1), assault (n=2), tumour (n=2), stroke (n=1), and infection (n=2). Intervention: Randomized into a diary only (DS) group (n=10) and a diary & self-instructional training (DSIT) group (n=10) intervention. The DS group participated in a 6 week “Bottom-Up” approach program that emphasized the development of functional skills using</p>	<ol style="list-style-type: none"> All subjects reported significantly fewer problems with memory (p<0.001) and lower levels of distress (p<0.01) during treatment phase when compared to baseline. There was a significant increase in the degree of strategy use during treatment (p<0.05) regardless of type of diary training. There were no significant differences between the DS and DSIT groups (p>0.05).

	<p>compensation based, on task,-specific learning. The DSIT group participated in a 10 week “Top-Down” approach program that emphasized the capacity for self-regulation and self-awareness using “Self Instructional Training.”</p> <p>Outcome Measure: Self report questionnaire on commonly experienced memory problems.</p>	
<p>Watanabe et al. (1998) USA RCT PEDro=3 N=30</p>	<p>Population: Mean Age: 53.4yr; Gender: male=24, female=6; Condition: TBI=16, ABI=14.</p> <p>Intervention: Patients were randomized into two groups, one group had in-room calendars (n=14) and the other did not (n=16). The Temporal Orientation Test was given daily, when errors were made, corrections were shown on the in-room calendars (for the experimental group).</p> <p>Outcome Measure: Temporal Orientation Test (TOT).</p>	<p>1. Presence of a calendar did not significantly affect TOT scores.</p>
<p>Bergquist et al. (2009) USA RCT N=14</p>	<p>Population: TBI; Mean Age=48yr; Gender: Male=7, Female=7.</p> <p>Intervention: Patients were allocated to either an active calendar acquisition intervention group or the control diary intervention group. Throughout each intervention, participants had 30 therapist-mediated sessions, which were completed via Instant Messaging (IM). At the end of the 30 sessions they crossed-over to the other group. During the calendar condition, participants were encouraged to use the online calendar to plan and remember events. IM sessions were used to review tasks completed.</p> <p>Outcome Measure: Neurobehavioural Functioning Inventory (NFI), Community Integration Questionnaire (CIQ), Compensation Techniques Questionnaire (CTQ).</p>	<p>1. There were no significant differences between the Calendar and the Diary conditions on patient- and family-rated mood and memory functioning as noted on the NFI; there were no differences on CIQ total score as well.</p> <p>2. From baseline to the last follow-up, improvement was found on the CTQ, specifically in the notes on calendar (p<0.02) and the use of cue cards (p<0.01). Family members also noted improvement in levels of depression (p<0.02) and reported fewer memory problems p<0.004).</p>

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Multiple RCTs have examined the use of calendars and calendar tools on learning and memory (Bergquist et al., 2009; McDonald et al., 2011; Ownsworth & McFarland, 1999; Watanabe et al., 1998). In one RCT by McDonald et al. (2011), the use of a Google calendar was compared to the use of diary tracking. It was found that although both groups achieved a fair amount of desired tasks, those using the Google calendar had a significant increase in task completion through the use of automated reminders and messages. A second RCT also compare the use of a calendar to diary use (Bergquist et al., 2009). However, in this instance no significant between group differences were found. In another RCT (Ownsworth & McFarland, 1999) diary use was examined alone as well as with the combination of self-instructional training. On self-reported memory scales, all subjects reported improvements in memory, as well as a significant increases

in the degree of memory strategies used regardless of diary training. There were no significant differences between groups on memory performance however (Ownsworth & McFarland, 1999). Lastly, Watanabe et al. (1998), found no significant effects of calendar use on a test of orientation, compared to no calendar use.

Conclusions

There is conflicting (level 2) evidence regarding whether or not the use of a calendar, compared to diary training, is effective for improving memory post ABI.

There is level 2 evidence that the presence of a calendar may not improve orientation post ABI.

There is level 2 evidence that diary training in combination with self-instructional training may be more effective than diary training alone at improving memory and task completion post ABI.

Calendars may be effective tools for improving memory and task completion post ABI.

The use of a diary may help to improve memory and task completion post ABI, but more so if diary training is combined with self-instructional training.

6.3.1.1.3 Virtual Reality

Virtual reality (VR) allows individuals to interact with and experience a virtual environment in three-dimensions, realistically simulating different situations/environments/tasks through immersive (head-mounted display) or non-immersive (computer monitor or projector screen) multimedia (Sisto et al., 2002). VR systems are constantly evolving, providing a safe and motivating environment for practicing real life scenarios (Shin & Kim, 2015). A systematic review by Shin and Kim (2015) found that VR may be an effective cognitive therapy, though the limited low quality evidence has prevented strong conclusions.

Table 6.13 The Effect of Virtual Reality Exercises on Learning and Memory Post ABI

Author/Year/ Country/ Study design	Methods	Outcome
<p>Yip & Man (2013) Hong Kong RCT PEDro=5 N=37</p>	<p>Population: ABI. <i>Treatment Group (TG, n=19):</i> Mean Age=37.83yr; Gender: Male=12, Female=7; Mean Time Post Injury=145.13d. <i>Control Group (CG, n=18):</i> Mean Age=38.53yr; Gender: Male=12, Female=6; Mean Time Post Injury=167.53d. Intervention: Participants were randomized to receive virtual-reality (VR) prospective memory (PM) training (TG) or control (CG). VRPM training consisted of event-based tasks, time-based tasks, ongoing tasks, and recall tasks in both visual and auditory formats. Control training consisted of</p>	<ol style="list-style-type: none"> In the TG, VRPMT showed significant improvements after treatment on immediate recall of tasks (p<0.05), number of time checks (p<0.001), and performance of event-based (p<0.001), time-based (p<0.001), and ongoing (p<0.01) tasks compared to baseline. No significant difference was found on delayed recall of tasks or total time lapsed. In the TG, RLPMT showed significant improvements after treatment in event-based (p<0.01) and time-based

	<p>reading and games. Both were received in 30min sessions 2/wk for a total of 6wk. Outcomes were assessed at baseline and after treatment.</p> <p>Outcome Measures: VR-based PM test (VRPMT); Real life behavioural PM test (RLPMT); Cambridge Prospective Memory Test–Chinese Version (CAMPROMPT-CV); Hong Kong List Learning Test (HKLLT); Frontal Assessment Battery (FAB); Word Fluency Test–Chinese Version (WFT-CV); Colour Trails Test (CTT); Community Integration Questionnaire–Chinese Version (CIQ-CV); Self-efficacy questionnaire (SEQ).</p>	<p>(p<0.01) tasks, but not ongoing tasks, compared to baseline.</p> <p>3. In the TG, significant improvements were found after treatment on CAMPROMPT-CV (p<0.05), FAB (p<0.01), WFT-CV (p<0.01), and SEQ (p<0.01) compared to baseline. No significant difference was found on HKLLT, CTT, or CIQ-CV.</p> <p>4. In the CG, no significant difference was found after treatment on any outcome measure compared to baseline.</p> <p>5. After treatment, a significant difference was found between groups on event-based tasks of RLPMT (p<0.05), FAB (p<0.01), WFT-CV (p<0.05), and CTT (p<0.05). No significant difference was found between groups on VRPMT, CAMPROMPT-CV, HKLLT, CIQ-CV, or SEQ.</p>
<p>Grealy et al. (1999) Scotland RCT PEDro=1 N=13</p>	<p>Population: TBI patients: Age Range: 19-64; Gender: male=8, female=5.</p> <p>Intervention: Crossover design: patients were allocated to 4-week interventions of receiving a single bout of Virtual reality (VR) exercise or a no-exercise control condition.</p> <p>Outcome Measure: Tests measuring attention, information processing, learning, memory, and reaction and movement times.</p>	<p>1. Intervention group (n=13) performed significantly better than control group (n=320) on digit symbol (p<0.01), verbal (p>0.01) and visual (p<0.05) learning tasks.</p> <p>2. Reaction (p<0.01) and movement (p<0.05) times improved significantly after a single VR session.</p>

Discussion

Virtual Reality training can be used to improve learning and memory deficits. The repetition of tasks in VR with feedback can improve performance on that specific activity. Gerber et al. (2014) found that VR repetition of tasks (clearing a workbench, spelling words from a set of tiles, preparing a sandwich, and tool use) reduced the time needed to complete each activity. Another pre-post study where participants moved the handle of a robot towards virtual targets found that performance on the second day of testing was improved compared to the first day in terms of the number of targets acquired (Dvorkin et al., 2013). Dahdah et al. (2017) also found that multiple Stroop tasks in VR environments resulted in improved performance on parts of those tasks. Haptic feedback using a gentle pulse of force or no haptic feedback were associated with better performance than break-through feedback similar to popping a balloon (Dvorkin et al., 2013). (Dahdah et al., 2017) Sorita et al. (2013) found that practicing a route-learning task in a real urban environment or in a virtual stimulation of that environment showed similar improvements in route recall, suggesting that VR training improvements in functional tasks may be due to repetition and not the presented medium.

In terms of cognitive functioning, two RCTs found that training in a virtual environment did not show significantly more improvement than general cognitive re-training or psychoeducation groups on executive functioning outcomes (Jacoby et al., 2013; Man et al., 2013). One RCT focusing on vocational problem-solving skills (Man et al., 2013) identified significant improvements in both VR intervention and conventional psychoeducation control groups, but no differences between groups for cognitive or vocational outcomes except on WCST % errors and % conceptual level response (Man et al., 2013).

Yip and Man (2013) found that a non-immersive prospective memory VR training program significantly improved some memory outcomes compared to a control with regular activities, suggesting larger scale trials may be needed to fully assess the effect. Virtual reality in combination with exercise has also been found to improve performance on learning and memory tasks (Grealy et al., 1999). (Man et al., 2013)

Conclusions

There is level 4 evidence that virtual reality (VR) training may improve learning performance post ABI, although the effect may not be different from non-VR training.

There is level 2 evidence that virtual reality training alone may be promising for improving memory outcomes, and has a positive impact on visual and verbal learning when in combination with exercise.

Virtual reality programs may enhance the recovery of memory, learning, but there is currently limited evidence supporting the use of virtual reality programs.

6.3.1.2 Internal Memory Strategies

The following studies examined how different cognitive strategies could be used to enhance learning and memory following an ABI.

Table 6.14 The Effect of Cognitive Strategies on Learning and Memory Post ABI

Author/Year/ Country/Study design/ PEDro Score	Methods	Outcome
<p>Powell et al. (2012) USA RCT PEDro=7 N=29</p>	<p>Population: TBI=23, ABI=6; Mean Age=42.31yr; Gender: Male=17, Female=12; Mean Time Post Injury=13.59yr. Intervention: Patients were assigned to either the systematic instruction group (n=15) or the conventional group (control; n=14). The systematic group was based on direct instruction and mastery, rather than exploratory learning (e.g., errorless learning). The control group received conventional, trial and error learning (e.g., errorful learning). Participant’s sessions targeted selected skills on a personal digital assistant (PDA; Palm Tungsten E2). All participants received 12 sessions (45min, 2-3x/wk for 4-6wk). Outcome Measure: Assessment of PDA skills, California Verbal Learning Test II-Short Form, Wechsler Memory Scale III (Logical Memory, Visual Reproduction), Controlled word Association Test, Trail Making A and B.</p>	<ol style="list-style-type: none"> 1. Those receiving systematic instruction performed significantly more (p<0.01) correct tasks at the 30 d follow-up than did participants receiving the conventional instruction. 2. Those receiving systematic instruction also performed the correct tasks more quickly (16sec) than the conventional instruction group (41.15 vs 57.73sec, p=0.05). 3. Fluency scores (ability to follow through with a task) were also found to be higher in those in systematic instruction group compared to those in the conventional instruction group at 30 d follow-up (p=0.05). 4. There was no statistically significant main effect on treatment condition for content generalization. 5. Overall systematic instruction resulted in better environmental generalization compared to trial and error learning

Author/Year/ Country/Study design/ PEDro Score	Methods	Outcome
		(p<0.05) at post-test, but not 30d follow-up.
<p>Zlotowitz et al. (2010) UK RCT PEDro=6 N=16</p>	<p>Population: TBI=5, Stroke=7, ABI=4; Mean Age=38.63yr; Gender: Male=11, Female=5; Mean Time Post Injury=4.44mo. Intervention: Participants were randomly assigned to either the modeling or moulding group. Participants were required to learn a sequence of 7 hand movements. The moulding condition involved a hand over hand technique and the modeling technique had the participant copy the experimenter's hand motions. Outcome Measure: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Patients' recall of sequences.</p>	<ol style="list-style-type: none"> 1. From the total sample, the RBANS mean immediate memory subtest score was 80.81±20.39 and the standardized score for delayed memory was 73.94±20.86. 2. No significant differences were seen in accuracy between groups after the short delay (p>0.05); however, after the longer delay, accurate recall was significantly better after using the modeling technique compared to moulding condition (mean 2.63±1.23 vs 1.56±1.63, p=0.028).
<p>Bourgeois et al. (2007) USA RCT PEDro=2 N=38</p>	<p>Population: TBI patients: Mean Age: 41.5yr; Gender: male=24, female=14; Mean Time Post-Injury: 11.3yr. Intervention: Participants were randomized to receive either Spaced Retrieval (SR) training (n=22) delivered over the telephone or didactic strategy instruction (DSI) (n=16). Participants in both groups identified three memory-related goals to master. Outcome Measure: Goal Mastery, Cognitive Difficulties Questionnaire (CDS).</p>	<ol style="list-style-type: none"> 1. Those in the SR group showed significant improvement in goal mastery compared to the SI group (p<0.05). This was maintained at the one month post intervention. 2. Results on the CDS showed both groups having fewer significant difficulties following treatment (p<0.001; p<0.005). 3. There were no significant between-groups differences in participant reports of generalized strategy use or reported memory problems at either time-point (p>0.05).
<p>Fasotti et al. (2000) Netherlands RCT PEDro=5 N=22</p>	<p>Population: TBI; <i>Experimental Group (n=12):</i> Mean Age=26.1yr; Gender: Male=8, Female=4; Mean Time Post Injury=9.8mo. <i>Control group (n=10):</i> Mean Age=30.1yr; Gender: Male=7, Female=3; Mean Time Post Injury=8.3mo. Intervention: Patients in the experimental group received Time Pressure Management (TPM) training (1hr, 2-3x/wk, 2-3wk). TPM training used videotaped short stories. The program was designed to increase awareness of errors and deficits, encourage the acceptance and acquisition of the TPM strategy, and emphasize strategy application and maintenance. The control group received concentration training (30min, 2-5hr/wk, 3-4hr). Patients were assessed 2wk prior to training, post-training, and at 6mo follow-up. Outcome Measure: Waterbed (WB) and Harvard Graphics (HG) tasks, Rey's 15-word test, Rivermead Behavioural Memory Test, Auditory Concentration Test, Paced Auditory Serial Addition Task, Visual Choice Reaction Time Task.</p>	<ol style="list-style-type: none"> 1. Training improved performances in both HG and WB tasks, but differences were not significant relative to control. 2. Scores on 2 of 3 standardized memory variables and all 3 attention variables increased significantly in the TPM group (p<0.05), whereas no memory variables and 1 of 3 attention variables increased significantly for the control group. 3. Follow-up (6 mo) data for 10 from the TPM group and 9 from the control group indicated that there was a significant time effect (p<0.05) but no significant group time interaction (p=0.23); this suggests that there still was a significant improvement after 6 mo but that this improvement could not be attributed specifically to the treatment or control training.
<p>Twum and Parente (1994)</p>	<p>Population: TBI; Mean Age=21yr; Time Post Injury>6mo.</p>	<ol style="list-style-type: none"> 1. MANOVA analysis revealed an overall significant main effect of mental imagery

Author/Year/ Country/Study design/ PEDro Score	Methods	Outcome
USA RCT PEDro=3 N=60	<p>Intervention: Patients were randomized into one of four treatment groups: 1) No Imagery/No Verbal Labeling (control); 2) No Imagery/ Verbal Labeling; 3) Imagery/No Verbal Labeling; and 4) Imagery /Verbal Labeling. Verbal labeling and imagery instructions were given through Verbal Paired Associated (VerPA) and Visual Paired Associated (VisPA) tasks, respectively.</p> <p>Outcome Measure: VerPA and VisPA tasks.</p>	instructions (p<0.0001) and a main effect of verbal labeling instructions on the VisPA (p<0.0001).
<p>Lindelov et al. (2016) Denmark PCT N_{Initial}=78, N_{Final}=35</p>	<p>Population: <i>ABI Group (n=17):</i> Mean Age=56.1yr; Gender: Male=13, Female=4; Mean Time Post Injury=57d. <i>Healthy Group (n=18):</i> Mean Age=56.1yr; Gender: Male=8, Female=10.</p> <p>Treatment: ABI and healthy participants were randomized and analyzed separately. Experimental group participants received 20 sessions of N-back training (N-back), where participants press a key when presented stimulus is identical to the stimulus N back in the sequence. Control group participants received 20 sessions of visual search training (VS), where participants press a key if a target symbol is present in an NxN array of symbols.</p> <p>Outcome Measure: Raven’s Advanced Progressive Matrices (RAPM), Wechsler Adult Intelligence Scale-IV (WAIS-IV), Working Memory Index (WMI Index, digit span, arithmetic, letter-number sequencing), Operation Span Test (OSPAN), WAIS-IV Processing Speed Index (PSI index, search, coding), Stroop Test.</p>	<ol style="list-style-type: none"> Both ABI and healthy groups showed significant improvement post-intervention on the assigned training tasks (Bayes factor >> 1000). The standardized mean difference was 0.45 for ABI N-back, 6.11 for healthy N-back, 1.06 for ABI VS, and 3.34 for Healthy VS. The healthy group showed greater improvement than the ABI group (Bayes factor >> 1000). No significant differences in improvements between N-back and VS treatments (time x treatment interaction) were found in ABI or healthy groups for WMI-digit span, WMI-arithmetic, WMI-letter-number sequencing, WMI index, PSI-search, PSI-coding, PSI index, RAPM, OSPAN, or Stroop. No significant differences in improvement between healthy and ABI groups (group x time x test interaction) were found for WMI-digit span, WMI-arithmetic, WMI-letter-number sequencing, WMI index, PSI-search, PSI-coding, PSI index, RAPM, OSPAN, or Stroop.
<p>Potvin et al. (2011) Canada PCT N=30</p>	<p>Population: TBI; <i>Rehabilitation Group (n=10):</i> Mean Age=35yr; Gender: Male=7, Female=3. <i>Control Group (n=20):</i> Mean Age=30.90yr; Gender: Male=11, Female=9.</p> <p>Intervention: Participants were assigned to either prospective memory (PM) rehabilitation programme or the standard neuropsychological interventions group (control). PM rehabilitation was based on the learning of visual imagery techniques.</p> <p>Outcome Measure: Test Ecologique de Memoire Prospective (TEMP), Visual Discrimination Task, Semantic Association Task, Letter Visualization Task, Digit Symbol, Cancellation Task, Trail Making Test A & B, Brown-Peterson Task, Digit Span, Sullivan Logical Memory, Rey Auditory Verbal Learning Test, Brief Visuospatial Memory Test, Semantic Verbal Fluency, Mazes, Stroop Interference and Flexibility, CAPM (relative and participant</p>	<ol style="list-style-type: none"> The experimental group performed significantly better on the TEMP post PM training than the control group (p<0.05). During the learning phase, cued recall improved for those in the experimental group, although this improvement was not found to be significant. Participants who took part in the rehabilitation program improved their performance on the PM experimental task (p<0.05). No significant group effects were found for any neuropsychological tests, except with the digit symbol test (p<0.05). Self-evaluated PM failures was significantly lower post-test in the rehabilitation group (p<0.05) but not the control group.

Author/Year/ Country/Study design/ PEDro Score	Methods	Outcome
	versions).	
<p>Sumowski et al. (2010) USA Case-Control N=28</p>	<p>Population: Mean Age of TBI=38.4yr; Etiology of injury: motor vehicle accidents (n=9), falls (n=2), sports injuries (n=2), and assault (n=1). Condition: TBI=14, Control=14. Intervention: Examining the effects of retrieval practice in delayed memory recall than simple restudy. Using a verbal paired associate paradigm examined recall abilities between controls and TBI patients. Outcome Measure: Delayed cue recall test.</p>	<ol style="list-style-type: none"> 1. A significant learning condition by group interaction was discovered (p<0.001). 2. Healthy controls benefited from spaced restudy over massed restudy (p<0.001). 3. Both groups greatly benefited from retrieval practice over massed and spaced restudy (p<0.001, p=0.23).
<p>Schefft et al. (2008) USA PCT N=20</p>	<p>Population: Mean Age: 31.8yr; Gender: male=13, female=7; Condition: TBI Intervention: Study 1: Read condition: words were presented in pairs-1 pair per card, which participants were asked to read aloud. Generate condition: participants were shown one word on the card with the first letter of second word, and asked to read aloud the words as soon as they knew the second word. The first recall test was given immediately after the presentation of the 50 word pairs, followed by the recognition memory test. Free recall test had patients write down as many of the second words from each pair that could be remembered. Recognition Test: 50 items corresponding to the appropriate input list and each item was composed of 2 previously unseen distractor words and 1 target word from the learning task. Word pairs were presented in the same order at testing as they had been presented during the learning trials. Population: Mean Age: 34.3yr; Gender: male=18, female=2, Condition: TBI. Study 2: Both the read and generate conditions were identical to study 1; however, here there was no recognition test. Patients were given a cued recall trail, where each word pair association rule was provided as a cue for memory and a cued recall trail where the first word in the pair was presented. Free recall test had participants write down as many of the second words from the pair they could remember. For the cued recall with rules test they were given a sheet of paper with the title on it and one example of each rule. They were then asked to write down as many of the second words they could remember.</p>	<p>Study 1:</p> <ol style="list-style-type: none"> 1. Self-generation encoding procedures improved recognition memory test performance, but not free recall, compared with the didactic presentation. <p>Study 2:</p> <ol style="list-style-type: none"> 1. Self-generation strategy improved cued recall but not free recall compared with the didactic condition. 2. Study results also indicated that cued recall was also important as it was found to be effective when presented with the first word of the word pair.
<p>Manasse et al. (2005) USA Case Series N=5</p>	<p>Population: TBI: Age Range: 29-48yr; Gender: male=3, female=2; Time Post-Injury: 1-29yr. Intervention: Subjects were shown pictures of individuals they interacted with daily and asked</p>	<ol style="list-style-type: none"> 1. Traditional treatment: results indicate that 2 of the 5 subjects mastered 6 names during treatment, 1 of the 5 mastered 3 names and 4 of the 5 mastered one of the

Author/Year/ Country/Study design/ PEDro Score	Methods	Outcome
	to identify them. Traditional treatment: To assist subjects in memory recall, pictures were paired with an imagery statement. There were 9 (3 weekly over a 3 week period) one on one training sessions to assist the individuals with face name recognition. Real-world treatment: Following the third week, “real-world” treatment was begun. During the next 15 days, 2 interactions were performed each day with 2 hours separating the interactions. Researchers recorded the subjects’ spontaneous use and knowledge of the staff’s name. Outcome Measure: Name recall.	names. 2. Real-world treatment: During the real-world cueing condition only 2 names were consistently used by each subject. 3. Improved name learning was seen regardless of the cueing strategy.
Hillary et al. (2003) USA Case Series N=20	Population: Age Range: 18-55yr; Gender: male=16, female=4; Mean Time Post-Injury: 4.1yr; Condition: moderate to severe TBI. Intervention: Examining if learning in TBI patients can be improved using spaced repetitions of a procedure compared to consecutive presentations of a procedure. A list of 115 words were chosen for recall, words were presented either once (single condition), twice consecutively (massed condition), or twice with 11 words between presentations (spaced condition). Outcome Measure: Immediate and Delay Recall; Delay Recognition Trials, neuropsychological tasks.	1. Spaced words were more likely to be recalled during the immediate recall than massed words (p=.018). 2. On the delayed recall spaced words were more likely to be correctly recalled than massed words or once presented words during delayed recall performance (p<0.001). 3. On the recognition performance test, individuals were able to correctly identify spaced words over massed (p=0.001) or once presented words (p=0.017). 4. Significant main effect for study condition on immediate recall in the neuropsychological tasks (p<0.001).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a recent study Potvin et al. (2011) assigned 30 patients with moderate to severe TBI to either an experimental group (n=10) or a control group (n=20). Both groups were matched based on age and education. All participants were initially assessed using the Test Ecologique de Memoire Prospective. Those in the experimental group participated in ten prospective memory training sessions. Each session lasted 90 minutes. The PM program was divided into 5 phases: understanding PM functioning; training to visualize simple images; learning visual imagery techniques; applying visual imagery in PM; and applying visual imagery in everyday situation. The scores on the Test Ecologique de Memoire Prospective, following treatment, improved for those in the experimental group. Study authors also noted that those in the experimental group reported fewer symptoms of depression than the control group.

Twum and Parente (1994) randomly assigned 60 patients with a TBI into one of 4 groups (one control and three mnemonic strategy groups) counterbalanced. The researches demonstrated improved performance for subjects who were taught a strategy (either verbal labeling or visual imagery) while learning paired-associations. Treatment groups showed greater efficiency in learning and greater delayed recall information.

Thoene and Glisky (1995) using a case series design also showed enhanced performance following the use of a mnemonic strategy (verbal elaboration and visual imagery) compared to vanishing cues and/or video presentation during paired associations.

Goldstein et al. (1996) evaluated a visual-imagery technique “Ridiculously Imaged Story” technique in training severely brain injured individuals to learn and recall lengthy word lists. Participants were asked to read a story where 20 words are presented in bold-face and subjects were instructed to remember the bold-face words for later recall. If subjects could not recall all the words they were provided with (1) the part of the story in which the word appeared and if that didn’t aid recall, they were then provided with (2) a category cue for the word. It should be noted that in both studies reviewed, a number of their subject pool (N=10) came from a previous study (Goldstein et al., 1988). Goldstein et al. (1996) evaluated whether there were differences between a computerized and non-computerized version of “Ridiculously Imaged Story” and another visual imagery technique (Pictorial Imagery). Results indicated that although the computerized versions resulted in a slightly better performance on learning trials, the difference was non-significant.

By using the various visual imagery techniques to aid learning and recall, researchers have demonstrated that increasing the saliency of features encoded, results in an increase in the amount recalled. Milder et al. (1998) examined performance on a name learning task by increasing the meaningfulness of people’s names with various strategies (e.g. when learning a new name-face association try to think of an occupation or object with the same name or a famous person with a similar name etc). When subjects (13 severely TBI versus 13 matched controls) were tested on 3 different memory tasks, results indicated a significant difference following training, more so for the control group than the TBI group. Also, learning procedures were more effective on one task (where subjects were required to learn the name-occupation-and town) compared to the other two tasks (famous-faces or name learning).

In a 4 year follow up study, to one conducted by Berg and colleagues, Milder et al. (1995) found the effects at 4 months were no longer evident at 4 years (all groups were equivalent). In the original study, Berg et al. (1991) demonstrated that severely brain injured patients demonstrated improved effects on objective measures of memory at 4 months following training in a strategy-use group compared to a pseudo-treatment and a no treatment control group. In the strategy group, individuals were taught general cognitive principles of memory functioning and aids (i.e., internal and external strategies were taught and practiced). In contrast, the pseudo-treatment group practiced memory games and tasks with no explanation.

How individuals learn (i.e., encode) information will determine to a large extent what is later recalled. Twum and Parente (1994) demonstrated that if an active strategy (either verbal labeling for visual information or visual imagery for verbal information) is taught to individuals while learning the paired associations, learning and recall is enhanced (i.e., fewer trials needed to reach criterion during learning and improved recall following a delay). Tailby and Haslam (2003) also examined how learning can improve or limit later recall of information. They had 24 ABI subjects matched on basis of age, gender, premorbid and current intellectual status divided into 3 groups based on performance of verbal memory (mild, moderate & severe). Each group (n=8) was randomly assigned to one of 3 learning conditions: errorless learning, self-generated; errorless learning, experimenter generated; and errorful learning. Results showed that regardless of severity level, subject recalled more information in the errorless learning

conditions (with self-generated superior to experimenter generated) than in the errorful learning condition.

Constantinidou and Neils (1995) examined the effects of stimulus modality on verbal learning of patients with moderate-to-severe closed head injury and a matched control group. Results indicated that when information is presented visually (with and/or without auditory presentation of names) more information is learned than when information is presented within the auditory modality alone. As expected, patients learn new information at a significantly slower rate compared to controls.

It is generally thought that while patients are experiencing post-traumatic amnesia (PTA), they are not able to learn and retain new information, and as a result, cognitive rehabilitation is usually postponed until PTA has resolved. This tends to be true if using tasks of explicit or declarative learning and recall. Two studies were reviewed that reported that PTA patients were capable of learning and retaining new information when task demands were dependent on implicit/procedural learning. Glisky and Delaney (1996) evaluated implicit memory (priming using a stem completion task) and the use of vanishing cues when learning semantic information in a small number of patients with a TBI (n=8 & 4) who were still experiencing PTA and a matched control group. Findings revealed that learning and recall of information (once PTA has resolved) had occurred, albeit at reduced levels compared to controls. Ewert et al. (1989) also demonstrated procedural learning and retention in a group of 16 severely closed head injured participants and matched controls.

Conclusions

There is level 2 evidence that internal strategies may be an effective aid in improving recall performance compared to X post ABI.

Internal strategies appear to be an effective aid in improving recall performance post ABI.

6.3.1.3 Learning and Memory Training Programs

Following an ABI or TBI one of the most persistent problems are memory deficits. Although the literature examining the efficacy of memory programs is limited, there is some support for training that stresses external memory strategies. Again the support for these programs is limited as many individuals post injury neglect their devices or simply stop using them (O'Neil-Pirozzi et al., 2010). Internal memory strategies have also been used with limited success.

Table 6.17 The Effect of Memory Retraining Programs on Memory Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Lindelov et al. (2017) Denmark RCT PEDro=7 N=68	Population: TBI=34, Stroke=20, Other=12, NA=2. <i>Group A (n=27):</i> Mean Age=45.2 yr; Gender: Male=12, Female=15; Mean Time Post Injury=5 yr. <i>Group B (N=22):</i> Mean Age=47.0 yr; Gender: males=8, females=25; Mean Time Post	1. In Phase 1, there was significantly more improvement in Group A compared to Group B for WMI (Bayes factor=342) and TMT (Bayes factor=37.5).

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>Injury=6.5 yr. <i>Control Group (n=19)</i>: Mean Age=54.1 yr; Gender: males=8, females=11; Mean Time Post Injury=7 yr.</p> <p>Treatment: Participants were randomly assigned to Group A or Group B; Control group was recruited separately and received no intervention. In Phase 1, Group A received the first version of a targeted hypnosis procedure (improving brain injury or working memory-relating abilities) and Group B received a non-targeted hypnosis procedure (4 weekly 1 h sessions). After a 7 wk break, Phase 2 occurred, with Group A receiving a second version of a targeted hypnosis procedure and Group B receiving the first version of a targeted hypnosis procedure.</p> <p>Outcome Measure: Working Memory Index (WMI), B-A Trail Making Index (TMT).</p>	<ol style="list-style-type: none"> 2. After the break, the WMI and MT showed no significant differences for either groups compared to before the break. 3. In Phase 2, Group B crossed over to the targeted intervention and showed significant improvements in WMI (Bayes factor=535) and TMT (Bayes factor=72813). Group A showed a small improvement for WMI (Bayes factor=1.5) and TMT (Bayes factor=30). 4. From baseline to last test, there were no significant difference in improvements between Group A and Group B for WMI and TMT.
<p>Chiaravalloti et al. (2016) USA RCT PEDro=9 N_{Initial}=69 N_{Final}=53</p> <p>Sandry et al. (2016) USA Post Hoc Analysis: Chiaravalloti et al. (2016)</p>	<p>Population: TBI. <i>Treatment Group (TG, n=35)</i>: Mean Age=37.17 yr; Gender: Male=27, Female=8; Mean Time Post Injury=120 mo; Mean GCS=4.83. <i>Control Group (CG, n=34)</i>: Mean Age=40.68 yr; Gender: Male=24, Female=10; Mean Time Post Injury=102 mo; Mean GCS=5.0.</p> <p>Intervention: Participants were randomized to receive the modified Short Memory Technique (TG) or conventional therapy (CG) in 10 sessions over 5 weeks. Participants in the TG were randomized to receive 5 monthly booster sessions (BS) or control sessions (CS) after treatment. Outcomes were assessed before and after treatment, and at 6 mo follow-up.</p> <p>Outcome Measures: California Verbal Learning Test (CVLT); Memory Assessment Scales, Prose Memory (MAS-PM); Rivermead Behavioural Memory Test (RBMT).</p> <p>Population: See above. Intervention: See above. Outcome Measures: Working memory capacity (WMC); Long-term memory percent retained (LTMPR).</p>	<ol style="list-style-type: none"> 1. On the CVLT, there was no significant difference between groups after treatment (F=0.686, p>0.05). 2. On the MAS-PM, the TG showed significantly greater improvement than the CG after treatment (F=4.45, p<0.025). 3. On the MAS-PM, 49% of the TG showed a significant improvement after treatment compared to 18% of the CG (p=0.006). 4. On the MAS-PM, 23% of the TG showed a reliable positive change after treatment compared to 9% of the CG. 5. On the MAS-PM, there was no significant difference between the TG and the CG in performance at follow-up (p>0.05). 6. On the MAS-PM, there was no significant difference between participants in the TG who received BS or CS (p>0.05). 7. On the RBMT, significantly more participants in the TG demonstrated improvement on the 'hidden belonging task' after treatment than participants in the CG (p=0.025). 1. Main effects of group (TG vs CG) and capacity (high vs low) were not significant (p>0.050), but the interaction between the two variables was significant (p=0.008).

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
		2. WMC and LTMPR were significantly positively correlated in the TG ($p < 0.001$) but not in the CG ($p = 0.220$). 3. LTMPR change scores did not differ as a function of group ($p = 0.450$). 4. LTMPR change scores were not significantly correlated with other cognitive domains ($p > 0.360$).
<p>Novakovic-Agopian et al. (2011) USA RCT Crossover PEDro=5 N=16</p>	<p>Population: TBI=11, Stroke=3, Other=2: Mean Age=50.4 yr; Gender: Male=7, Female=9; Time Post Injury Range=1-23 yr. Intervention: Participants were randomized to 5 wk interventions consisting of a goals training program (n=8) or an educational instruction group (n=8). Goal training focused on mindfulness-based attentional regulation and goal management strategies for participant-defined goals. Educational training was didactic instructional sessions about brain injury. At the end of 5 wk, participants were switched to the other intervention. All participants were assessed at baseline, Week 5 and again at Week 10. Outcome Measure: Auditory Consonant Trigrams, Letter Number Sequencing (working memory); Digit Vigilance Test (sustained attention); Stroop Inhibition Delis-Kaplan Executive Function System (Inhibition); Trails B, Design Fluency-switching (mental flexibility), Hopkins Verbal Learning Test-Revised, Brief Visual Memory Test-Revised.</p>	5. At the end of wk 5 participants in the goals-edu group showed significant improvement on measures of attention and executive function from baseline ($p < 0.0001$), while the edu-goals group showed no change or minimal change ($p > 0.050$). 6. The goals-edu group had significantly greater improvements than the edu-goals group on the following at wk 5: working memory (<i>Mean</i> 1.12 vs -0.12, $p < 0.0001$); mental flexibility (<i>Mean</i> 0.64 vs 0.04, $p = 0.009$); inhibition (<i>Mean</i> 0.62 vs 0.04, $p = 0.005$); sustained attention (<i>Mean</i> 0.96 vs 0.27, $p = 0.01$); learning (<i>Mean</i> =0.51 vs 0.08, $p = 0.020$); and delayed recall (<i>Mean</i> 0.39 vs -0.27, $p = 0.01$). 7. At wk 10, the edu-goals group significantly improved compared to wk 5 on: attention and executive function (0.79 vs 0.03, $p < 0.0001$); working memory (1.31 vs -0.12, $p < 0.0008$); mental flexibility (0.66 vs 0.04, $p < 0.0008$); inhibition (0.50 vs 0.04, $p = 0.010$); sustained attention (0.44 vs 0.27, $p = 0.010$); memory (0.609 vs -0.10, $p = 0.020$); learning (0.66 vs 0.08, $p = 0.050$); and delayed recall (0.55 vs -0.27, $p = 0.020$). 1. Those in the goals-edu group who had completed the training session were able to maintain their gains and there were significant improvements in attention and executive function ($p < 0.040$) and working memory ($p < 0.020$).
<p>Shum et al. (2011) Australia RCT PEDro=7 N=45</p>	<p>Population: TBI patients: Age Range=19-57 yr; Gender: male=37, female=8; Mean Glasgow Coma Score: 6.25, Mean time since injury=273 day. Intervention: Participants were randomized to one of four treatment groups: self-awareness training, active control for self-awareness with training, compensatory prospective memory (PM) training, and active control for</p>	2. All 4 groups showed no significant differences on the CAMPROPT during the pre-intervention phase. 3. Following intervention, those with a self-awareness training component were not significantly different from those without on the change scores. 4. Groups with a compensatory training component were found to have a

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>compensatory PM training. All interventions involved 8 weekly attendances (1.5 hr each). Participants were assessed at baseline and after intervention.</p> <p>Outcome Measure: Cambridge Prospective Memory Test (CAMPROPT); number of valid diary entries; Comprehensive Assessment of Prospective Memory (CAPM); Sydney Psychosocial Reintegration Scale (SPRS).</p>	<p>significantly larger change score than those without (p=0.007).</p> <ol style="list-style-type: none"> 5. There was a significant increase in the number of participants who took notes (p=0.008). 6. Post intervention the groups with a compensatory training component were found to have larger change scores than those without (p<0.017). 7. Scores on the CAPM and SPRS were not significantly different among the 4 groups pre- or post-intervention.
<p>Vas et al. (2011) USA RCT PEDro=6 N=28</p>	<p>Population: TBI: <i>Strategic Memory and Reasoning Training (SMART) Group</i> (n=14): Mean Age=39 yr; Gender: Male=9, Female=5; Mean Time Post Injury=16.71 yr. <i>Brain Health Workshop Group</i> (n=14): Mean Age=47 yr; Gender: Male=7, Female=7; Mean Time Post Injury=16.35 yr.</p> <p>Intervention: Participants were randomly assigned to the SMART group or the BHW group. Participants received a total of 12 group sessions over an 8 wk period. The SMART group learned about strategies they could apply in their daily lives; homework was given at the end of each session. The BHW group sessions were designed to be information-based and reading assignments were given each week. Participants were assessed at baseline, post-training (3 weeks) and at a 6 month follow-up.</p> <p>Outcome Measure: Test of Strategic Learning (TOSL); Working memory listening span task; Community Integration Questionnaire (CIQ); Wechsler Adult Intelligence Scale III (WAIS III).</p>	<ol style="list-style-type: none"> 1. The SMART group had significantly greater TOSL scores compared to the control group post-training (SMART Mean=19.76, BHW Mean=13.69, p=0.030). 2. The SMART group had significant improvements in TOSL scores: post-training (Mean=19.76, p=0.007) and at 6-month follow-up (Mean=21.15, p=0.004) from baseline (Mean=14). 3. The SMART group had significantly greater improvements than the control group on the working memory listening span task post-training (SMART Mean=4.23, BHW Mean=2.59, p<0.001). 4. The SMART group had significant improvements post-training in the working memory listening span task (Mean=4.23, p=0.005) and at 6-month follow-up (Mean=4.96, P=0.0001) compared to baseline (Mean=2.76). 5. The SMART group had significantly greater improvements on CIQ compared to the BHW group (SMART Mean=18.73, BHW Mean=16.45, p=0.020). 6. The SMART group had significant improvements in the CIQ at the 6-month (Mean=19.88, p=0.010) follow-up from baseline (Mean=15.19). 7. Those in the SMART group showed significant improvement on 3 executive functions following training (inhibition: p=0.010; nonverbal reasoning: p=0.001; and cognitive flexibility: p=0.010) on the WAIS-III.
<p>Couillet et al. (2010) France RCT PEDro=5 N=12</p>	<p>Population: severe TBI; Gender: Male=9, Female=3. <i>Group 1</i> (n=5): Mean Age=23.8 yr; Mean GCS=4.8; Mean Time Post Injury=6.3 mo. <i>Group 2</i> (n=7): Mean Age=26.7 yr; Mean GCS=4.8; Mean Time Post Injury=16.1 mo.</p>	<ol style="list-style-type: none"> 1. Following training, there was a significant improvement in the 2 tasks that targeted divided attention (TAP-divided attention, Go-no go and Digit Span: p<0.0001 for both).

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>Intervention: Randomized AB versus BA design, where “A” represents the control phase and “B” represents the treatment (dual-task training) phase. In the dual-task phase, patients were trained to conduct two concurrent tasks simultaneously. Group 1 started with the control phase (AB) and Group 2 (BA) with the treatment phase. Each phase lasted 6 wk (4, 1 hr sessions/wk).</p> <p>Outcome Measure: Test Battery for Attentional Performance (TAP: divided attention and flexibility subtests), Go-no go and Digit Span, Trail Making Test, Stroop Test, Brown-Peterson Paradigm, Rating Scale of Attentional Behaviour.</p>	<p>2. The two groups differed significantly at 6 wk with those in the BA design doing better on TAP reaction times ($p<0.010$), the digit span dual-task ($p<0.001$), and the Rating Scale of Attentional Behaviour ($p<0.01$).</p> <p>3. There was a significant difference between groups at 6 wks on the Stroop test ($p<0.001$) and the flexibility subtest of the TAP ($p<0.001$), but not the Trail Making Test or the Brown-Peterson task.</p> <p>4. Experimental training had no significant effects on non-target measures.</p>
<p>Thickpenny-Davis & Barker-Collo (2007) New Zealand RCT PEDro=5 N=14</p>	<p>Population: Age Range: 16.2-50 yr; Gender: male=12, female=2; Time Post-Injury: 1-30 yr; Condition: TBI=12, CVA=2.</p> <p>Intervention: Those assigned to the treatment group participated in a memory rehabilitation program. The memory group consisted of 8 learning modules, each 1 hr in length and held 2 x a week for 4 weeks.</p> <p>Outcome Measure: Neuropsychological assessments of memory (California Verbal Learning Test (CVLT); Wechsler Memory Scale-Revised logical memory, Visual-paired Associates, Rey Complex Figure, Self-report Questionnaires).</p>	<p>1. Participation in the memory group increased participants’ knowledge of memory, memory strategies and reduced behaviours</p> <p>2. Significant improvement was seen in the treatment group from pre-test to post-test on the neuropsychological tests ($p<0.050$).</p> <p>3. When comparing pre-group results on the various memory scales, improvement was seen at time of post group testing and again at follow-up.</p>
<p>Dou et al. (2006) China RCT PEDro=5 N=37</p>	<p>Population: TBI; Mean Age=38.07 yr; Gender: Male=27, Female=10; <i>Computer Assisted Memory Training Group (CAMG; n=13)</i>: Mean Time Post Injury=270.15 d. <i>Therapist Administered Memory Training Group (TAMG; n=11)</i>: Mean Time Post Injury=161.27 d. <i>Control Group (n=13)</i>: Mean Time Post Injury=226.77 d.</p> <p>Intervention: Patients were randomized to the CAMG, TAMG, or control group. Each group received memory training with similar content; however, it was delivered differently within groups (computer vs therapist). The control group received no training. Both treatment groups received 20 training sessions (45 min, approximately 6/wk for 1 mo).</p> <p>Outcome Measure: Neurobehavioural Cognitive Examination (NCSE), Rivermead Behavioural Memory Test (RBMT), Hong Kong List Learning Test.</p>	<p>1. Scores from the NCSE indicate that there was a significant increase in the TAMG ($p=0.015$) and the CAMG ($p=0.020$) on the memory subtest of each scale compared to the control group, but the two treatment groups were not significantly different from each other ($p=0.256$).</p> <p>2. When looking at the results of the scores on the RBMT, there was only a significant difference between the CAMG and the control group ($p=0.0001$), as well as the TAMG and control ($p=0.0001$); there were no significant differences between the two treatment groups.</p> <p>3. On the Hong Kong List Learning test, CAMG showed a significant positive change in encoding, storage and retrieval in the random and blocked arrangement of words ($p<0.050$).</p>
<p>Rath et al. (2003) USA RCT PEDro=2</p>	<p>Population: TBI: Mean Age=43.6 yr; Gender: Male=23, Female=37; Mean Time Post Injury=48.2 mo.</p>	<p>1. The innovative group showed significant improvements in visual memory immediate recall ($p<0.001$).</p>

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>N=46</p>	<p>Intervention: Patients were randomized into the innovative (n=32) or conventional (n=28) treatment groups. The innovative group received 24, 2 hr sessions focusing on emotional self-regulation and clear thinking. The conventional group received 24, 2-3 hr sessions focusing on cognitive remediation and psychosocial groups.</p> <p>Outcome Measure: Weinberg Visual Cancellation Test, Stroop Color–Word Task, FAS—Controlled Oral Word Association Test, Will-Temperament Scale, Visual Reproduction, Immediate and Delayed recall, Watson-Glaser Critical Thinking Appraisal, Wechsler Adult Intelligence Scale—III.</p>	<ol style="list-style-type: none"> 2. The conventional and the innovative group showed significant improvements: on logical memory recall ($p<0.001$), logical memory delayed recall ($p=0.010$), and visual memory delayed recall ($p=0.010$). 3. The conventional group had significant improvements in reasoning ($p<0.050$). 4. The innovative group had significant improvements in executive function ($p<0.050$); problem-solving self-appraisal ($p=0.005$); self-appraised clear thinking and emotional self-regulation ($p<0.01$); and observer ratings of roleplayed scenarios ($p<0.005$).
<p>Sohlberg et al. (2000) USA PEDro=8 N=14</p>	<p>Population: TBI=11, ABI=1, Other=2. <i>Attention Process Training (APT) Group (n=7):</i> Mean Age=33.1 yr; Mean Time Post Injury=7.5 yr; <i>Control Group (n=7):</i> Mean Age=38.1 yr; Mean Time Post Injury=1.6 yr.</p> <p>Intervention: Patients were randomized to receive either the APT training (treatment) or the brain injury education and supportive listening (control), in a cross over design. APT was 24 hr over 10 wk and the control group received 10 hr over 10 wk. All subjects worked directly with a therapist and assessed pre and post intervention.</p> <p>Outcome Measure: Trail Making Test, Paced Auditory Serial Addition Task (PASAT), Gordon Diagnostic Vigilance and Distraction, Controlled Oral Word Association Task (COWAT), Stroop Task, Attention Questionnaire.</p>	<ol style="list-style-type: none"> 1. Those in the APT group reported significantly more changes than the control group (0.91 and 0.58 respectively, $p<0.050$). 2. The effect of type of change was significant ($p<0.0001$); a greater number of memory/ attention changes were reported for the APT group, whereas more psychological changes were reported for the control. 3. Changes in PASAT scores corresponded with perceived cognitive improvement in the interview; changes in PASAT scores were greater for those who reported >2 cognitive changes ($p<0.050$). 4. Results of the PASAT, Stroop Task, Trail Making Test B, and COWAT also found that those with higher levels of vigilance had improved scores ($p<0.010$). 5. For the aforementioned tasks, there were also specific improvements in performance associated with APT that were greater than those associated with brain injury education ($p<0.050$).
<p>Novack et al. (1996) USA RCT PEDro=5 N=44</p>	<p>Population: Severe TBI; <i>Focused Stimulation Group (n=22):</i> Mean Age=28.7 yr; Mean Time Post Injury=5.9 wk. <i>Unstructured Stimulation Group (n=22):</i> Mean Age=26.4 yr; Mean Time Post Injury=6.4 wk</p> <p>Intervention: Participants were randomly placed into a focused or unstructured stimulation group. Patients in the focused group received hierarchical attentional learning training (30 min, 5 x/wk). Skills were not taught</p>	<ol style="list-style-type: none"> 1. Analysis of primary outcome measures revealed no significant differences between the focused and unstructured stimulation groups, both at baseline and discharge. 2. There was a significant time effect with participants performing significantly better at the time of discharge than on admission ($p<0.0001$).

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>in a hierarchical or sequential fashion in the unstructured group.</p> <p>Outcome Measure: Digit Span and Mental Control subtests of Wechsler Memory Scale-Revised (WMS-R), computer-based simple and choice reaction time tests. <i>Secondary outcome measures:</i> Logical Memory I & II, Sentence Repetition, Judgment of Line Orientation, Trail Making A & B, Arithmetic subtest Wide Range Achievement Test-Revised, Visual imperceptions.</p>	<p>3. There were no significant differences between the groups with respect to any secondary outcome measures studied.</p>
<p>O'Neil-Pirozzi and Hsu (2016) PCT N_{Initial}=14, N_{Final}=12</p>	<p>Population: TBI=4, CVA=2, Brain tumour=1; Severity: moderate/severe. <i>Experimental Group (n=7):</i> Mean Age=51.3 yr; Gender: Male=5, Female=2; Mean Time Post Injury=20.9 yr; Etiology: TBI=5, CVA=2. <i>Control Group (n=7):</i> Mean Age=46.9 yr; Gender: Male=7; Mean Time Post Injury=25.0 yr.</p> <p>Treatment: Experimental group participants received BrainHQ, a commercially available online computerized cognitive exercise program (Attention, Brain Speed, Memory, People Skills, Intelligence, and Navigation) for 5 mo, 5 d/wk. Control group participants did not have a private computer and received no intervention.</p> <p>Outcome Measure: Number/percentage of sessions completed, Number/percentage of sessions initiated by participants, Number/percentage of sessions completed independently by participants, Mean amount of external cues provided for session completion, Wisconsin Card Sorting Test (WCST), Hopkins Verbal Learning Test-Revised (HVLTR immediate, delayed), Controlled Oral Word Association Test-FAS (COWAT), Trail Making Test (TMT A and B accuracy and speed), Satisfaction with Life Scale (SWLS), Semi-Structured Interview Questions.</p>	<ol style="list-style-type: none"> 1. Of the five experimental group participants that completed the study, they completed an average 87% of sessions, initiated an average 25% of sessions, and independently completed an average 7% of sessions. Two participants needed minimum external cues, two participants needed moderate external cues, and one participant needed maximum external cues. 2. Comparing 3 mo prior to intervention with 1 wk prior to intervention, there were no significant differences within either group for WCST, HVLTR, COWAT, TMT A or B, or SWLS. 3. There were no significant differences between groups at 1 wk prior to intervention (baseline) for WCST, HVLTR, COWAT, TMT A or B, or SWLS. 4. Compared to baseline, experimental group showed significant improvement post-intervention for HVLTR-immediate (p=0.0255) and SWLS (p=0.0075). There were no significant improvements for WCST, HVLTR-delayed, or TMT A or B. 5. Compared to baseline, control group did not show significant differences post-intervention for WCST, HVLTR, TMT A or B, or SWL. 6. Compared to control group, experimental group showed significantly higher post-intervention improvements on HVLTR-immediate (p=0.0068) and COWAT (p=0.0310). No significant differences between groups were found for changes in WCST, HVLTR-delayed, TMT A or B, or SWL. 7. Of the experimental group participants who completed the study, 60% reported improved everyday

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
		<p>thinking abilities, 60% reported improved memory, and 20% reported improved attention, organization, and/or problem solving skills, but 60% reported they would not continue with exercise program post-study completion.</p>
<p>Gabbatore et al. (2015) Italy Pre-Post N_{Initial}=20, N_{Final}=15</p>	<p>Population: TBI; Mean Age=36.7 yr; Gender: Male=10, Female=5; Mean Time Post Injury=76.1 mo; Mean GCS=4.5. Intervention: Participants completed a cognitive group rehabilitation program focussed on mental representations underlying one's behaviours (2 x/week for 3 months). Each session consisted of comprehension activities (discussing specific communication modalities) and production activities (role-playing activities). Participants were assessed at T0 (3 months before intervention (regular activities during this time), T1 (before intervention), T2 (after intervention) and T3 (3 month follow-up – regular activities during this time). Total study duration was 9 months. Outcome Measure: : Assessment Battery for Communication (ABaCo-comprehension, production, linguistic, extralinguistic, paralinguistic, and context), Verbal Span Task (VST), Spatial Span Task (SST), Attentive Matrices Test (AMT), Trail Making Test (TMT), Tower of London Test (TOL), Colored Progressive Matrices Raven (CPM Raven), Aachener Aphasie Test-Denomination Scale (AAT), Sally-Ann Task, Strange Stories Task, Immediate and Deferred Recall Test (IDR), Wisconsin Card Sorting Test (WCST).</p>	<ol style="list-style-type: none"> 1. No significant improvements in ABaCo (production and comprehension) were observed from T0 to T1. 2. Participants showed significant improvements from T1 to T2 for ABaCo comprehension (p<0.001), production (p<0.001), linguistic (p=0.005), extralinguistic (p=0.008), paralinguistic (p=0.020), and context (p=0.010). 3. The improvements made during the treatment period were stable between T2 and T3 for both Comprehension (p=0.860) and Production (p=0.320). At T3, AbaCo scores did not show significant differences from T2. 4. There was no significant difference between T1 and T2 on the VST (p=0.490), SST (p=0.740), AMT (p=0.350), TMT (p=0.450), TOL (p=0.500), CPM Raven (p=0.090), AAT (p=0.220), Sally-Ann (p=0.580), or strange stories task (p=1.000). 5. There was a significant improvement between T1 and T2 on the IDR (p=0.010) and WCST (p=0.003).
<p>Hellgren et al. (2015) Sweden Case Series N=48</p>	<p>Population: Cerebral infarction=23%, TBI=21%, Infection=19%, Intracerebral hemorrhage=13%, Subarachnoid hemorrhage=10%, Brain tumor=8%, Other=6%; Mean Age=43.7 yr; Gender: Male=30, Female=18; Mean Time Post Injury=51.2 mo. Treatment: Participants received a working memory training program (Cogmed) consisting of various visuospatial and verbal working memory tasks. There were 4-5 sessions/wk for 5-7 wk, consisting of 45-60 min of intense exercise with one break. Occupational therapist coaches were present during every session and provided weekly feedback in addition to continuous feedback from the computer program. Outcome Measure: Paced Auditory Serial Attention Test (PASAT 2.4), Forward and Backward Block Repetition, Listening Span Task,</p>	<ol style="list-style-type: none"> 4. At 20 wk post-training, there were significant improvements in PASAT (p<0.001), Listening Span (p<0.001), Forward block repetition (p<0.001), Backward block repetition (p<0.001), COPM performance (p<0.001), COPM satisfaction (p<0.001), EQ-5D index (p=0.009), and EQ-VAS (p<0.001) compared to baseline. 5. Compared to baseline, all participants significantly improved their WM Index at 20 wk follow-up (p<0.001). 6. No significant differences in treatment effect were found for all outcomes in terms of sex or time post-injury, except for ≤18 mo since injury exhibiting more improvement than >18 mo in terms of WM index difference (p<0.050), COPM

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	Canadian Occupational Performance Measure (COPM performance and satisfaction), EuroQol descriptive (EQ-5D Index), EuroQol Visual Analogue Scale (EQ-VAS), Working Memory Index (WM Index).	performance improvement ($p<0.050$), and COPM satisfaction improvement ($p<0.050$).
<p>Li et al. (2015) USA Pre-Post N_i=13, N_f=12</p>	<p>Population: Stroke=5, TBI=5, Brain tumor=2; Mean Age=61 yr; Gender: Male=10, Female=2. Treatment: Participants received the computer-based cognitive retraining program, Parrot Software. The following eight modules were each completed in separate 1 h sessions: Visual Instructions, Attention Perception and Discrimination, Concentration, and Visual Attention Training, Remembering Written Directions, Remembering Visual Patterns, Remembering Written Letters, and Remembering Written Numbers. Outcome Measure: Montreal Cognitive Assessment (MoCA overall, attention, memory), Medication-box Sorting Task.</p>	<ol style="list-style-type: none"> 1. Compared to baseline, there was a significant mean increase in overall MoCA of 3.25 ($p=0.030$) post-intervention. However, the attention and memory subscales did not show significant differences. 2. There were no significant differences before and after intervention for the medication-box sorting task. 3. Participants with previous computer-based cognitive retraining experience had significantly more MoCA improvement than those without ($p<0.010$). 4. Age, education level, or type of ABI diagnosis did not have any significant effects on MoCA or medication-box scores.
<p>Li et al. (2013) USA Pre-Post N=11</p>	<p>Population: ABI; Mean Age=49.45 yr; Mean Time Post Injury=21.27 yr. Intervention: All participants completed eight 60 minute sessions using the attention and memory sub programs of the computer-based cognitive retraining Parrot Software. The participants focused on one of the eight subprograms during each session with each subprogram containing 10 lessons with increasing difficulty. Assessments were conducted before and after intervention. Outcome Measure: The Cognitive Assessment (Attention & Memory).</p>	<ol style="list-style-type: none"> 1. There was a significant improvement in attention cognitive assessment scores from pre to post intervention (mean change=2.091; $p<0.005$). 2. There was a significant improvement in memory cognitive assessment score from pre to post intervention (mean change=1.73; $p<0.050$).
<p>Johansson and Tornmalm (2012) Sweden Cohort N=18</p>	<p>Population: TBI: Mean age =47.5 yr; Gender: female=5, male=13; Injury Etiology: TBI=5, brain tumour=6, stroke=7. Intervention: Treatment consisted of a computerized training program designed to train working memory. Visual and auditory working memory tasks are given and the difficulty level was automatically adjusted to the individual and past performances. Groups participating consisted of 4 to 6 individuals who attended 3 sessions per week for 7-8 weeks. Coaching was provided by trained staff throughout the training. Outcome Measure: Cognitive failures questionnaire (CFQ); Canadian Occupational Performance Measures (COPM)</p>	<ol style="list-style-type: none"> 1. Results of the Cognitive failures questionnaire (CFQ) showed a significant reduction of cognitive problems for all participants ($p<0.050$). 2. The Canadian Occupational Performance Measures (COPM) also showed significant improvement on both performance (<0.010) and satisfaction with performance ($p<0.050$)
<p>Serino et al. (2007) Italy</p>	<p>Population: TBI: Age range=16-57 yr; Gender: male=6, female=3; Time since injury=6-78</p>	<ol style="list-style-type: none"> 1. Study results indicate the greatest improvement in performance

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Case Series N=9	<p>months.</p> <p>Intervention: A long sequence of numbers is presented and patients were asked to add each new number to the number preceding it and say the sum out loud. Two additional tests (the Months tasks and the Word tasks) were also administered in a similar way. The GST and the WMT were each 4 sessions/week, for 4 weeks. To vary tasks and their level of difficulty, in the interstimulus interval was varied.</p> <p>Outcome Measure: Working memory training (WMT), Paced Auditory Serial Addition Test (PASAT), Months task</p>	<p>occurred from the intermediate to the final sessions ($p<0.0005$) after the WMT.</p> <ol style="list-style-type: none"> 2. Improvement from the initial to intermediate sessions did not show any significant improvement in working memory ($p<0.460$) after GST. 3. Working memory ($p<0.050$), divided attention ($p<0.050$), executive function ($p<0.050$), and long term memory ($p<0.050$) for subjects were significantly improved in the final session compared to the intermediate session. 4. The same was not noted on the speed processing and sustained attention tasks ($p>0.050$). Working memory training tasks were also found to improve scores on various psychosocial outcomes.
<p>Boman et al. (2004) Sweden Pre-Post N=10</p>	<p>Population: TBI: Mean age=47.5 yr; Gender: male=5, female=5; Time Post injury=9-40 months.</p> <p>Intervention: Each participated in an individual cognitive training session for 1 hr/3x a week for 3 weeks at home or work. The program included attention process training (APT), generalization for training and teaching of compensatory strategies for self-selected cognitive problems. Identification of cognitive problems in everyday life was also part of the compensatory strategy.</p> <p>Outcome Measure: Digit Span Test, Claeson-Dahl test, Rivermead Behavioural Memory test (RBMT), Assessment of Motor and Process Skills, European Brain Injury Questionnaire.</p>	<ol style="list-style-type: none"> 1. For the following: sustained attention, selective attention and alternating attention significant changes ($p<0.050$, $P<0.050$, $p<0.010$ respectively) were noted in the scores of the APT test and Digit Span task between the pre to post training session and the 3 month follow up. 2. Score increases ($p<0.050$) on the RBMT were found at the 3 month follow up compared to the RBMT scores at the pretest. 3. When looking at changes in the RBMT score pre to post training, changes were not found. 4. No significant changes were found (pre to post and pre to 3 month follow up) when looking at the scores on the Claeson-Dahl Memory
<p>Quemada et al. (2003) Spain Pre-Post N=12</p>	<p>Population: Mean Age: 33.1 yr; Gender: male=6, female=6; GCS Score=5.7; Condition: TBI.</p> <p>Intervention: Individualized treatment using Wilson's Structured Behavioral Memory Program in 50 minute sessions daily for 6 months.</p> <p>Outcome Measure: Rey-Osterrieth Complex Figure Test (REY), California Verbal Learning Test (CVLT), Rivermead Behavioural Memory Test (RBMT), Memory Failures in Everyday Memory Questionnaire (MFE) Tests .</p>	<ol style="list-style-type: none"> 1. All patients achieved meaningful functional gains. 2. Improvements were not found using REY, RBMT or MFE measures. 3. There were modest improvements in some scales of the CVIL ($p=0.030$, $p=0.090$, $p=0.050$).
<p>Laatsch et al. (1999) USA Case series</p>	<p>Population: TBI; Age=18-65 yr; Time Post-Injury=2-48 months;</p> <p>Intervention: Cognitive rehabilitation therapy</p>	<ol style="list-style-type: none"> 1. NP measures: WAIS-R, WMS-R, CVLT, RCFT, SCWT, WCST or ACT, SPECT image.

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
N=5	(CRT) programme in a longitudinal protocol involving a resting SPECT and neuropsychological evaluation are pre-treatment, post-treatment and post non-treatment intervals. Outcome Measure: Neuropsychological Measures.	2. SPECT data revealed significant increases in cerebral blood flow during the treatment period (p<0.050). 3. CRT was found to be effective in improving both NP and everyday functioning. All patients were able to be more productive in their lives following treatment.
Parente et al. (1999) USA Pre-Post N=72	Population: TBI: Mean Age=32 yr; Gender: Male=39, Female=33; Injury Etiology: Motor Vehicle Accident=46, Other=26. Intervention: Participants were given tasks that trained working memory for 1 hour between pre- and post-test measurement. Control clients matched to treatment group by sex and chronicity. Outcome Measure: Digit Span Task; Letter/Number Sequencing Tasks from WAIS-III.	1. No significant differences between Digit Span test. WAIS-III differed significantly pre/post treatment (p<0.050).
Chen et al. (1997) USA Case-Control N=40	Population: Age=18+years; Gender: Male=27, Female=13; Condition: TBI. Intervention: Divided retrospectively into computer-assisted rehabilitation (CACR) and tradition therapy groups Outcome Measure: Neurophysiological Test Scores (WAIS-R; WMS).	1. Both groups made significant post-treatment gains on the neurophysiological test scores (p<0.050), with the CACR group making significant gains on 15 measures (p<0.050) and the comparison group making significant gains on seven measures (p<0.005). 2. However no significant difference was found between groups on their post-treatment gains.

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

A group out of Denmark investigated the effects of hypnosis, as delivered in a targetter or non targeted manner, on memory, attention, and cognitive function in a mixed TBI and stroke population (Lindelov et al. 2017). The researchers showed that working memory, attention, and cognitive function could be transiently increased during targeted hypnosis, however the benefits of the treatment were not sustained when the treatment was discontinued. This last finding calls into question the practicality of the intervention, as it may not be feasible to deliver targeted hypnosis to patients post brain injury on a continual basis.

Chiaravalloti et al. (2016) compared the efficacy of the modified Short Memory Technique to conventional therapy for the improvement of memory post TBI. Amongst the memory assessments quantified, significant improvements were seen only in two specific categories; the Memory Assessment Scale- Prose Memory (MAS-PM) and “hidden belonging task” of the Rivermead Behavioural Memory Test (RBMT). A follow-up study further recognized the lack of improvement in the treatment group compared to controls in terms of memory capacity, however they did note that working memory capacity and long-term memory retainment were positively correlated with each other.

Further, similar results were found in an RCT by Novakovic-Agopian et al. (2011), where a goals training group showed significant improvement on attention and execute function assessments compared to the educational group. Despite switching interventions at the 5 week mark to the educational intervention, the goal training group continued to improve significantly.

In another RCT, 45 individuals were randomly assigned into one of 4 treatment groups (Shum et al., 2011). The treatment groups consisted of 4 different intervention programs: self-awareness plus compensatory prospective memory training; self-awareness training plus active control; active control plus compensatory prospective memory training and active control only. Pre intervention scores on the CAMPRMPT did not reveal any significant differences between any of the groups. Those assigned to the compensatory prospective memory training groups showed greater changes in strategies used to improve memory. Compensatory prospective memory training included use of a diary or organizational devices, and group members were encouraged to use written reminders, appointments and note taking. Although at total of 45 participants started the study, only 36 completed it.

In an RCT conducted by Vas et al. (2011), 28 individuals who had sustained a TBI and were at least 2 years post injury, were assigned to one of two groups: the strategic memory and reasoning training group or the Brain Health Workshop group. Each groups received 15 hours of training over an eight week period. Those in the strategic memory and reasoning training group were given information about brain injuries, were asked to read pieces of literature on brain injury and were given homework assignments to be completed for the next meeting. The strategic memory and reasoning training sessions were built around three strategies: strategic attention, integration (*combining important facts to form higher order abstracted meaning*) and innovation (*derive multiple abstract interpretations*). Those in the brain health workshop group participated in information sessions. Sessions for the brain health workshop groups included an introduction to brain anatomy, functions of the brain, neuroplasticity, and the effects of lifestyle on the brain (diets, exercises and cognitive changes following a TBI). Study results indicate that those assigned to the strategic memory and reasoning training group showed significant improvement on gist reasoning and measures of executive function.

Further lending support for attention training post TBI, one RCT showed that attention and information processing outcomes could be improved with dual-task training (Couillet et al., 2010; Sacco et al., 2016). Specifically, the group found that dual-task training significantly improved attentional behaviour and reaction time compared to a non-specific cognitive program.

An RCT conducted by Dou et al. (2006), found there were no significant differences in memory and cognitive improvements between participants receiving computer-administered or therapist-administered memory training, though both groups showed significant improvements compared to the control group that received no training

Thickpenny and Barker-Collo (2007) randomly assigned 14 individuals to either the treatment or control groups. Those in the treatment group participated in a memory rehabilitation program. The memory groups consisted of eight learning modules each 60 minutes long. They ran twice a week for 4 weeks. Memory improvement and difficulties were evaluated. Overall a reduction in memory impairment was noted at the end of the 4 weeks of intervention and again at the one month follow-up time period.

Further support for emotional oriented intervention can be found in an earlier study by Rath et al. (2003). The group completed an RCT comparing two cognitive rehabilitation therapies: conventional (cognitive remediation and psychosocial components) versus an innovative rehabilitation approach focusing on emotional self regulation and clear thinking. Outcomes were measured across multiple domains of cognition including attention, memory, reasoning, psychosocial functioning, and problem solving measures. Significant changes comparing baseline to post intervention outcomes were seen for each group, however, the improvements were different for the interventions. No between-group comparisons were made.

With respect to attention process training, it was shown that individuals receiving attention remediation significantly improved in memory and attention measurements compared to controls- who TBI education alone (Sohlberg et al., 2000).

). Similarly, two trials did not find significant differences between groups for attentional, functional, and/or cognitive skills assessed (Lindelov et al., 2016; Novack et al., 1996). Novack et al. (1996) compared focused hierarchical attentional learning with an unstructured non-sequential, non-hierarchical intervention, while Lindelov et al. (2016) compared N-back training with visual search training. Overall there is weak evidence in support of training programs as an effective rehabilitation intervention for attention.

Recently, BrainHQ, a commercially available online computerized cognitive exercise program, did not significantly improve attention outcomes over time or compared to no intervention (O'Neil-Pirozzi & Hsu, 2016)

Gabbatore et al. (2015) implemented a cognitive group rehabilitation program for patients post TBI, and discovered that compared to before the intervention, patient's recall (IDR), attention (WCST), and communication skills (ABaCo) all significantly improved.

Hellgren et al. (2015), found that a memory training program was successful in improving attentional scores on the Paced-Auditory Serial Attention Test, as well as further enhancing memory in general which is discussed later on in the chapter.

The Parrot Software is another computer-based cognitive retraining program, and was investigated by a pre-post study assessing the efficacy of using eight modules focussed on attention and memory (Li et al., 2015; Li et al., 2013). While significant post-treatment improvements in attention and memory on the Cognistat assessment were found in a pilot study (Li et al., 2013), a subsequent study did not find significant improvements on the attention and memory subscales of the Montreal Cognitive Assessment (MoCA) or a medication-box sorting task despite significantly improved overall MoCA scores (Li et al., 2015).

In a recent prospective cohort study, Johansson and Tornmalm (2012) looked at the benefits of a working memory program on 18 individuals who had sustained either a TBI or had had a stroke resulting in moderate to severe cognitive deficits. The working memory training program used the Cogmed QM (computerized training software) coaching, education and peer support to help improve the daily functioning of participants. Results show the Cogmed QM program helped to improve working memory and these benefits were seen at the 6th month follow up.

. Only one study (Serino et al., 2007) described the specific task which was successful in improving attention. This cognitive task involved mental addition in combination with two other standardized tasks and was an effective strategy for improving attention.

Boman et al. (2004) in a study of 10 individuals with mild or moderate TBI, after completing 1 hour of an individual cognitive training 3 times a week for 3 weeks, significant improvement was noted on the attention processing training test in sustained attention ($p < 0.05$), selective attention ($p < 0.05$), and alternating attention ($p < 0.01$) pre to post training and at 3 month follow-up. Scores on the Rivermead Behavioural Memory Test were also seen to have significantly increased at the 3 month follow-up compared to pre test scores ($p < 0.05$). Changes on the Claeson-Dahl Memory test did not increase pre to post to 3 month follow-up.

Quemada et al. (2003) examined memory rehabilitation following severe TBI in 12 individuals (no controls). The program ran for 6 months (50 minute sessions 5 days a week for 5 months and then 3 days a week for one month) and followed a specified format utilizing behavioural compensation techniques, mnemonic strategies, and environmental adaptations, external and internal aides. Results indicated little improvement in standard measures of memory functioning, although patients and family members report meaningful functional gains (self-report and observed behaviour in everyday functioning).

The findings of the previous experiment agree with the findings of the study by Laatsch et al. (1999), where cognitive rehabilitation therapy was found to increase productivity and everyday functioning. This older study also had the benefit of reporting SPECT imaging results, which revealed increases in cerebral blood flow during the intervention.

Parente et al. (1999) also studied retraining of working memory post traumatic brain injury. Although working memory would at first glance appear to be a primarily memory related brain function, the authors describe the concept of working memory as involving three main elements. These elements are the articulatory loop which hold verbal information, the visuospatial sketchpad which stores and interprets visual information and the executive system which organizes, prioritizes and allocates information processing resources. In this pilot study, 10 subjects were assigned to the intervention group who completed tasks to enhance working memory functioning between testing sessions. The testing sessions were only one hour apart. A control group matched for age, gender and injury type completed the same testing without training. The results showed a significant improvement for the letter number sequencing task for the intervention group, however there was no difference between groups on digit span task performance.

Finally, Chen et al. (1997) studied the effect of computer assisted cognitive rehabilitation versus traditional therapy methods. While measures of attention significantly improved in both groups after treatment, no significant differences were observed between groups (Chen et al., 1997). Cumulatively, by observing studies from across a period of nearly 20 years, the literature reveals little support for the use of computer software programs for the improvement of executive function post TBI.

Conclusions

There is level 1b evidence that hypnosis compared to no treatment may not be effective at

improving memory in individuals post ABI.

There is level 1b evidence that the Short Memory Technique may not be more effective than standard memory therapy at improving memory in individuals post ABI.

There is level 2 evidence that participation in a goals training program, followed by an educational program, may be more effective for improving memory in individuals post ABI compared to receiving the treatment conditions in reverse order.

There is level 1b evidence that compensatory memory strategies, self-awareness training, and participation in memory group sessions may be effective for improving memory in individuals post ABI compared to no treatment.

There is level 2 evidence that Strategic Memory and Reasoning Training (SMART) may improve learning and working memory compared to no memory training in individuals post ABI.

There is level 2 evidence that dual-task training may be effective for improving memory in individuals post ABI when presented before the control condition, compared to the reverse.

There is level 2 evidence that both computer-administered and therapist-administered memory training may be more effective than no treatment for improving memory in ABI participants. However, no treatment appears to be better than the other.

There is level 2 evidence that both cognitive remediation and emotional self-regulation may be effective at improving different elements of memory in individuals post ABI.

There is level 1b evidence that attention processing training compared to supportive listening may improve memory in individuals post ABI.

There is level 2 evidence that BrainHQ is not an effective program for improving memory and learning compared to no intervention in individuals post ABI.

There is level 4 evidence that using mental representations and role-playing may not be effective at improving memory in individuals post ABI.

There is level 4 evidence that Cogmed training software may improve working memory performance and occupational performance in individuals post ABI.

There is conflicting (level 4) evidence regarding whether or not Parrot software is effective at improving memory and learning in individuals post ABI.

There is level 4 evidence that mental addition tasks may improve working memory in individuals post ABI.

There is level 4 evidence that the Wilson's Structured Behavioral Memory Program is not effective for improving memory post ABI.

Memory-retraining programs appear effective, particularly for functional recovery although performance on specific tests of memory may or may not change.

Specific computer-based softwares seem to be effective for improving memory post-ABI.

Computer-based interventions may be as effective as therapist administered interventions.

Emotional self-regulation therapy may be effective for improving specific elements of memory.

Recall and recognition of words can be enhanced by using a spaced learning condition.

6.3.1.4 Cranial Electrotherapy Stimulation

Cranial electrotherapy stimulation (CES) is the application of less than 1 mA of electric current to the cranium. This intervention has been used to treat a variety of disorders, including withdrawal of patients with substance abuse (Michals et al., 1993). The effect of CES for the improvement of memory following brain injury was investigated.

Table 6.15 The Effect of Cranial Electrotherapy Simulation on Memory Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Michals et al. (1993) USA RCT PEDro=7 N=22	<p>Population: Mean Age: 24.8 yr; Gender: male=17, female=5; Mean Time Post-Injury: 4.2 yr; Condition: TBI.</p> <p>Intervention: A double blind, sham controlled trial on the effectiveness of cranial electrotherapy stimulation (CES) evaluating short-term memory and cognitive functions in TBI patients.</p> <p>Outcome Measure Wechsler Memory Scale-Revised; California Verbal Learning Test, Recurring Figures Test.</p>	<ol style="list-style-type: none"> Results revealed that CES stimulation in brain-injured patients did not improve memory or immediate and delayed recall compared with controls. Repeated trial effects showed significant increase in both intervention and control group, however there was no significant differences between groups.

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Michals et al. (1993) studied cranial electrotherapy stimulation and its effect on post-traumatic memory impairment in clinical care patients with a closed head injury. Patients received CES or sham CES treatments for 40 minutes daily over a period of four weeks. The group receiving CES treatment did not improve in their memory performance, nor did their immediate or delayed recall improve. Further, with retesting, both the CES and the sham CES group showed a similarly significant trend with no group performing any better than the other. These results suggest that CES stimulation in brain-injured patients does not improve memory functioning.

Conclusions

There is level 1b evidence that cranial electrotherapy stimulation may not improve memory and recall compared to sham stimulation post TBI.

Cranial electrotherapy stimulation is likely not effective at enhancing memory and recall abilities following TBI.

6.3.2 Pharmacological Interventions

6.3.2.1 Donepezil

The effectiveness of donepezil, a cholinesterase inhibitor, in improving cognitive and memory functions following brain injury has been assessed. Cognitive impairments negatively impact patient autonomy, affecting one’s ability to return to work or school, and live alone (Masanic et al., 2001). When tested in individuals diagnosed with Alzheimer’s disease, donepezil has been found to be useful in treating memory problems (Morey et al., 2003; Walker et al., 2004). The impact of Donepezil impact on cognitive function and memory in a TBI population is explored in the table below.

Table 6.16 The Effect of Donepezil on Memory and Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Zhang et al. (2004) USA RCT PEDro=7 N=18</p>	<p>Population: TBI; <i>Group A</i> (n=9): Mean Age=33 yr; Gender: Male=6, Female=3; Mean GCS=9.3; Mean Time Post Injury=4.6 mo; <i>Group B</i> (n=9): Mean Age=31 yr; Gender: Male=7, Female=2; Mean GCS=8.9; Mean Time Post Injury=3.9 mo. Intervention: In a randomized crossover trial, <i>Group A</i> received oral donepezil for the first 10 wk, followed by a washout period of 4 wk. At the conclusion of the washout period, patients received a placebo for 10 wk. <i>Group B</i> received the treatments in the opposite order. Donepezil was administered at 5 mg/d for the first 2 wk, and at 10 mg/d for the remaining 8 wk. Outcome Measure: Auditory (All) and Visual (VII) subtests of Wechsler Memory Scale-III, Paced Auditory Serial Addition Test (PASAT).</p>	<ol style="list-style-type: none"> At week 10, <i>Group A</i> achieved significantly better scores in All (95.4±4.5 versus 73.6±4.5; p=0.002), VII (93.5±3.0 versus 64.9±3.0; p<0.001), and in the PASAT (p<0.001) compared to <i>Group B</i>. This increase in scores in <i>Group A</i> were sustained after washout and placebo treatment (week 24), leading to no significant differences in All (105.9±4.5 versus 102.4±4.5; p=0.588), VII (91.3±3.0 versus 94.9±3.0; p=0.397), and PASAT (p>0.100) compared to <i>Group B</i> at study end. Within-group comparisons showed that patients in both <i>Group A</i> and <i>Group B</i> improved significantly in All and VII (p<0.050), as well as in PASAT (p<0.001), after receiving donepezil.
<p>Khateb et al. (2005) Switzerland Pre-Post N_{initial}=15, N_{final}=10</p>	<p>Population: TBI; Mean age=43 yr; Gender: Male=8, Female=7; Mean Time Post Injury=42 mo. Intervention: Patients were administered donepezil 5 mg/day for 1mo, followed by 10 mg/day for 2 mos. Outcome Measure: Stroop test, Trail Making Test (TMT), Rey Auditory Verbal Memory Test (RAVMT), Test for Attentional Performance (TAP).</p>	<ol style="list-style-type: none"> 4 of 15 participants stopped due to side effects within the first week (e.g., nausea, sleep disorders, anxiety, dizziness, etc.). Changes on the neuropsychological evaluation show modest improvement, the comparison of the global score of all questionnaires before and after therapy was marginally significant (p=0.058). A significant improvement in executive function was only found for the Stroop Colour naming test (87.3±22.9 to 79.5±19.1, p=0.030); for learning and memory the RAVMT-learning (47.7±6.9 to 53.5±5.0, p=0.050); and for attention, the errors subsection of divided attention (5.8±3.3 to

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Morey et al. (2003) USA Case Series N=7</p>	<p>Population: TBI; Mean Age=30.7 yr; Gender: Male=5, Female=2; Mean Time Post Injury=33.3 mo. Intervention: Following baseline cognitive testing (T1), each participant began a 6mo treatment phase with 5 mg/d donepezil for the first 4 wk, then with 10 mg/d for the final 5 mo (T2). Washout period then occurred for 6 wk (T3). Another 6 mo treatment period took place with participants receiving 5 mg/d donepezil for the entire period (T4). Outcome Measure: Brief Visual Memory Test-Revised (BVMT-R), Hopkins Verbal Learning Test, digit span and letter-number sequence subtests of Wechsler Adult Intelligence Scale-Revised III, Controlled Oral Word Association Test, Memory Functioning Questionnaires.</p>	<p>2.9±2.7, p=0.030).</p> <p>1. Significant improvements (p<0.050) from T1 to T2 were observed for the following: Trial 1 of the BVMT-R, Trial 3 of the BVMT-R, total score of the BVMT-R, and delayed recall trial of the BVMT-R. No significant differences were identified for other measures, or across other testing intervals.</p>
<p>Masanic et al. (2001) Canada Pre-Post N=4</p>	<p>Population: TBI; Age Range=24-35 yr; Gender: Male=4, Female=0; GCS Range=3-8; Time Post Injury Range=35-46 mo. Intervention: Participants received 5mg donepezil daily for 8 wk, followed by 10mg daily for 4 wk. Washout period then occurred for 4 wk. Assessments occurred at baseline, and at weeks 4, 8, 12, and 16. Outcome Measure: Rey Auditory Verbal Learning Test (RAVLT), Complex Figure Test (CFT), Rivermead Behavioural Memory Test (RBMT).</p>	<p>1. Mean scores for short-term and long-term recall on the RAVLT improved by 1.03 (1.25±1.89 at baseline to 3.00±2.70 at week 12) and 0.83 (0.50±0.58 at baseline to 2.50±2.38 at week 12) standard deviations above baseline, respectively.</p> <p>2. Mean scores for short-term and long-term recall on the CFT improved also by 1.56 (13.88±8.45 at baseline to 20.13±12.93 at week 12) and 1.38 (14.00±5.60 at baseline to 19.38±11.46 at week 12) standard deviations above baseline, respectively.</p> <p>3. Perceived memory deficit (RBMT) showed a trend toward improvement over the first 12wk, followed by deterioration after the washout period.</p>

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

In an RCT, Zhang et al. (2004) demonstrated that donepezil was associated with improvements in tasks of sustained attention and short-term memory, and that these improvements were sustained even after the treatment had finished. Benefits associated with donepezil were also documented in an open-label study by Masanic et al. (2001) who found that the treatment tended to improve both short- and long-term memory of patients living with TBI. Improvements in memory were also reported by Morey et al. (2003) in their retrospective study who demonstrated that donepezil led to significant benefits in visual memory function.

The most recent study, a pre-post by Khateb et al. (2005), found only modest improvement on the various neuropsychological tests used to measure executive function, attention, and learning and memory. Of note results from the learning phase of the Rey Auditory Verbal Memory Test (RAVMT) showed significant improvement (p<0.050). The Donepezil intervention

also demonstrated improvement in executive function, as the results from the Stroop-colour naming test showed significant improvements ($p < 0.030$). On the test for Attentional Performance a significant change was noted on the divided attention (errors) subsection of the test. Overall, donepezil was found to be effective in improving learning, memory, divided attention, and executive function. However, possible benefits of donepezil administration must be balanced against the observed side effects in 27% of the population. Further randomized control trials are required to better explore the efficacy of donepezil post TBI.

Conclusion

There is level 1b evidence that donepezil improves short-term memory compared to X post ABI.

There is level 4 evidence that donepezil may be effective in improving short-term, long-term, verbal, and visual memory post ABI.

Donepezil likely improves attention and memory following TBI.

6.3.2.2 Methylphenidate

Methylphenidate is a stimulant whose exact mechanism of action in the CNS (?) is unknown (Napolitano et al., 2005). One theory is that methylphenidate acts on the presynaptic nerve to prevent the reabsorption of serotonin and norepinephrine, thereby increasing neurotransmitter concentrations within the synaptic cleft and leading to increased neurotransmission (Kim et al., 2006). In the past, methylphenidate has been extensively used as a treatment for attention deficit disorder, as well as narcolepsy (Glenn, 1998). A total of six RCTs examined the efficacy of methylphenidate as a treatment for the recovery of cognitive deficits post ABI.

Table 6.17 The Effect of Methylphenidate on Learning and Memory Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Dymowski et al. (2017) Australia RCT PEDro=9 N_{Initial}=11, N_{Final}=10</p>	<p>Population: TBI. <i>Methylphenidate Group (n=6):</i> Mean Age=35 yr; Gender: Male=4, Female=2; Mean Time Post Injury=366 d; Mean Worst GCS=4.83. <i>Placebo Group (n=4):</i> Mean Age=32.5 yr; Gender: Male=2, Female=2; Mean Time Post Injury=183.5 d; Mean Worst GCS=4.50. Treatment: Participants were randomly assigned to receive either methylphenidate (0.6 mg/kg/d rounded to the nearest 5mg with maximum daily dose of 60 mg) or placebo (lactose). Outcomes relating to processing speed, complex attentional functioning, and everyday attentional behaviour were assessed at baseline, 7 wk (on-drug), 8 wk (off-drug), and 9 mo follow-up.</p>	<p>1. After applying Bonferroni corrections, no significant differences between groups from baseline to 7 wk, baseline to 8wk, or baseline to 9 mo were observed for SDMT, TMT A, TMT B, Hayling A, Hayling B, Hayling error, DS Forward, DS Backward, DS Sequencing, DS Total, 2&7 ASRS, 2&7 CSRS, SSAT RT, CSAT RT, N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, or RSAB SO.</p>

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>Outcome Measure: Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT) A and B; Hayling (A, B, error), Digit Span (DS-Forward, Backward, Sequencing, Total), Ruff 2&7 Selective Attention Test Automatic Speed Raw Score (2&7 ASRS), Ruff 2&7 Selective Attention Test Controlled Speed Raw Score (2&7 CSRS), Simple Selective Attention Task Reaction Time (SSAT RT), Complex Selective Attention Task Reaction Time (CSAT RT), N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, Rating Scale of Attentional Behaviour Significant Other (RSAB SO).</p>	
<p>Willmott et al. (2013) Australia RCT PEDro=10 N=32</p>	<p>Population: TBI; Gender: Male=21, Female=11; Mean Time Post Injury=68 d; <i>TBI Val/Val Group (n=11):</i> Mean Age=22.64 yr; Mean GCS=4.67; <i>TBI Val/Met Group (n=14):</i> Mean Age=28.57 yr; Mean GCS=5.38; <i>TBI Met/Met Group (n=7):</i> Mean Age=30.57 yr; Mean GCS=6.83. Intervention: Participants with TBI, in a crossover design, received 0.3 mg/kg methylphenidate (2 x/d) for 6 sessions in total (spanning 2 wk), alternating between treatment and placebo for every other session. Results were compared against those from healthy controls (n=40). Groups were stratified by the presence of the Val158Met gene Outcome Measures: Ruff 2 & 7 Selective Attention Test – automatic (2 & 7 ASRS) and controlled (2 & 7 CSRS), Selective Attention Task, Four Choice Reaction Time Task (4CRT) – dissimilar compatible (DC) and similar incompatible (SI), Symbol Digit Modalities Test (SDMT), Letter Number Sequencing Task, Wechsler Test of Adult Reading.</p>	<ol style="list-style-type: none"> 1. At baseline, there were no significant differences across various genotypes on attentional performance. 2. Participants with TBI and Met/Met alleles performed significantly poorer on the SDMT (p<0.0005), 2 & 7 ASRS (p=0.001), 2 & 7 CSRS (p<0.0005), DC RT (p=0.005), and SI RT (p=0.002), when compared to controls. Analyses with participants with TBI and Val/Val alleles showed even worse outcomes, demonstrating poorer performance on 7/8 outcome measures. 3. Following methylphenidate treatment one significant drug and genotype interaction was seen between Met/Met carriers and performance on the SDMT (F=4.257; p=0.024), suggesting Met/Met carriers were more responsive to methylphenidate than either the others.
<p>Willmott & Ponsford (2009) RCT PEDro=10 N=40</p>	<p>Population: TBI; Mean Age=26.93 yr; Gender: Male=28, Female=12; Time since injury=68.38 d. Intervention: Patients received either methylphenidate (0.3 mg/kg 2x/d, rounded to the nearest 2.5 mg) or a placebo. Patients were seen for 6 sessions across 2 week period. Patients then crossed-over. Outcome Measure: Ruff 2 and 7 Selective Attention Test, Selective Attention Task, Four Choice Reaction Time Task, Sustained Attention to Response Task, Symbol Digit Modalities Test, Letter Number Sequencing Task, Wechsler Test of Adult Reading.</p>	<ol style="list-style-type: none"> 1. Methylphenidate significantly increased speed of information processing on the Symbol Digit Modalities Test (p=0.020); Ruff 2 and 7 Test-Automatic Condition (p=0.003); Simple Selective Attention Task (p=0.001); Dissimilar compatible (p=0.003), and Similar Compatible (p=0.002).
<p>Plenger et al. (1996) USA RCT PEDro=5 N=23</p>	<p>Population: TBI; Gender: Male=17, Female=6; <i>Placebo Group (n=13):</i> Mean Age=26.6 yr; Mean GCS=8.1; <i>Methylphenidate Group (n=10):</i> Mean Age=31.4 yr; Mean GCS=9.3.</p>	<ol style="list-style-type: none"> 1. At 30 d follow-up (n=15), significant differences were obtained on DRS, suggesting better outcome for the methylphenidate group. This

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>Intervention: Patients were randomly allocated to receive either methylphenidate or placebo. Methylphenidate was administered at 30 mg/kg, 2 x/d, for 30 d.</p> <p>Outcome Measure: Disability Rating Scale (DRS), Continuous Performance Test (CPT), 2 & 7 Test (2 & 7), Paced Auditory Serial Addition Test (PASAT), Digit Span & Attention/Concentration from Wechsler Memory Scale-Revised (Attn/Conc from WMS-R).</p>	<p>difference however was not seen at 90d follow-up (n=11).</p> <p>2. Significant differences were found on the attention-concentration domain at the 30 d follow-up, as indicated by CPT, PASAT, 2 & 7, and Attn/Conc from WMS-R (p<0.030). The treatment group performed better in these measures compared to the placebo group.</p>
<p>Speech et al. (1993) USA RCT PEDro=7 N=12</p>	<p>Population: TBI; Mean Age=27.6 yr; Gender: Male=5, Female=7; Mean Time Post Injury=48.5 mo.</p> <p>Intervention: In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate, 2 x/d, for 1 wk, followed by 1 wk of placebo, or receive the treatment in a reverse order.</p> <p>Outcome Measure: Gordon Diagnostic System, Digit Symbol and Digit Span subtests of the Wechsler Adult Intelligence Scale-Revised, Stroop Interference Task, Sternberg High Speed Scanning Task, Selective Reminding Test, Serial Digit Test, ++ Katz Adjustment Scale.</p>	<p>1. No significant differences were found between methylphenidate and placebo condition in any of the outcome measures studied.</p>

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Dymowski et al. (2017) investigated the effects of short-term, 7 wk, methylphenidate administration (0.6 mg/kg/d) in patients post TBI compared to a placebo (control). After analysis, it was concluded that there was no significant improvement, or difference between groups for various measures and tests of attention. More than 2 decades earlier, Speech et al. (1993) conducted a double blind placebo controlled trial evaluating the effects of methylphenidate (0.3 mg/kg, 2 x/d, for 1 wk,) following closed head injury. Both studies arrived at similar conclusions, as the treatment and placebo group did not vary in any measurements of memory, intelligence, or attention. Conversely, Plenger et al. (1996) found methylphenidate administration (30 mg/kg, 2 x/d, 30 d) significantly improved attention and concentration when compared to a placebo. The conflicting literature on the effect of methylphenidate on attention and concentration makes it difficult to draw a conclusion; especially due to the high methodological quality of all studies involved. However, the positive results seen by Plenger’s group may be due to the use of much higher doses of methylphenidate (30 mg/kg/d vs. 0.6 mg/kg/d for the other studies). Although side effects were unreported, the literature suggest that high doses can lead to acute methylphenidate intoxication; a state comparable to acute amphetamine intoxication, which may cause psychological distress in patients. As a result, the group who most recently published on the topic were likely deterred from increasing the dose past a safely accepted value.

In the first of two studies by Willmott, they and Ponsford (2009) found that administering methylphenidate (0.3 mg/kg, 2x/d, 6 wk) during inpatient rehabilitation significantly improved

the patient’s speed of information processing and attention post TBI. In the more recent RCT (Willmott et al. 2013), the authors hypothesized that an individuals’ response to methylphenidate depends on their genotype. More specifically, that individuals possessing the methionine (Met) allele at the catechol-O-methyltransferase (COMT) gene would confer greater response to methylphenidate compared to those with the valine (Val) allele. While both Met/Met and Val/Val carriers performed more poorly in various attentional tasks compared to healthy controls, Met/Met carriers did show greater improvements in strategic control in attention than Val/Val carriers. As well, the authors were able to identify one significant drug and genetic interaction between Met/Met carriers and performance on the Symbol Digit Modalities Test (SDMT). These findings suggest Met/Met carriers may in fact be more responsive to methylphenidate than individuals with the Val genotype. However, further studies are needed to draw firm conclusions.

Conclusions

There is conflicting (level 1b) evidence regarding the effectiveness of the administration of methylphenidate compared to X following brain injury for the improvement of memory in patients post TBI.

There is conflicting evidence that methylphenidate administration post TBI improves attention, memory, concentration and processing speed.

Response to methylphenidate likely varies depending on genotype at the catechol-O-methyltransferase (COMT) gene.

6.3.2.3 Sertraline

Sertraline, better known under its trade name Zoloft (Pfizer), is a selective serotonin reuptake inhibitor (SSRI) used for the treatment of depression and mood (Khouzam et al., 2003; Jorge et al., 2016). The majority of sertraline TBI research focuses on the prevention or treatment of major depressive symptoms post brain injury. However, recent studies have shifted focus and begun to evaluate the benefits of sertraline at improving cognitive disorders (Banos et al., 2016; Jorge et al., 2016; Lee, 2005). The studies reviewed below investigated the effect of sertraline on cognitive outcomes post TBI.

Table 6.18 The Effect of Sertraline on Memory and Learning Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
<p>Banos et al. (2010) USA RCT PEDro=9 N=99</p>	<p>Population: TBI. <i>Treatment group (n=49):</i> Gender: Male=39, Female=10; Mean Age=35.3 yr; Mean Time Post Injury=21.5 d; Mean GCS=5.8. <i>Placebo group (n=50):</i> Gender: Male=33, Female=17; Mean Age=34.5 yr; Mean Time Post Injury=19.2 d; Mean GCS=5.8. Intervention: Participants were randomized to either the treatment</p>	<ol style="list-style-type: none"> 1. More subjects in the treatment group dropped out at each time point. 2. Those in the placebo groups at the 6th and 12th month assessment period were older than the control group and had higher GCS. 3. Overall, there were no significant differences between the two groups on any of the cognitive measures.

	<p>group which took sertraline daily (50 mg) or placebo. Patients were assessed at 3, 6 and 12 months.</p> <p>Outcome Measure: Wechsler Memory Index (Wechsler Adult Intelligence Scale III), Symbol-Digit Modalities Test, Logical Memory, Trial Making Test and 64-item Wisconsin Card Sorting Test.</p>	
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PEdro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The effect of early administration of sertraline on cognitive functioning, intelligence and memory was evaluated by Banos et al. (2010) in an RCT. When comparing the sertraline group, who received 50mg per day, to a control group (placebo), there were no significant between group differences on any of the neuropsychological tests. The assessments examined attention and concentration, speed of processing, memory, and executive function at 3, 6 and 12 months. Cognitive functioning was not found to improve following the administration of sertraline. Of note, more patients in the sertraline group dropped out of the study compared to the control group when this was quantified at all assessment points— indicating the potential side effects associated with the treatment. Combined with the lack of apparent benefit to using the drug, use of sertraline is not currently recommended.

Conclusions

There is level 1b evidence that sertraline may not improve memory compared to placebo in individuals who have sustained a moderate to severe TBI.

Sertraline has not been shown to improve learning, or memory within the first 12 months post TBI, and may be associated with side effects.

6.3.2.4 Amantadine

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and has been used as an antiviral agent, prophylaxis for influenza A, treatment of neurological diseases such as Parkinson’s Disease, and the treatment of neuroleptic side-effects such as dystonia, akinesia and neuroleptic malignant syndrome (Schneider et al., 1999). Amantadine is also thought to work pre- and post-synaptically by increasing the amount of dopamine (in... the synapse? Pre-synaptic junction? Post-synaptic cell?) (Napolitano et al., 2005). Two studies were identified that investigated the effectiveness of amantadine as a treatment for the remediation of learning and memory deficits and cognitive functioning following TBI.

Table 6.19 The Effect of Amantadine on Learning and Memory Post ABI

Author/Year/ Country/Study design/PEdro/ N	Methods	Outcome
<p>Schneider et al. (1999) USA RCT PEdro=5</p>	<p>Population: TBI; Mean Age=31 yr; Gender: Male=7, Female=3; GCS Score Range=3-11. Intervention: Patients randomized to either amantadine (50-150 mg 2x/d) or</p>	<p>1. There was a general trend towards improvement in the study sample over the 6 wk. 2. There were no significant between group</p>

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
N=10	placebo for 2 wk in a crossover design with a 2 wk washout period. Outcome Measure: Battery of Neuropsychological Tests, Neurobehavioural Rating Scale.	differences in terms of orientation (p=0.062), attention (p=0.325), memory (p=0.341), executive flexibility (p=0.732) or behaviour (p=0.737).
Kraus et al. (2005) USA Pre-Post N=22	Population: TBI; Mean Age=36yr; Gender: Male=17, Female=5; Severity of Injury: Mild=6, Moderate=6, Severe=10; Mean Time Post Injury=63.2mo. Intervention: Positron emission tomography (PET) scan was done and participants received amantadine (100mg titrated to up to 400mg/d over 3wk). Amantadine was administered 3x/d (200mg at 8AM, 100mg at 12PM, and 100mg at 4PM) for 12wk. Outcome Measure: Trail Making Test part A and B (TMT A, TMT B), Controlled Oral Word Association Test (COWAT), Digit Span, California Verbal Learning Test (CVLT), Rey Osterreith Complex Figure-immediate (Rey Im) and delayed (Rey De) recall.	<ol style="list-style-type: none"> Measures of executive function, as indicated by TMT B and COWAT, were significantly improved in patients following treatment with amantadine (t=-2.47; p<0.02). No significant differences were found for attention (TMT A and Digit Span) or memory (CVLT, Rey Im, and Rey De). Correlational analyses with PET scan results suggest that there may be a strong relationship between executive domain improvement and changes in left pre-frontal metabolism (r=0.92; p=0.01) and left medial temporal metabolism (r=0.91; p=0.01).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

In a small sample RCT by Schneider et al. (1999) the effects of Amantadine on cognition and memory was assessed. In this six week cross-over study, patients received both placebo and amantadine. Although the study found that patients improved over the six week study period, statistical comparison of results evaluating the five subsets of attention, executive/flexibility, memory, behaviour and orientation did not demonstrate any significant effect for the use of amantadine. Similarly, Kraus et al. (2005) demonstrated that the administration of amantadine over a 12-week treatment period does not improve memory deficits or attention; however, significant improvements in executive functioning were observed. Given the quality and sample size of the current studies, future studies exploring the efficacy of amantadine for learning and memory are warranted.

Conclusions

There is level 2 evidence that amantadine may not improve learning and memory deficits in patients post TBI.

Amantadine might not be effective at improving learning and memory deficits post TBI.

6.3.2.5 Pramiracetam

Pramiracetam is a nootropic (cognitive) activator that is used to facilitate learning, memory deficiencies, and other cognitive problems. Pramiracetam produces an increased turnover of acetylcholine in hippocampal cholinergic nerve terminals and it is at least 100 times more potent than its original compound piracetam (McLean et al., 1991).

Table 6.20 The Effect of Pramiracetam on Memory Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcomes
McLean Jr. et al. (1991) USA RCT PEDro=5 N=4	Population: TBI; Age Range=23-37 yr; Gender: Male=4, Female=0. Intervention: Patients were treated in two, 3 wk blocks of oral pramiracetam (400 mg, 2x/d) and placebo over 12wk. Outcome Measure: Wechsler Memory Scale (WMS), Selective Reminding Test, Trail Making Test A&B, Finger Tapping Test, Digit Symbol Test, Word Fluency Test.	1. Improvements in immediate and delayed recall in the WMS (logical memory and selecting reminding test) were found for the treatment group. *statistical values not provided in the study

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

McLean Jr. et al. (1991) conducted a study evaluating Pramiracetam in four males post brain injury. Improvements were found for memory and these improvements remained at one month following discontinuation of the drug. Given the small sample size and the lack of data reported to support the findings, future studies should be conducted.

Conclusions

There is level 2 evidence that pramiracetam may improve males' memory compared to placebo post TBI.

Pramiracetam might improve memory in males post TBI; however, additional studies are required.

6.3.2.6 Physostigmine

Physostigmine is a cholinergic agonist that temporarily inhibits acetylcholinesterase. The inhibition of acetylcholinesterase in turn slows the destruction of acetylcholine, thus increasing the concentration of the neurotransmitter in the synapse. The use of physostigmine in Alzheimer's disease has been examined at length, however it has also been proposed to improve memory in patients with head injury (McLean et al., 1987).

Table 6.21 The Effect of Physostigmine on Memory Post ABI

Author/Year/ Country/Study design/PEDro/N	Methods	Outcomes
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<p>Cardenas et al. (1994) USA RCT PEDro=6 N=36</p>	<p>Population: TBI; Mean Age=29.5 yr; Gender: Male=36, Female=0; Mean GCS=5.31; Mean Time Post Injury=4.33 yr. Intervention: Patients randomized to one of 4 treatment protocols: 1) scopolamine, oral physostigmine, washout, placebo (for scopolamine), then placebo (for physostigmine); 2) placebo (for scopolamine), oral physostigmine, washout, scopolamine, then placebo (for physostigmine); 3) placebo (for scopolamine), placebo (for physostigmine), washout, scopolamine, then oral physostigmine; and 4) scopolamine, placebo (for physostigmine), washout, placebo (for scopolamine), then oral physostigmine. Scopolamine was administered at 5 µg/hr via a transdermal patch placed behind the ear. Oral physostigmine was administered initially at 2 mg 3 ×/d, but titrated up to 4 mg 3×/d over 1 wk. Washout period was 1 wk, and each treatment phase lasted 8 d. Outcome Measure: Selective Reminding Test (SRT), Wechsler Memory Scale I & II, Digit Symbol, Trail Making Test A & B, Memory Questionnaire, Clinical Balance Tests, Serum Cholinesterase Levels.</p>	<ol style="list-style-type: none"> 1. A total of 16 (44%) participants had improved memory scores while taking oral physostigmine (improvement was defined as >50% increase on Long-term storage or Sum Consistent Long-term Retrieval of the SRT). 2. Participants were divided into either responder (n=16) or non-responder (n=20) groups based on the SRT. 3. Responders showed significantly improved standing time compared to non-responders (p<0.050), suggesting better balance.
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PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

In a double-blind, placebo-controlled randomized trial, oral physostigmine was administered to males with TBI as an active treatment (Cardenas et al., 1994). The authors found that physostigmine led to significant improvements in long-term memory scores in 44% (n=16) of study participants. Those who responded favourably to the treatment, as indicated by their performance on the Selective Reminding Test, also demonstrated improved balance compared to non-responders (Cardenas et al., 1994).

Conclusions

There is level 1b evidence that oral physostigmine may improve long-term memory compared to placebo in men with TBI.

Physostigmine likely improves long-term memory in men with TBI.

6.3.2.7 Bromocriptine

Bromocriptine is a dopaminergic agonist which primarily exerts its actions through binding and activating D₂ receptors (Whyte et al., 2008). It has been suggested that dopamine is an important neurotransmitter for prefrontal function, an important area of the brain that contributes to cognitive function, memory, intelligence, language, and visual interpretation (McDowell et al., 1998; Siddiqui et al., 2008). In a study looking at the effects of bromocriptine

on rats, Kline et al. (2002) noted that the animals showed improvement in working memory and spatial learning; however, this improvement was not seen in motor abilities. Two studies have been identified investigating the use of bromocriptine as an adequate treatment for the recovery of cognitive impairments following TBI.

Table 6.22 The Effect of Bromocriptine on Learning Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
McDowell et al. (1998) USA RCT PEDro=4 N=24	<p>Population: TBI; Median Age=32.5 yr; Gender: Male=20, Female=4; GCS Range=3-8; Time Post injury Range=27 d-300 mo.</p> <p>Intervention: In a crossover design, participants were randomly assigned to receive 2.5 mg bromocriptine (2.5 mg) then placebo, or receive treatment in the reverse order.</p> <p>Outcome Measure: Dual-task Paradigm (counting and digit span), Stroop Test, Spatial Delayed-response Task, Wisconsin Card Sorting Test (WCST), Reading Span Test, Trail Making Test (TMT), Controlled Oral Word Association Test (COWAT), Control Tasks.</p>	<p>3. Following bromocriptine treatment there were significant improvements on the dual-task counting (p=0.028), dual-task digit span (p=0.016), TMT (p=0.013), Stroop Test (p=0.050), COWAT (p=0.020), and WCST (p=0.041).</p> <p>4. Bromocriptine had no significant effects on working memory (e.g. spatial delayed-response task and reading span test; p=0.978), or on control tasks (p=0.095).</p>
Powell et al. (1996) UK Case Series N=11	<p>Population: TBI=8, SAH=3; Mean Age=36 yr; Gender: Male=6, Female=5; Time Post Injury Range=2 mo-5 yr.</p> <p>Intervention: Patients received bromocriptine (a maximum dose of 5-10 mg/d). Patient assessments included two baseline evaluations (BL1 and BL2), evaluation when stabilized at maximum bromocriptine dose (MAXBROMO), and two post withdrawal evaluations (POST1 and POST2).</p> <p>Outcome Measure: Percentage Participation Index (PPI), Spontaneity, Motivation, Card Arranging Reward Responsivity Objective Test (CARROT), Digit Span, Buschke Selective Reminding Test (BSRT), Verbal Fluency, Hospital Anxiety and Depression Scale.</p>	<p>1. Reported PPI (p<0.0001), motivation, and spontaneity (both p<0.005) increased significantly from BL2 to MAXBROMO. Improvements were seen in CARROT as well (p<0.0001).</p> <p>2. Significant improvements were observed from BL2 to MAXBROMO on the digit span (p<0.001), BSRT (p<0.010), and verbal fluency (p<0.001). Scores on all three tests decreased (non-significant) from MAXBROMO to POST1, scores recovered to near MAXBROMO levels by POST2.</p> <p>3. Bromocriptine was not associated with improvements in mood state.</p>

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The question of whether bromocriptine improves learning and memory in patients with ABI was explored in one RCTs (McDowell et al., 1998; Whyte et al., 2008), and one case series (Powell et al., 1996). In an earlier investigation, low-dose bromocriptine (2.5 mg daily) improved functioning on tests of executive control including a dual task, Trail Making Test, the Stroop test, the Wisconsin Card Sorting Test and the controlled oral word association test (McDowell et al., 1998). However, bromocriptine did not significantly influence working memory tasks. Although McDowell et al. (1998) demonstrated some benefits following administration of bromocriptine, there was only a single administration of bromocriptine and the dose was considerably lower than that given by other studies that did not meet our criteria. Spontaneous recovery may have been a factor leading to the improved abilities in individuals receiving a single dose (2.5 mg daily) of the medication; however, study results did not answer this question. Powell et al. (1996) conducted a multiple baseline design on 11 patients with TBI or subarachnoid

hemorrhage who received bromocriptine. Improvements were found on all measures assessed—memory, attention, motivation spontaneity— except mood. In light of the fact that the last RCT investigating the effects of bromocriptine was conducted 20 years ago, new studies are required to build on the promising results of these very early conclusions.

Conclusions

There is level 2 evidence that low-dose bromocriptine may improve cognitive function, but not working memory in patients post TBI.

There is level 4 evidence that bromocriptine may improve memory in patients post TBI.

Bromocriptine may improve dual task performance and motivational deficits but its effect on memory is controversial. More research is needed before the benefits of using bromocriptine to enhance learning and memory deficits are required.

6.3.2.8 Cerebrolysin

As explained by Alvarez et al. (2003), “Cerebrolysin (EBEWE Pharma, Unterach, Austria) is a peptide preparation obtained by standardized enzymatic breakdown of purified brain proteins, and comprises 25% low-molecular weight peptides and free amino acids” (pg. 272). Cerebrolysin has been demonstrated to have neuroprotective and neurotrophic effects, and has been linked to increased cognitive performance in an elderly population.

Table 6.23 The Effect of Cerebrolysin on Memory Post ABI

Author/Year/ Country/Study Design/N	Methods	Outcomes
<p>Alvarez et al. (2003) Spain Pre-Post N=20</p>	<p>Population: TBI; Mean Age=30.1yr; Gender: Male=15, Female=5; Mean GCS=6.1; Time Post Injury Range=23-1107d. Intervention: Patients with TBI received a total of 20 intravenous infusions of cerebrolysin solution (30mL/infusion) over 4wk. Assessments were made at baseline, during treatment, and after the 4wk treatment period. Outcome Measure: Syndrome Kurztest (SKT), electroencephalogram (EEG)/brain mapping recordings, and Glasgow Outcome Scale (GOS).</p>	<p>4. Compared to baseline, patients with TBI showed a significant decrease in slow bioelectrical activity frequencies (delta: $p<0.01$; theta: $p<0.05$), and a significant increase in fast frequencies (beta: $p<0.01$) after receiving cerebrolysin, suggesting improvement in brain bioelectrical activity. 5. Significant improvements in SKT performance was noted from pre to post treatment (15.9 ± 2.4 versus 12.0 ± 2.1; $p<0.01$). 6. GOS scores significantly improved from pre to post treatment (3.7 ± 0.3 versus 3.95 ± 0.3; $p<0.05$).</p>

Discussion

In an open-label trial of 20 patients with TBI Alvarez et al. (2003) found that cerebrolysin was associated with improved brain bioelectrical activity, as evidenced by a significant increase in fast beta frequencies. A brief neuropsychological battery (Syndrome Kurztest) consisting of nine subtests was administered to evaluate memory and attentional functions in patients undergoing treatment with cerebrolysin. There was an overall significant improvement in performance post

treatment, suggesting patients experienced cognitive benefits from cerebrolysin treatment. Improvements were also seen in terms of recovery, as measured by the Glasgow Outcome Scale (Alvarez et al., 2003). Together these findings suggest that cerebrolysin may represent an effective neuroprotective therapy with tangible cognitive benefits for individuals living with an ABI. Controlled trials are necessary to further explore the efficacy of this drug.

Conclusions

There is level 4 evidence that cerebrolysin may improve memory function post ABI.

Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning following brain injury; however, controlled trials are needed to further evaluate its efficacy.

6.3.2.9 Growth Hormone (GH) Replacement Therapy

Following an ABI, it is not uncommon for individuals to be diagnosed with hypopituitarism. As many as 25 to 40% of individuals with a moderate to severe ABI have demonstrated chronic hypopituitarism (Bondanelli et al., 2007; Kelly et al., 2006; Schneiderman et al., 2008). Despite this, few patients are screened for growth hormone deficiencies; thus, the link between cognitive impairment and growth hormone deficiencies has not yet been definitively established (High et al., 2010). There is very little literature available on the benefits of GH replacement therapy after a TBI.

Table 6.24 The Effect of rh(GH) on Memory Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
High Jr et al. (2010) USA PEDro=8 N=23	<p>Population: TBI. <i>Placebo</i> (n=11): Mean Age=39.1yr; Time Post Injury=5.1yr. <i>Active rhGH</i> (n=12): Mean Age=36.1yr; Time Post Injury=11yr.</p> <p>Intervention: Participants were randomized to either a growth hormone replacement group (rhGH) injection or a placebo injection. Initially the drug was administered at 200ug, followed by a 200ug increase every month until the dosage reached 600ug. Both groups received these injections for one year.</p> <p>Outcome Measure: Wechsler Adult Intelligence Scale-III, Delis-Kaplan Executive Function System.</p>	<ol style="list-style-type: none"> 1. Overall study results did not show great improvements on the majority of assessments between groups. 2. There was a significant improvement on the Finger tapping demonstrated in the treatment group. 3. Processing Speed Index: the treatment group improved significantly over the one year period (p<0.05). The control group showed improvement at the end of the first 6mo (p<0.01) but this was not seen at the end of the 1yr. 4. Significant improvement was also noted on the Wisconsin Card Sorting Test (executive functioning) for the treatment group (p<0.01). 5. On the California Verbal learning Test-II improvement was noted for the treatment group on learning and memory.
Moreau et al. (2013) France	<p>Population: TBI. Treatment Group (TG, n=23): Mean Age=37.9yr; Gender:</p>	<ol style="list-style-type: none"> 1. Both groups showed significant improvement in instrumental ADL

<p>PCT N=50</p>	<p>Male=19, Female=4; Mean Time Post Injury=7.8yr; Mean GCS=8.1. Control Group (CG, n=27): Mean Age=37.1yr; Gender: Male=24, Female=3; Mean Time Post Injury=5.5yr; Mean GCS=9.4. Intervention: Participants were allocated to receive GH therapy (TG, 0.2-0.6mg/d) or no treatment (CG) for 1yr. Outcomes were assessed before (T1) and after (T2) treatment. Outcome Measures: Activities of Daily Living (ADL); Quality of Life Brain Injury (QOLBI); Verbal Memory (VM); Rey Complex Figure (RCF); Reaction Time (RT).</p>	<p>(iADL, p=0.001) at T2, but not personal ADL (pADL). 2. Both groups showed significant improvement in QOLBI total scores (p=0.019) and intellectual (p=0.001), functional (p=0.023), and personal (p=0.044) subscores at T2, but not physical, psychological, and social subscores. 3. Both groups showed significant improvement (p<0.05) in aspects of attention (RT), memory (VM), and visuospatial (RCF) abilities at T2. 4. The TG showed significantly greater improvement in QOLBI functional (p=0.023) and personal (p=0.019) subscores, as well as RCF (p=0.037), but no significant difference was found for other outcome measures. 5. There was a significant correlation (p<0.05) between QOLBI total and pADL (r=0.49). 6. There was a significant negative correlation (p<0.01) between attention (RT) and pADL (r=-0.59) and iADL (r=-0.56).</p>
<p>Reimunde et al. (2011) Spain Cohort N=19</p>	<p>Population: TBI; Gender: Male=19, Female=0. With Growth Hormone Deficiency (GHD) Group (n=11): Mean Age=53.36yr; Mean Time Post Injury=44.55mo. Without GHD group (n=8): Mean Age=47.12yr; Mean Time Post Injury=46.6mo. Intervention: Those with GHD received recombinant human GH (rhGH), subcutaneously (0.5mg/d for 20d then 1mg/d for 5d). Those without GHD were given a placebo. Cognitive rehabilitation was given to everyone (1hr/d, 5d for 3mo). Outcome Measure: Weschler Adult Intelligence Scale (WAIS).</p>	<p>1. Results of the WAIS indicated that the control group improved significantly on the digits and manipulative intelligence quotient (p<0.05). 2. For those in the treatment groups improvement was noted in cognitive parameters: understanding digits, numbers and incomplete figures (p<0.05) and similarities vocabulary, verbal IQ, Manipulative IQ, and total IQ (p<0.01).</p>

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

A 2010 RCT compared the long term (6 mo and 1 yr) effects of rhGH administration to placebo in a TBI population (High Jr et al. 2010). Significant improvements were noted in processing speed, executive functioning (Wisconsin Card Sorting Test), and learning (California Verbal learning test II) for both the rhGH and placebo groups. It is important to note while processing speed also improved in both groups at 6 mo, the improvement was only sustained in the treatment group at 1 yr. Further positive results were reported in a more recent PCT by Moreau et al. (2013). Patient quality of life, instrumental activities of daily living, attention, memory and visuospatial ability improved over the treatment period in both the treatment and control group. However, the treatment group improved significantly more in the functional and personal subscales of quality of life assessments. Reimunde et al. (2011) in a cohort study looking at the benefits of

administering rhGH to a group of patients who have sustained either a moderate or severe TBI. Results of the study indicate that those receiving the rhGH improved significantly on the various cognitive subtests such as: understanding, digits, numbers and incomplete figures ($p < 0.05$) and similarities vocabulary, verbal IQ, Manipulative IQ, and Total IQ ($p < 0.01$). The control group also showed significant improvement but only in digits and manipulative intelligence quotient ($p < 0.05$). Of note IGF-I levels were similar between both groups at the end of the study.

Conclusions

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is similar to placebo at improving processing speed (6 mo), memory, executive function and learning in patients post TBI.

There is level 2 evidence that growth hormone (GH) therapy is similar to placebo at improving quality of life, instrumental activities of daily living (iADL), attention, memory, and visuospatial ability in patients post TBI.

The administration of recombinant human Growth Hormone (rhGH) is likely not different than placebo at improving executive functioning, memory, or learning in patients post TBI; however certain aspects of patient quality of life may be improved.

The administration of recombinant human Growth Hormone (rhGH) might be superior at improving intelligence and cognition in patients with a growth hormone deficiency, versus those who do not, post TBI. Molecular markers of growth however may not be different post treatment between groups.

6.3.2.10 Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors prevent the enzyme acetylcholinesterase from breaking down acetylcholine. This increases the concentration of acetylcholine in synapses. Acetylcholine has been most strongly linked with the hippocampus and memory deficits, however it is also implicated in attentional processing.

Table 6.25 The Effect of Rivastigmine on Learning and Memory Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Silver et al. (2006) USA RCT PEDro=9 N=123	<p>Population: TBI. <i>Rivastigmine</i> (n=80): Mean Age=37 yr; Gender: Male=53, Female=27. <i>Placebo</i> (n=77): Mean Age=37.1 yr; Gender: Male=53, Female=24.</p> <p>Intervention: Participants were randomized to receive either rivastigmine (3-6 mg/d) or placebo. At the end of the first 4 wk, rivastigmine doses were increased to 3.0 mg, 2x/d. If necessary doses were decreased to 1.5 mg or 4.5 mg 2x/d.</p>	<p>3. Results of the CANTAB RVIP A' and HVLt found no significant differences between the placebo group and the treatment group.</p> <p>4. Rivastigmine was found to be well tolerated and safe.</p>

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	<p>Outcome Measure: Trails A and B, Hopkins verbal learning test (HVLTL), Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).</p>	
<p>Silver et al. (2009) USA Pre-Post N=127</p>	<p>Population: TBI. <i>Ex-Rivastigmine</i> (n=65): Mean Age=36.9 yr; Gender: Male=43, Female=22; Time Post Injury=73.5 mo. <i>Ex-placebo</i> (n=62): Mean Age=38 yr; Gender: Male=42, Female=20; Time Post Injury=100.1 mo.</p> <p>Intervention: Participants were randomized to receive rivastigmine injections (1.5 mg 2x/d to a max of 12 mg/d) or placebo injection.</p> <p>Outcome Measure: Trails A and B, Hopkins verbal learning test (HVLTL), Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).</p>	<p>4. The mean final dose of rivastigmine was 7.9 mg/day.</p> <p>5. 40% of patients were responders on CANTAB RVIP A' or HVLTL score at week 38.</p> <p>6. At the end of the study period all (n=98) were seen to improve of the CANTAB RVIP A' (p<0.001), the HVLTL (P<0.001), and the Trails A and B (p<0.001).</p>

Discussion

In two studies rivastigmine was administered to patients who had sustained a moderate to severe TBI (Silver et al., 2006; Silver et al., 2009). Results from both studies indicate that rivastigmine improved cognitive function and memory impairment, although results were not significant. In Silver’s (2009) follow-up open-label cohort study to their original RCT, participants (n=98) showed significant improvement on the CANTAB RVIP A’, the HVLTL and the trail A and B scales at the end of 38 week study period; however when further sub-analysis was performed depending on what group the patient previously belonged to, those in the ex-rivastigmine group to those in the ex-placebo group, the improvements were not significant.

Conclusions

There is level 1b evidence that rivastigmine may be effective in improving memory in ABI populations.

Rivastigmine may not be effective in treating memory deficits post-ABI.

6.4 Rehabilitation of Executive and General Cognitive Functioning

Executive functions refer to higher-level cognitive functions that are primarily mediated by the frontal lobes. These functions include insight, awareness, judgment, planning, organization, problem solving, multi-tasking and working memory (Lezak, 2004). Executive deficits are particularly relevant following traumatic brain injury from both a pathophysiologic as well as a psychosocial perspective. The frontal lobes tend to be one of the brain areas most likely to be injured following trauma (Greenwald et al., 2003). Frequently bilateral frontal lobe injury occurs

following TBI in contrast to typical unilateral insults following vascular injury. Not only direct contusion to the frontal and temporal lobes but also diffuse axonal injury sustained as a result of TBI affects executive functioning. Patients with a TBI often present with cognitive and behavioral deficits in the presence of little physical impairment.

Cicerone et al. (2000) reviewed 14 studies dealing with executive functioning and problem-solving (Table 6.13). Only 3 of the identified studies were classified as a randomized controlled trial or non-randomized cohort study.

In the more current reviews by Cicerone et al. (2005; 2011) 9 and 18 additional studies were identified. Some of these studies were not included in our review as they did not meet our inclusion criteria. Based on the results of the studies in their review, Cicerone et al. (2000) recommended, “*training of formal problem-solving strategies and their application to everyday situations and functional activities*”.

Executive function deficits are particularly relevant to brain injury survivors who tend to be younger (average age less than 40) and who often desire to re-integrate back into pre-injury life roles. Patients with executive function deficits may have the capacity to be independent for basic activities of daily living where actions tend to be more ingrained and one-dimensional. However, instrumental activities of daily living such as banking, scheduling and household activities require intact executive functions due to the increased cognitive complexity and variability of the tasks. Of particular importance are the advanced tasks such as return to driving and competitive employment which are of increased relevance to the younger age demographic associated with TBI (Miller et al., 2003).

6.4.1 Non-Pharmacological Interventions

6.4.1.1 Rehabilitation of Executive Functioning

Within the typical medical and rehabilitation settings, executive function deficits themselves are difficult to identify and evaluate since there is a tendency to focus on other cognitive functions such as memory and attention. The importance of evaluating effective interventions for treating executive dysfunction following brain injury is apparent since impairment can ultimately hinder successful community re-integration. Further to this, it is also important to address the issue of self-awareness which is particularly important in those who sustain moderate to severe TBI. If individuals are not aware they have a problem they are less likely to work on compensating for it.

6.4.1.1.1 Individual Interventions

Although executive function deficits post TBI are a common there is little overall research directly addressing the impact of rehabilitation on executive function. Individual interventions aimed at improving executive and general cognitive function are reviewed below.

Table 6.26 The Effect of Individual Therapies on Executive Function Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Lindelov et al. (2017) Denmark RCT PEDro=7	Population: TBI=34, Stroke=20, Other=12, NA=2. <i>Group A (n=27):</i> Mean Age=45.2 yr; Gender: Male=12, Female=15; Mean Time Post Injury=5 yr.	1. In Phase 1, there was significantly more improvement in Group A compared to Group B for WMI (Bayes

<p>N=68</p>	<p><i>Group B (N=22):</i> Mean Age=47.0 yr; Gender: males=8, females=25; Mean Time Post Injury=6.5 yr. <i>Control Group (n=19):</i> Mean Age=54.1 yr; Gender: males=8, females=11; Mean Time Post Injury=7 yr.</p> <p>Treatment: Participants were randomly assigned to Group A or Group B; Control group was recruited separately and received no intervention. In Phase 1, Group A received the first version of a targeted hypnosis procedure (improving brain injury or working memory-relating abilities) and Group B received a non-targeted hypnosis procedure (4 weekly 1 h sessions). After a 7 wk break, Phase 2 occurred, with Group A receiving a second version of a targeted hypnosis procedure and Group B receiving the first version of a targeted hypnosis procedure.</p> <p>Outcome Measure: Working Memory Index (WMI), B-A Trail Making Index (TMT).</p>	<p>factor=342) and TMT (Bayes factor=37.5).</p> <ol style="list-style-type: none"> After the break, the WMI and MT showed no significant differences for either groups compared to before the break. In Phase 2, Group B crossed over to the targeted intervention and showed significant improvements in WMI (Bayes factor=535) and TMT (Bayes factor=72813). Group A showed a small improvement for WMI (Bayes factor=1.5) and TMT (Bayes factor=30). From baseline to last test, there were no significant difference in improvements between Group A and Group B for WMI and TMT.
<p>Powell et al. (2017) USA RCT PEDro=4 N=23</p>	<p>Population: TBI=17, Stroke/aneurysm=4, Other=6, More than 1 brain injury=3; Mean Age=44 yr; Gender: Male=11, Female=12; Mean Time Post Injury=4 yr.</p> <p>Treatment: Coaches were randomly assigned to ProSolv intervention or usual care. Participants new to the outpatient rehabilitation programme were randomized to coaches and clients already working with coaches were offered the opportunity to participate in the study with that coach. In six 1 h sessions over 8wk, ProSolv group (n=14) received training on using ProSolv app and Usual Care group (n=9) received usual care including training in goal planning/management, time pressure management, and problem-solving skills. ProSolv group had access to the ProSolv app outside of the sessions as a resource for remembering steps to effective problem solving and creating personalized problem-solution lists.</p> <p>Outcome Measure: Project-specific knowledge test, Problem Solving Questionnaire (PSQ clear thinking and emotional self-regulation subscales), Problem Solving Rating Scale (PSRS), TBI Self-Efficacy Questionnaire (TBI-SE), Satisfaction with Life Scale (SWLS), System Usability Scale (SUS).</p>	<ol style="list-style-type: none"> No significant differences between groups were found for knowledge test, PSQ clear thinking, PSQ emotional self-regulation, TBI-SE, or SWLS. The average SUS score reported at post-test was 3.5 for the tutorial and 3.6 for the app, suggesting that on average, ProSolv participants were slightly higher than neutral on whether the programme components were usable.
<p>Jacoby et al. (2013) Israel RCT</p>	<p>Population: TBI; <i>Experimental group (EG; n=6):</i> Mean Age=27.83 yr; Gender: Male=4, Female=2; Mean Time Post</p>	<ol style="list-style-type: none"> Participants in the EG group improved more in their final scores on the MET-

<p>PEDro=7 N=12</p>	<p>Injury=126 d; Mean GCS=8. <i>Control group (CG; n=6)</i>: Mean Age=30.67 yr; Gender: Male=4, Female=2; Mean Time Post Injury=100 d; Mean GCS=6.25. Intervention: Participants were randomly assigned to the EG group or the CG group. All participants in the EG received 10 sessions of virtual reality (VR) training (45 min/session, 3-4 x/wk). The CG received general cognitive re-training treatment identical in length and duration to the EG. Outcome Measure: Multiple Errands Test – Simplified Version (MET-SV), Executive Function Performance Test (EFPT).</p>	<p>SV relative to their initial scores compared to the CG group (p=0.046). 2. Participants in the EG improved more in their final scores on the EFPT relative to their initial scores compared to the CG (p=0.046). 3. Between group differences showed no significant difference at baseline.</p>
<p>Man et al. (2013) Hong Kong RCT PEDro=4 N=40</p>	<p>Population: TBI. Age Range=18-55yr; Gender: Unspecified; Time Post Injury: Unspecified; Mean GCS=10. Intervention: Participants received twelve 20-25 minute sessions of a vocational problem-solving skill training program. Participants were randomized to either artificial intelligence virtual reality (treatment group, TG) or conventional psychoeducation (control group, CG). Outcomes were assessed before and after treatment, and at follow-up of 1, 3, and 6 months. Outcome Measures: Wisconsin Card Sorting Test (WCST); Tower of London Test (TLT); Vocational Cognitive Rating Scale (VCRS); Self efficacy (SE); Vocational outcomes.</p>	<p>1. Both groups showed significant improvements on WCST, TLT, VCRS, SE, and vocational outcomes after treatment compared to baseline (p<0.050). 2. On WCST, the TG performed better than the CG after treatment (p<0.020). No other significant between-group differences were found.</p>
<p>Couillet et al. (2010) France RCT PEDro=5 N=12</p>	<p>Population: severe TBI; Gender: Male=9, Female=3. <i>Group 1 (n=5)</i>: Mean Age=23.8 yr; Mean GCS=4.8; Mean Time Post Injury=6.3 mo. <i>Group 2 (n=7)</i>: Mean Age=26.7 yr; Mean GCS=4.8; Mean Time Post Injury=16.1 mo. Intervention: Randomized AB versus BA design, where “A” represents the control phase and “B” represents the treatment (dual-task training) phase. In the dual-task phase, patients were trained to conduct two concurrent tasks simultaneously. Group 1 started with the control phase (AB) and Group 2 (BA) with the treatment phase. Each phase lasted 6 wk (4, 1 hr sessions/wk). Outcome Measure: Test Battery for Attentional Performance (TAP: divided attention and flexibility subtests), Go-no go and Digit Span, Trail Making Test, Stroop Test, Brown-Peterson Paradigm, Rating Scale of Attentional Behaviour.</p>	<p>1. Following training, there was a significant improvement in the 2 tasks that targeted divided attention (TAP-divided attention, Go-no go and Digit Span: p<0.0001 for both). 2. The two groups differed significantly at 6 wk with those in the BA design doing better on TAP reaction times (p<0.010), the digit span dual-task (p<0.001), and the Rating Scale of Attentional Behaviour (p<0.010). 3. There was a significant difference between groups at 6 wks on the Stroop test (p<0.001) and the flexibility subtest of the TAP (p<0.001), but not the Trail Making Test or the Brown-Peterson task. 4. Experimental training had no significant effects on non-target measures.</p>
<p>Spikman et al. (2010) Netherlands RCT</p>	<p>Population: Mean Age: 42.5 yr; Gender: male=50, female=25; Condition: TBI=33, Stroke=32, Other=10.</p>	<p>1. The experimental group improved significantly more over time than the controls on the RRL and attained</p>

<p>PEDro=7 N=75</p>	<p>Intervention: Individuals were randomly assigned to either the experimental group which comprised of multifaceted strategy training (n=38) or the control group (n=37). The primary goal of the treatment group was to improve 8 aspects of executive functioning. Outcome Measure: Role resumption list (RRL); treatment goal attainment (TGA) and Executive Secretarial Task (EST).</p>	<p>significantly higher scores on the TGA and EST ($p<0.010$).</p>
<p>Levine et al. (2000) Canada UK RCT PEDro=4 N=30</p>	<p>Population: TBI: <i>Goal Management Training (GMT) Group</i> (n=15): Mean Age=29.0 yr; Gender: Male=5, Female=10; Mean GCS=10.7; Mean Time Post Injury=3.7 yr. <i>Motor Skill Training (MST) Group</i> (n=15): Mean Age=30.8 yr; Gender: Male=9, Female=6; Mean GCS=10.8; Mean Time Post Injury=3.8 yr. Intervention: Patients were randomized into the GMT or MST group. The GMT was comprised of five steps: 1) orienting and alerting to task, 2) goal selection, 3) partitioning goals into sub-goals, 4) encoding and retention of sub-goals, and 5) monitoring. The MST was training that was unrelated to goal management: reading and tracing mirror-reversed text and designs. Participants were tested on everyday paper and pencil tasks that focused on holding goals in mind, sub-goal analysis and monitoring. Outcome Measure: Goal Neglect (Everyday paper and pencil tasks), Stroop Interference Procedure, Trail Making A and B, Wechsler Adult Intelligence Scale Revised (WAIS-R).</p>	<p>Everyday paper and pencil Task</p> <ol style="list-style-type: none"> 1. The GMT group compared to the MST group had significantly greater accuracy on the everyday paper and pencil tasks post-training ($p<0.050$). 2. The MST group also had significantly more errors during the everyday paper and pencil tasks ($p<0.010$). 3. The GMT group significantly reduced their errors from pre-post training during the everyday paper and pencil tasks ($p<0.010$). 4. The GMT also devoted significantly more time to proofreading and the room-layout tasks than the MST group from pre to post-training ($p<0.050$). <p>Neuropsychological Tasks</p> <ol style="list-style-type: none"> 1. The GMT group was generally slower on timed neuropsychological tests: Stroop Interference Procedure, Trail Making Part A and B ($p<0.050$ and $p<0.060$, respectively). 2. No significant differences between groups for the WAIS-R ($p>0.050$).
<p>Sohlberg et al. (2000) USA PEDro=8 N=14</p>	<p>Population: TBI=11, ABI=1, Other=2. <i>Attention Process Training (APT) Group</i> (n=7): Mean Age=33.1 yr; Mean Time Post Injury=7.5 yr; <i>Control Group</i> (n=7): Mean Age=38.1 yr; Mean Time Post Injury=1.6 yr. Intervention: Patients were randomized to receive either the APT training (treatment) or the brain injury education and supportive listening (control), in a cross over design. APT was 24 hr over 10 wk and the control group received 10 hr over 10 wk. All subjects worked directly with a therapist and assessed pre and post intervention. Outcome Measure: Trail Making Test, Paced Auditory Serial Addition Task (PASAT), Gordon Diagnostic Vigilance and Distraction, Controlled Oral Word Association Task (COWAT), Stroop Task, Attention Questionnaire.</p>	<ol style="list-style-type: none"> 1. Those in the APT group reported significantly more changes than the control group (0.91 and 0.58 respectively, $p<0.050$). 2. The effect of type of change was significant ($p<0.0001$); a greater number of memory/ attention changes were reported for the APT group, whereas more psychological changes were reported for the control. 3. Changes in PASAT scores corresponded with perceived cognitive improvement in the interview; changes in PASAT scores were greater for those who reported >2 cognitive changes ($p<0.050$). 4. Results of the PASAT, Stroop Task, Trail Making Test B, and COWAT also found that those with higher levels of

		<p>vigilance had improved scores (p<0.01).</p> <p>5. For the aforementioned tasks, there were also specific improvements in performance associated with APT that were greater than those associated with brain injury education (p<0.050).</p>
<p>Dahdah et al. (2017) USA Pre-Post N_{Initial}=21, N_{Final}=15</p>	<p>Population: CVA=6, TBI=5, Tumor=2, Anoxia brain injury=2; Mean Age=40.3 yr; Gender: Male=12, Female=3. Treatment: Participants received the virtual reality (VR) intervention sessions (apartment and classroom) twice per week for a 4 wk period. Sessions 1 and 8 included all types of distractors, sessions 2 and 3 included no distracting stimuli, sessions 4 and 5 included only auditory distracting stimuli, and sessions 6 and 7 included only visual distracting stimuli. Outcome Measure: Woodcock-Johnson, 3rd edition (WJ-III pair cancellation subtest), Delis-Kaplan Executive Function System (D-KEFS Color-Word Interference subtest), Automated Neuropsychological Assessment Metrics (ANAM Go/No-Go and unimodal Stroop subtests), VR Stroop task (apartment and classroom).</p>	<p>1. No statistically significant performance differences were found from baseline to conclusion of the study for the VR apartment Stroop or D-KEFS Stroop test.</p> <p>2. For the VR classroom, participants' shortest response time on the word-reading condition was significantly reduced by session 8 (p=0.0383). All other VR classroom Stroop variables did not show significant differences.</p> <p>3. No significant differences from session 1 to session 8 were found for all pair cancellation subtest scores.</p> <p>4. From session 1 to 8, the ANAM Stroop word-reading percentage of items with a correct response (p=0.0293), ANAM Stroop word-reading number of correct responses per minute (p=0.0321), and ANAM Go/No-Go number of impulsive/bad responses (p=0.0408) significantly increased. All other ANAM variables did not show significant differences.</p>
<p>O'Neil-Pirozzi and Hsu (2016) PCT N_{Initial}=14, N_{Final}=12</p>	<p>Population: TBI=4, CVA=2, Brain tumour=1; Severity: moderate/severe. <i>Experimental Group (n=7):</i> Mean Age=51.3 yr; Gender: Male=5, Female=2; Mean Time Post Injury=20.9 yr; Etiology: TBI=5, CVA=2. <i>Control Group (n=7):</i> Mean Age=46.9 yr; Gender: Male=7; Mean Time Post Injury=25.0 yr. Treatment: Experimental group participants received BrainHQ, a commercially available online computerized cognitive exercise program (Attention, Brain Speed, Memory, People Skills, Intelligence, and Navigation) for 5 mo, 5 d/wk. Control group participants did not have a private computer and received no intervention. Outcome Measure: Number/Percentage of Sessions Completed, Number/Percentage of Sessions Initiated by Participants, Number/Percentage of Sessions Completed Independently by Participants, Mean Amount of External Cures Provided for Session Completion, Wisconsin Card Sorting Test (WCST), Hopkins Verbal Learning Test-Revised (HVLT-R immediate, delayed), Controlled</p>	<p>1. Of the five experimental group participants that completed the study, they completed an average 87% of sessions, initiated an average 25% of sessions, and independently completed an average 7% of sessions. Two participants needed minimum external cues, two participants needed moderate external cures, and one participant needed maximum external cues.</p> <p>2. Comparing 3 mo prior to intervention with 1 wk prior to intervention, there were no significant differences within either group for WCST, HVLT-R, COWAT, TMT A or B, or SWLS.</p> <p>3. There were no significant differences between groups at 1 wk prior to intervention (baseline) for WCST, HVLT-R, COWAT, TMT A or B, or SWLS.</p> <p>4. Compared to baseline, experimental group showed significant improvement post-intervention for HVLT-immediate (p=0.0255) and SWLS (p=0.0075). There were no significant improvements for WCST, HVLT-delayed, or TMT A or B.</p>

	<p>Oral Word Association Test-FAS (COWAT), Trail Making Test (TMT A and B accuracy and speed), Satisfaction with Life Scale (SWLS), Semi-structured interview questions.</p>	<ol style="list-style-type: none"> 5. Compared to baseline, control group did not show significant differences post-intervention for WCST, HVLTL, TMT A or B, or SWL. 6. Compared to control group, experimental group showed significantly higher post-intervention improvements on HVLTL-immediate ($p=0.0068$) and COWAT ($p=0.0310$). No significant differences between groups were found for changes in WCST, HVLTL-delayed, TMT A or B, or SWL.. 7. Of the experimental group participants who completed the study, 60% reported improved everyday thinking abilities, 60% reported improved memory, and 20% reported improved attention, organization, and/or problem solving skills, but 60% reported they would not continue with exercise program post-study completion.
<p>Li et al. (2015) USA Pre-Post $N_i=13$, $N_f=12$</p>	<p>Population: Stroke=5, TBI=5, Brain tumor=2; Mean Age=61 yr; Gender: Male=10, Female=2. Treatment: Participants received the computer-based cognitive retraining program, Parrot Software. The following eight modules were each completed in separate 1 h sessions: Visual Instructions, Attention Perception and Discrimination, Concentration, and Visual Attention Training, Remembering Written Directions, Remembering Visual Patterns, Remembering Written Letters, and Remembering Written Numbers. Outcome Measure: Montreal Cognitive Assessment (MoCA overall, attention, memory), Medication-box sorting task.</p>	<ol style="list-style-type: none"> 1. Compared to baseline, there was a significant mean increase in overall MoCA of 3.25 ($p=0.030$) post-intervention. However, the attention and memory subscales did not show significant differences. 2. There were no significant differences before and after intervention for the medication-box sorting task. 3. Participants with previous computer-based cognitive retraining experience had significantly more MoCA improvement than those without ($p<0.010$). 4. Age, education level, or type of ABI diagnosis did not have any significant effects on MoCA or medication-box scores.
<p>Laatsch et al. (1999) USA Case Series $N=5$</p>	<p>Population: TBI; Age Range=18-65 yr; Time Post-Injury=2-48 months; Intervention: Cognitive rehabilitation therapy (CRT) programme in a longitudinal protocol involving a resting SPECT and neuropsychological evaluation are pre-treatment, post-treatment and post non-treatment intervals. Outcome Measure: Neuropsychological measures.</p>	<ol style="list-style-type: none"> 1. NP measures: WAIS-R, WMS-R, CVLT, RCFT, SCWT, WCST or ACT, SPECT image. 2. SPECT data revealed significant increases in cerebral blood flow during the treatment period ($p<0.050$). 3. CRT was found to be effective in improving both NP and everyday functioning. All patients were able to be more productive in their lives following treatment.
<p>Chen et al. (1997) USA Case-Control $N=40$</p>	<p>Population: Age=18+ yr; Gender: male=27, female=13; Condition: TBI. Intervention: Divided retrospectively into computer-assisted rehabilitation (CACR) and tradition therapy groups Outcome Measure: Neurophysiological</p>	<ol style="list-style-type: none"> 1. Both groups made significant post-treatment gains on the neurophysiological test scores ($p<0.050$), with the CACR group making significant gains on 15 measures ($p<0.050$) and the

	Test Scores (WAIS-R; WMS).	comparison group making significant gains on seven measures ($p < 0.005$). 2. However no significant difference was found between groups on their post-treatment gains.
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Discussion

A group out of Denmark investigated the effects of hypnosis, as delivered in a targetter or non targeted manner, on memory, attention, and cognitive function in a mixed TBI and stroke population (Lindelov et al. 2017). The researchers showed that working memory, attention, and cognitive function could be transiently increased during targeted hypnosis, however the benefits of the treatment were not sustained when the treatment was discontinued. This last finding call into question the practicality of the intervention, as it may not be feasible to deliver targeted hypnosis to patients post brain injury on a continual basis.

With respect to attention process training, it was shown that individuals receiving attention remediation significantly improved in memory and attention measurements compared to controls- whoTBI education alone (Sohlberg er al., 2000). Further lending support for attention training post TBI, one RCT showed that attention and information processing outcomes could be improved with dual-task training (Couillet et al., 2010; Sacco et al., 2016). Specifically, the group found that dual-task training significantly improved attentional behaviour and reaction time compared to a non-specific cognitive program.

In a recent RCT, Spikman et al. (2010) randomly divided a group of individuals who had sustained a TBI to either a multifaceted strategy training group or a control group. Those in the treatment group were taught a comprehensive cognitive strategy which allowed them to tackle the issues and problems of daily living, compared to the control group which received a computerized training package that was aimed at improving general cognitive functioning. Overall results indicate both groups improved on many aspects of executive functioning; however, those in the treatment group showed greater improvement in their ability to set and accomplish realistic goals and to plan, initiate real life tasks (Spikman et al., 2010). The findings of the previous experiment agree with the findings of the study by Laatsch et al. (1999), where cognitive rehabilitation therapy was found to increase productivity and everyday functioning. This older study also had the benefit of reporting SPECT imaging results, which revealed increases in cerebral blood flow during the intervention.

With the development of technology, the use of virtual-reality training and computer programs have gained traction as an intriguing tool used for improving executive function in patients post TBI. In terms of cognitive functioning, two RCTs found varying results executive functioning outcomes after training in a virtual environment (Jacoby et al., 2013; Man et al., 2013). One RCT focusing on vocational problem-solving skills (Man et al., 2013) identified significant improvements in both VR intervention and conventional psychoeducation control groups, but no differences between groups for cognitive or vocational outcomes except on WCST % errors and % conceptual level response (Man et al., 2013). On the other hand, Jacoby et al (2013) found that patients receiving virtual reality training improved more on multi-tasking measures and executive function when compared to the control group— who received general cognitive re-training treatment. The most recent study by Dadah et al. (2017), a pre-post investigation, investigated virtual reality interventions in a mixed ABI population. The researchers found that

repetition of the Stroop test in different virtual reality environments showed limited improvement in performance on those specific tests (Dahdah et al., 2017). As a result of the mixed results reported on the efficacy of virtual reality training post ABI, it is difficult to make a conclusive decision on what aspects of executive functioning virtual reality benefits, and to what degree.

As previously mentioned, computer software programs have also been investigated for their efficacy in improving executive dysfunctions post TBI. Recently, BrainHQ, a commercially available online computerized cognitive exercise program, did not significantly improve attention outcomes over time or compared to no intervention (O'Neil-Pirozzi & Hsu, 2016). The Parrot Software is another computer-based cognitive retraining program, and was investigated by a pre-post study assessing the efficacy of using eight modules focussed on attention and memory (Li et al., 2015; Li et al., 2013). While significant post-treatment improvements in attention and memory on the Cognistat assessment were found in a pilot study (Li et al., 2013), a subsequent study did not find significant improvements on the attention and memory subscales of the Montreal Cognitive Assessment (MoCA) or a medication-box sorting task despite significantly improved overall MoCA scores (Li et al., 2015). This lack of improvement compared to a control group was also seen by Powell et al. (2017) when the ProSolv smartphone application was used to improved pressure management and problem—solving skills. Finally, Chen et al. (1997) studied the effect of computer assisted cognitive rehabilitation versus traditional therapy methods. While measures of attention significantly improved in both groups after treatment, no significant differences were observed between groups (Chen et al., 1997). Cumulatively, by observing studies from across a period of nearly 20 years, the literature reveals little support for the use of computer software programs for the improvement of executive function post TBI.

Levine et al. (2000) completed an RCT comparing a group of patients taking goal management training strategies to a control group who were exposed to only motor skills training. The treatment group improved on paper and pencil everyday tasks as well as meal preparation— which the authors used as an example of a task heavily reliant on self-regulation— in comparison to the motor treatment group. It is important to note however that the motor group performed superiorly on timed neuropsychological tests, and no differences were found between treatments in terms of intelligence.

Conclusions

There is level 1b evidence that targeted hypnosis may transiently improve cognitive function in patients post TBI or stroke.

There is level 1b evidence that an attention remediation intervention is superior to TBI education alone and improving executive function in patients post TBI.

There is level 2 evidence that dual-task training may improve general cognitive functioning compared to a non-specific cognitive program in patients post TBI.

There is level 1b evidence that a comprehensive cognitive treatment strategy may be superior to a computerized training package at improving task initiating and goal achievement post TBI.

There is level 4 evidence that cognitive rehabilitation may increase productivity in everyday functioning, and cerebral blood flow during treatment in patients post TBI.

There is conflicting (level 1b and level 2) evidence as to whether virtual-reality training is or is not superior to conventional cognitive training at improving cognitive and executive function outcomes post TBI.

There is level 2 evidence that computer or smartphone software programs, such as BrainHQ, Parrot Software, ProSolv app, may not be superior to no intervention at improving problem-solving skills and general functioning in patients post TBI.

There is level 2 evidence that goal management training may be superior to motor skills training at improving everyday skills like meal preparation, but not neuropsychological tests or intelligence in patients post TBI.

Targeted hypnosis may improve memory, attention, and cognitive function in patients post TBI or stroke; however, only as long as the intervention is being administered.

Attention improvement interventions may be superior to non-specific cognitive or education programs at improving memory and attention in patients post TBI.

A comprehensive cognitive treatment strategy is likely superior to a computerized training package at improving task initiation and completion in patients post TBI; this intervention may also improve cerebral blood flow.

It is unclear whether virtual-reality training is superior to conventional training at improving cognitive and executive function outcomes post TBI. Conflicting evidence exists, and further studies are required.

Computer or smartphone software programs (BrainHQ, Parrot Software, ProSolv app) may not be superior to common interventions at improving memory, attention, and problem-solving skills in patients post TBI.

Goal management training may superior to motor skills training at improving every day skills (meal preparation), but not intelligence or neuropsychological outcomes in patients post TBI.

6.4.1.1.2 Group-based Interventions

Although executive function deficits are a common there is little overall research directly addressing the impact of rehabilitation on executive function. However, community integration and other similar group-based interventions are highly related to executive function and it is possible that programs and interventions presented in a group-based setting may in fact be focusing efforts on instrumental activities of daily living which may reflect (or are dependent on)

executive functions. The efficacy of group-based interventions on cognitive and executive function are discussed below.

Table 6.27 The Effect of Group Therapy on Executive Function Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Tornas et al. (2016) Norway RCT PEDro=9 N_{Initial}=70, N_{Final}=67</p>	<p>Population: TBI=45, Stroke=15, Tumour=6, Anoxia=2, Other=2. Mean Age=42.89 yr; Gender: Male=38, Female=32; Mean Time Post Injury=97.47 mo.</p> <p>Intervention: Participants were randomized to receive Goal Management Training (TG) or Brain Health Workshop (CG) group sessions. GMT group (n=33) discussed distinctions between absentmindedness/presentmindedness, slip-ups in daily life, habitual responding, stopping and thinking, working memory, importance of goals, defining/splitting goals into subtasks, and checking. BHW control group (n=37) discussed brain function/dysfunction, brain plasticity, memory, executive function, and attention. Treatment was received one day every second week, for a total of eight two-hour sessions distributed over four days. Outcomes were assessed at baseline (T1), after treatment (T2), and at six-month follow-up (T3).</p> <p>Outcome Measures: Behaviour Rating Inventory of Executive Function–Adult (BRIEF-A); Dysexecutive Questionnaire (DEX); Cognitive Failures Questionnaire (CFQ); Continuous Performance Test II (CPT-II); UCSD Performance-Based Skills Assessment (UPSA); Delis-Kaplan Executive Function System Battery–Colour-Word Interference Test (CWI), Verbal Fluency Test (VFT), and Tower Test (TT); Trail Making Test (TMT); Hotel Task (HT).</p>	<ol style="list-style-type: none"> In the TG, significant improvements were found on BRIEF-A, DEX, and CFQ at T3 (p<0.010). In the CG, significant improvements were found on only BRIEF-A at T2 (p<0.050). The TG showed significant improvements on BRIEF-A and DEX (p<0.010), but not CFQ, compared to the CG over time In the TG, significant improvements were found on CPT-II, CWI, TT, and HT at T2 and T3 (p<0.050), VFT at T3 (p<0.050), and UPSA at T2 (p<0.001). In the CG, significant improvements were found on CPT-II, TT, and HT at T2 and T3 (p<0.050), and VFT and UPSA at T2 (p<0.050). The TG showed a significant improvement on CWI, VFT, and TT (p<0.050), but not CPT-II, UPSA, and HT, compared to the CG over time. No significant differences were found on TMT within or between groups over time.
<p>Cantor et al. (2014) USA RCT PEDro=6 N=98</p>	<p>Population: TBI; Mean Age=45.3 yr; Gender: Male=37, Female=61; Mean Time Post Injury=12.6 yr; Severity: Mild=49, Moderate=19, Severe=30.</p> <p>Intervention: Participants were randomly assigned to either immediate start (IS; n=49) or waitlist control (WL; n=49) groups. Participants received group sessions of emotional regulation (2 sessions, 45 min) and an individual problem solving session of attention training (1 session, 60 min) per day (3 days/wk for 12 weeks). Group sizes were</p>	<ol style="list-style-type: none"> There was a significant treatment effect for the EF index favoring the IS group (p=0.008). There was no significant difference between groups in the DERS of ARMS. Secondary analysis revealed a significant treatment effects for the FeSBe scale (p=0.049) and the PSI (p=0.016). There were no other significant treatment effects. Variance of depression, age, severity and time

	<p>generally 4-6 participants.</p> <p>Outcome Measure: Attention Rating and Monitoring Scale (ARMS), Behavioural Assessment of the Dysexecutive Syndrome, Difficulties in Emotion Regulation Scale (DERS), Executive Function Composite from Factor Analysis (EF index), Problem Solving Inventory (PSI), Frontal System Behavioural Scale (FrSBe).</p>	<p>since injury did not change treatment effects.</p>
<p>Chen et al. (2011) USA RCT PEDro=5 N=12</p>	<p>Population: TBI=9, Other=3: Mean Age=48 yr; Gender: Male=5, Female=7; Time Post-Injury Range=6 mo-6 yr.</p> <p>Intervention: Participants were randomized to receive either the goals training intervention (n=7) or education intervention (n=5) for 5 wk, after which they switched to the other condition for another 5 wk. The goals training was spread over 5 wk and involved: group, individual and home-based training. The education program was a 5 wk didactic educational instruction regarding brain injury.</p> <p>Outcome Measures: Letter number sequencing, Wechsler Adult Intelligence Scale-III, Auditory consonant trigrams, Digit Vigilance Test, Design and Verbal Fluency Switching, Trails B, Stroop Inhibition, Hopkins Verbal Learning Test, Brief Visual Memory Test Revised, Trails A test, Visual Attention Task.</p>	<ol style="list-style-type: none"> 1. On the domain of attention and executive functions, all participants in the goal training intervention showed an increase from pre to post goals training; while only 7/12 in the education intervention showed an increase from pre to post education (p<0.0001). 2. For learning and memory performance scores increased an average of 0.70 units after participation in goals training than after participation in education intervention (p=0.020). 11/12 participants improved in the goals training group while 4/12 improved in the education group (p=0.009). 3. Tests of motor speed of processing showed no significant differences between the two interventions with a non-significant trend for greater improvements in goal-training compared to education (p=0.070).
<p>Novakovic-Agopian et al. (2011) USA RCT Crossover PEDro=5 N=16</p>	<p>Population: TBI=11, Stroke=3, Other=2: Mean Age=50.4 yr; Gender: Male=7, Female=9; Time Post Injury Range=1-23 yr.</p> <p>Intervention: Participants were randomized to 5 wk interventions consisting of a goals training program (n=8) or an educational instruction group (n=8). Goal training focused on mindfulness-based attentional regulation and goal management strategies for participant-defined goals. Educational training was didactic instructional sessions about brain injury. At the end of 5 wk, participants were switched to the other intervention. All participants were assessed at baseline, Week 5 and again at Week 10.</p> <p>Outcome Measure: Auditory Consonant Trigrams, Letter Number Sequencing (working memory); Digit Vigilance Test (sustained attention); Stroop Inhibition Delis-Kaplan Executive Function System (Inhibition); Trails B, Design Fluency-switching (mental flexibility), Hopkins</p>	<ol style="list-style-type: none"> 1. At the end of wk 5 participants in the goals-edu group showed significant improvement on measures of attention and executive function from baseline (p<0.0001), while the edu-goals group showed no change or minimal change (p>0.050). 2. The goals-edu group had significantly greater improvements than the edu-goals group on the following at wk 5: working memory (<i>Mean</i> 1.12 vs -0.12, p<0.0001); mental flexibility (<i>Mean</i> 0.64 vs 0.04, p=0.009); inhibition (<i>Mean</i> 0.62 vs 0.04, p=0.005); sustained attention (<i>Mean</i> 0.96 vs 0.27, p=0.010); learning (<i>Mean</i>=0.51 vs 0.08, p=0.020); and delayed recall (<i>Mean</i> 0.39 vs -0.27, p=0.010). 3. At wk 10, the edu-goals group significantly improved compared to wk 5 on: attention and executive function (0.79 vs 0.03, p<0.0001); working memory (1.31 vs -0.12, p<0.0008); mental flexibility (0.66 vs 0.04, p<0.0008); inhibition (0.50 vs 0.04,

	<p>Verbal Learning Test-Revised, Brief Visual Memory Test-Revised.</p>	<p>p=0.010); sustained attention (0.44 vs 0.27, p=0.010); memory (0.609 vs -0.10, p=0.020); learning (0.66 vs 0.08, p=0.050); and delayed recall (0.55 vs -0.27, p=0.020).</p> <p>4. Those in the goals-edu group who had completed the training session were able to maintain their gains and there were significant improvements in attention and executive function (p<0.040) and working memory (p<0.020).</p>
<p>Rath et al. (2003) USA RCT PEDro=2 N=46</p>	<p>Population: TBI: Mean Age=43.6 yr; Gender: Male=23, Female=37; Mean Time Post Injury=48.2 mo. Intervention: Patients were randomized into the innovative (n=32) or conventional (n=28) treatment groups. The innovative group received 24, 2 hr sessions focusing on emotional self-regulation and clear thinking. The conventional group received 24, 2-3 hr sessions focusing on cognitive remediation and psychosocial groups. Outcome Measure: Weinberg Visual Cancellation Test, Stroop Color-Word Task, FAS-Controlled Oral Word Association Test, Will-Temperament Scale, Visual Reproduction, Immediate and Delayed recall, Watson-Glaser Critical Thinking Appraisal, Wechsler Adult Intelligence Scale-III.</p>	<p>1. The innovative group showed significant improvements in visual memory immediate recall (p<0.001). 2. The conventional and the innovative group showed significant improvements: on logical memory recall (p<0.001), logical memory delayed recall (p=0.010), and visual memory delayed recall (p=0.010). 3. The conventional group had significant improvements in reasoning (p<0.050). 4. The innovative group had significant improvements in executive function (p<0.050); problem-solving self-appraisal (p=0.005); self-appraised clear thinking and emotional self-regulation (p<0.010); and observer ratings of roleplayed scenarios (p<0.005).</p>
<p>Copley et al. (2015) Australia Pre-Post N=8</p>	<p>Population: ABI; Mean Age=44.5 yr; Gender: Male=5, Female=3; Mean Time Post Injury=12 mo; Severity: Moderate-Severe. Intervention: All participants completed a treatment consisting of metacognitive strategy instruction (MSI) during 3 components. 1) Individualized sessions (IS) consisted of identifying language based goals and strategies to accomplish them (2 hr x2 sessions). 2) Group sessions (GS) where participants work on their goals in a group setting completing auditory and written comprehension tasks (1.5 hrs). 3) Daily home practice sessions (HS) involved transferring the skills learnt in the first 2 components into everyday life by teaching the significant other how to implement MSI. Outcome Measure: Measure of Cognitive-Linguistic Abilities Subtests: Paragraph Comprehension, Story Recall, Verbal Abstract Reasoning, Functional Reading, Factual Comprehension, Inferential Reasoning Skills (Low Level and High Level).</p>	<p>1. There was no significant difference in pre-post scores for paragraph comprehension (p=0.340). 2. There was no significant difference in pre-post scores for story recall (p=0.028). 3. There was no significant difference in pre-post scores for verbal abstract reasoning (p=0.111). 4. There was no significant difference in pre-post scores for functional reading (p=0.204). 5. There was no significant difference in pre-post scores for factual comprehension (p=0.891). 6. There was no significant difference in pre-post scores for inferential reasoning skills, both low level (p=0.125) and high level (p=0.020).</p>

<p>Gabbatore et al. (2015) Italy Pre-Post N_{Initial}=20, N_{Final}=15</p>	<p>Population: TBI; Mean Age=36.7 yr; Gender: Male=10, Female=5; Mean Time Post Injury=76.1 mo; Mean GCS=4.5. Intervention: Participants completed a cognitive group rehabilitation program focussed on mental representations underlying one’s behaviours (2 x/week for 3 months). Each session consisted of comprehension activities (discussing specific communication modalities) and production activities (role-playing activities). Participants were assessed at T0 (3 months before intervention (regular activities during this time), T1 (before intervention), T2 (after intervention) and T3 (3 month follow-up – regular activities during this time). Total study duration was 9 months. Outcome Measure: : Assessment Battery for Communication (ABaCo- comprehension, production, linguistic, extralinguistic, paralinguistic, and context), Verbal Span Task (VST), Spatial Span Task (SST), Attentive Matrices Test (AMT), Trail Making Test (TMT), Tower of London Test (TOL), Colored Progressive Matrices Raven (CPM Raven), Aachener Aphasia Test-Denomination Scale (AAT), Sally-Ann Task, Strange Stories Task, Immediate and Deferred Recall Test (IDR), Wisconsin Card Sorting Test (WCST).</p>	<ol style="list-style-type: none"> 1. No significant improvements in ABaCo (production and comprehension) were observed from T0 to T1. 2. Participants showed significant improvements from T1 to T2 for ABaCo comprehension (p<0.001), production (p<0.001), linguistic (p=0.005), extralinguistic (p=0.008), paralinguistic (p=0.02), and context (p=0.01). 3. The improvements made during the treatment period were stable between T2 and T3 for both Comprehension (p=0.86) and Production (p=0.32). At T3, AbaCo scores did not show significant differences from T2. 4. There was no significant difference between T1 and T2 on the VST (p=0.49), SST (p=0.74), AMT (p=0.35), TMT (p=0.45), TOL (p=0.50), CPM Raven (p=0.09), AAT (p=0.22), Sally-Ann (p=0.58), or strange stories task (p=1.00). 5. There was a significant improvement between T1 and T2 on the IDR (p=0.01) and WCST (p=0.003).
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PEdro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

A group out of Norway investigated the effects of Goal Management Training (TG) to a Brain Health workshop (CG) group sessions on cognitive outcomes post brain injury (Tornas et al. 2016). The study showed that individuals receiving goal management training improved significantly in cognitive and executive outcomes after treatment, and a 6 mo follow up. While this study showed promising results, it is important to remember that despite its rigorous methodology, the patient population was very heterogenous and it is unclear how different injuries impacted the outcomes. Further, similar results were found in an RCT by Novakovic-Agopian et al. (2011), where a goals training group showed significant improvement on attention and execute function assessments compared to the educational group. Despite switching interventions at the 5 week mark to the educational intervention, the goal training group continued to improve significantly. Interestingly, an RCT published in the same year demonstrated that a goal training intervention (although beneficial) may not be more beneficial than other interventions such as educational training with respect to processing speed (Chen et al., 2011). In this study both groups significantly improved in attention directed goal completion.

Emotional regulation was also examined as a potential intervention for the remediation of attention and executive dysfunction post ABI (Cantor et al., 2014). While this treatment was not seen to be effective in the recovery of attention, significant improvements on executive function were noted (EF, FeSBe, PSI). Further support for emotional oriented intervention can be found

in an earlier study by Rath et al. (2003). The group completed an RCT comparing two cognitive rehabilitation therapies: conventional (cognitive remediation and psychosocial components) versus an innovative rehabilitation approach focusing on emotional self regulation and clear thinking. Outcomes were measured across multiple domains of cognition including attention, memory, reasoning, psychosocial functioning, and problem solving measures. Significant changes comparing baseline to post intervention outcomes were seen for each group, however, the improvements were different for the interventions. No between-group comparisons were made.

A pre-post study by Copley et al. (2015) investigated the effects of a Metacognitive Strategy Instruction (MSI) intervention on verbal and cognitive outcomes post ABI. The program was delivered individually, in a group-setting, and at home. Despite the multi-step process, no improvements were seen in cognitive or verbal abilities from baseline after the intervention. Gabbatore et al. (2015) implemented a cognitive group rehabilitation program for patients post TBI, and discovered that compared to before the intervention, patient's recall (IDR), attention (WCST), and communication skills (ABaCo) all significantly improved.

Parente and Stapleton (1999) in a descriptive study compared brain injury survivors who completed a cognitive skills group to comparable controls. The cognitive skills group interventions included education regarding "thinking skills" such as problem solving, concentration/ attention, decision making, remembering names and faces, study skills, functional mnemonics, prosthetic memory devices, social cognition, organizational skills and goal setting. Other important aspects of the cognitive skills group included computer training, prosthetic aid training, interviewing skills training and focus on a model of clients teaching clients. There was no statistical analysis completed, however, the return to work rate for 13 of 33 participants assigned to the cognitive skills group training was 76% as compared to 58% for the control group. Competitive employment for the intervention group was maintained at 6-month follow up.

Conclusions

There is conflicting evidence (level 1b and level 2) as to whether goal orientated group interventions are more than or equally as successful as educational interventions at improving cognitive and executive function in patients post ABI.

There is level 2 evidence that emotional regulation group interventions are effective at improving executive function in patients post TBI.

There is conflicting (level 4) evidence that group cognitive interventions (ie. Metacognitive Strategy Instruction) improves executive function in patients post TBI.

It is unclear whether goal oriented interventions delivered in a group setting are more successful than educational interventions at improving cognitive and executive function post ABI. However, no detrimental effects have been found with the intervention.

Emotional regulation interventions delivered in a group setting may improve executive function in patients post TBI; however, it is unclear if it is superior at doing so compared to conventional cognitive remediation.

It is unclear whether cognitive interventions (such as the Metacognitive Strategy Instruction program) improves language ability, and executive/ cognitive function in patients post TBI.

6.4.1.2 Rehabilitation of General Cognitive Functioning

Interventions for the treatment of cognitive deficits post TBI tend to be diverse with variability between the interventions themselves and the outcome measures used to document results.

Gordon et al. (2006) conducted an extensive review of the TBI rehabilitation literature and identified 13 studies dealing with rehabilitative treatments of cognitive deficits. Studies included in this review had a multitude of inclusion criteria. The studies identified were of limited methodological quality, but suggested that compensatory strategy training improved attention deficits and mild memory impairments (Gordon et al., 2006). Several researchers have noted that training-based therapies that target executive control, such as “*attention, problem solving, and the use of metacognitive strategies*” (Novakovic-Agopian et al., 2011) may improve functioning in those who sustain an ABI (Cicerone, 2002; Kennedy et al., 2008; Sohlberg et al., 2003b). Studies included in this section have examined the effects of cognitive rehabilitation strategies.

Table 6.27 The Effect of Cognitive Rehabilitation Strategies on General Cognitive Function Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Neistadt et al. (1992) USA RCT PEDro=6 N=45	Population: TBI: Mean Age=33.2 yr; Gender=Male; Time since injury=7.9 yr. Intervention: Participants were randomly assigned to an adaptive (n=23) or a remedial (n=22) approaches for their occupational therapy. Outcome Measure: The Parquetry Block test; Block design subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).	1. After treatment, the remedial group improved significantly more than the adaptive group on the Parquetry Block test (p=0.019), but there were no significant differences on the WAIS-R Block Design subtest. 2. There was a non-significant tendency in the expected direction to support that the adaptive group would perform better than the remedial group on the RKE-R after treatment.
Rasquin et al. (2010) Netherlands Cohort N=52	Population: Mean Age: 49.5 yr; Gender: male=14, female=13; Mean Time Post-Injury:1.9 yr; Condition: CVA=9, TBI=5, Other ABI=13. Controls whom were relatives of the patients=25. Intervention: Participants were asked to formulate individual strategies to address specific cognitive issues (attention memory or problem solving) and to develop methods to ask for help with problems resulting from the head injury. Caregivers were asked to attend sessions. Sessions lasted approximately 2.5 hours and ran for approximately 15 weeks. Assessment was	1. Results from the Goal Attainment Scaling, the Stroke Adapted Impact Scale and the Cognitive Failure Questionnaire all indicate there was significant improvement from baseline (T0) to immediately after treatment (T1) (p<0.05). 2. Patients improved on significantly on individual goals (p<0.05) between T0 to T1.

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	conducted at baseline, 21 weeks after treatment, 6 months after treatment. Outcome Measure: Goal Attainment Scaling; Stroke Adapted Impact Scale; Cognitive Failure Questionnaire	3. No further changes were noted on the primary outcomes 6 months post intervention (T2).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

Two studies investigating the remediation of general cognitive functioning were observed. Neistadt (1992) divided 45 patients into one of two groups: a remedial group who received individual training with parquetry block assembly, and an adaptive group who received functional skills training over a six-week period. Outcomes for the effect of treatment for constructional test performance revealed that the remedial group improved significantly more than the adaptive group on the Parquetry Block test. However, there were no significant differences on the WAIS-R Block Design subtest after treatment. Training-specific learning appears to be an effective approach to rehabilitation as demonstrated by the treatment effect.

In a more recent cohort study, Rasquin and colleagues (2010) investigated the effectiveness of a low intensity outpatient cognitive rehab program on those (n=27) who had sustained an ABI. All participants were in the chronic phase of recovery and all were asked to invite a care giver to attend sessions with them (n=25). Sessions ran for 2.5 hours each week for a total of 15 weeks. All were assessed prior to the session beginning, immediately afterward and again 6 months later. Participants worked on developing strategies to assist them with their attention, memory and problem solving difficulties. Social skills training sessions were also held. Changes were noted immediately after the cognitive rehab program ended and this improvement in goal attainment, and cognitive impairment was maintained at the 6th month follow-up.

Conclusions

There is level 1b evidence that a remedial occupational therapy intervention may be superior compared to an adaptive occupational therapy intervention at improving general cognitive functioning in patients post TBI.

There is level 4 evidence that a low intensity outpatient cognitive rehabilitation program may improve goal attainment and cognitive impairment in patients post ABI.

Remedial occupational therapy is likely superior to adaptive occupational therapy at improving general cognitive functioning in patients post TBI.

Low intensity outpatient cognitive rehabilitation might improve goal attainment and cognitive function in patients post ABI.

6.4.2 Pharmacological Interventions

6.4.2.1 Donepezil

The effectiveness of donepezil, a cholinesterase inhibitor, in improving cognitive and memory functions following brain injury was assessed. Cognitive impairments negatively impact patient autonomy, affecting one’s ability to return to work or school, and live alone (Masanic et al., 2001). When tested in individuals diagnosed with Alzheimer’s disease, donepezil has been found to be useful in treating memory problems (Morey et al., 2003; Walker et al., 2004). The impact of Donepezil impact on cognitive function and memory in a TBI population is explored in the table below.

Table 6.28 The Effect of Donepezil on Executive and General Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Khateb et al. (2005) Switzerland Pre-Post N_{initial}=15, N_{final}=10</p>	<p>Population: TBI; Mean age=43 yr; Gender: Male=8, Female=7; Mean Time Post Injury=4 2mo. Intervention: Patients were administered donepezil 5 mg/day for 1 mo, followed by 10 mg/day for 2 mos. Outcome Measure: Stroop test, Trail Making Test (TMT), Rey Auditory Verbal Memory Test (RAVMT), Test for Attentional Performance (TAP).</p>	<ol style="list-style-type: none"> 4 of 15 participants stopped due to side effects within the first week (e.g., nausea, sleep disorders, anxiety, dizziness, etc.). Changes on the neuropsychological evaluation show modest improvement. However, The comparison of the global score of all questionnaires before and after therapy was not significant (p=0.058). A significant improvement in executive function was only found for the Stroop Colour naming test (87.3±22.9 to 79.5±19.1, p=0.030); the RAVMT-learning for learning and memory (47.7±6.9 to 53.5±5.0, p=0.050); and the errors subsection of divided attention for attention, (5.8±3.3 to 2.9±2.7, p=0.030).

Discussion

Khateb et al. (2005) found only modest improvement on the various neuropsychological tests used to measure executive function, attention, and learning and memory. Of note results from the learning phase of the Rey Auditory Verbal Memory Test (RAVMT) showed significant improvement (p<0.050). The Donepezil intervention also demonstrated improvement in executive function, as the results from the Stroop-colour naming test showed significant improvements (p<0.030). On the test for Attentional Performance a significant change was noted on the divided attention (errors) subsection of the test. Overall, donepezil was found to be effective in improving learning, memory, divided attention, and executive function. However, possible benefits of donepezil administration must be balanced against the observed side effects in 27% of the population. Further randomized control trials are required to better explore the efficacy of donepezil post TBI.

Conclusions

There is level 4 evidence that donepezil is effective in improving learning, memory, divided attention, and executive function in patients post TBI.



Donepezil might improve attention, learning and short-term memory following TBI; however, side effects may incur from its use.

6.4.2.2 Methylphenidate

Methylphenidate is a stimulant whose exact mechanism of action in the CNS (?) is unknown (Napolitano et al., 2005). One theory is that methylphenidate acts on the presynaptic nerve to prevent the reabsorption of serotonin and norepinephrine, thereby increasing neurotransmitter concentrations within the synaptic cleft and leading to increased neurotransmission (Kim et al., 2006). In the past, methylphenidate has been extensively used as a treatment for attention deficit disorder, as well as narcolepsy (Glenn, 1998). A total of six RCTs examined the efficacy of methylphenidate as a treatment for the recovery of cognitive deficits post ABI.

Table 6.29 The Effect of Methylphenidate on Executive and General Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
<p>Dymowski et al. (2017) Australia RCT PEDro=9 N_{Initial}=11, N_{Final}=10</p>	<p>Population: TBI. <i>Methylphenidate Group (n=6):</i> Mean Age=35 yr; Gender: Male=4, Female=2; Mean Time Post Injury=366 d; Mean Worst GCS=4.83. <i>Placebo Group (n=4):</i> Mean Age=32.5 yr; Gender: Male=2, Female=2; Mean Time Post Injury=183.5 d; Mean Worst GCS=4.50. Treatment: Participants were randomly assigned to receive either methylphenidate (0.6 mg/kg/d rounded to the nearest 5mg with maximum daily dose of 60 mg) or placebo (lactose). Outcomes relating to processing speed, complex attentional functioning, and everyday attentional behaviour were assessed at baseline, 7 wk (on-drug), 8 wk (off-drug), and 9 mo follow-up. Outcome Measure: Symbol Digit Modalities Test (SDMT), Trail Making Test (TMT) A and B; Hayling (A, B, error), Digit Span (DS-Forward, Backward, Sequencing, Total), Ruff 2&7 Selective Attention Test Automatic Speed Raw Score (2&7 ASRS), Ruff 2&7 Selective Attention Test Controlled Speed Raw Score (2&7 CSRS), Simple Selective Attention Task Reaction Time (SSAT RT), Complex Selective Attention Task Reaction Time (CSAT RT), N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, Rating Scale of Attentional Behaviour Significant Other (RSAB SO).</p>	<p>1. After applying Bonferroni corrections, no significant differences between groups from baseline to 7 wk, baseline to 8 wk, or baseline to 9 mo were observed for SDMT, TMT A, TMT B, Hayling A, Hayling B, Hayling error, DS Forward, DS Backward, DS Sequencing, DS Total, 2&7 ASRS, 2&7 CSRS, SSAT RT, CSAT RT, N-back 0-back RT, N-back 1-back RT, N-back 2-back RT, or RSAB SO.</p>
<p>Zhang and Wang (2017) China RCT PEDro=10 N_{Initial}=36, N_{Final}=33</p>	<p>Population: TBI; Severity: mild to moderate. <i>Methylphenidate Group (n=18):</i> Mean Age=36.3 yr; Gender: Male=13, Female=5. <i>Placebo Group (n=18):</i> Mean Age=34.9 yr; Gender: Male=14, Female=4. Treatment: Participants were randomly assigned to receive methylphenidate (flexibly titrated from 5 mg/d at the beginning, then</p>	<p>1. At baseline, there were no significant differences between groups in terms of demographics, MFS, CRT, CTT, MAT, DSST, MMSE, BDI, or HAMD. 2. Post-intervention, the experimental group had significantly lower scores compared to control group for MFS (p=0.005), CRT (p<0.001), CTT</p>

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
	gradually increased by 2.5 mg/d until reaching 20 mg/d or placebo for 30 wk. Outcome Measure: Mental Fatigue Scale (MFS), 3. Choice Reaction Time (CRT), Compensatory Tracking Task (CTT), Mental Arithmetic Test (MAT), Digit Symbol Substitution Test (DSST), Mini-Mental State Examination (MMSE), Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAMD).	(p<0.001), BDI (p=0.040), and HAMD (p=0.005). 3. Post-intervention, the experimental group had significantly higher scores compared to control group for MAT (p=0.020), DSST (p<0.001), MMSE (p<0.001).
Speech et al. (1993) USA RCT PEDro=7 N=12	Population: TBI; Mean Age=27.6 yr; Gender: Male=5, Female=7; Mean Time Post Injury=48.5 mo. Intervention: In a crossover design, participants were randomly assigned to receive 0.3 mg/kg methylphenidate, 2x/d, for 1 wk, followed by 1wk of placebo, or receive the treatment in a reverse order. Outcome Measure: Gordon Diagnostic System, Digit Symbol and Digit Span subtests of the Wechsler Adult Intelligence Scale-Revised, Stroop Interference Task, Sternberg High Speed Scanning Task, Selective Reminding Test, Serial Digit Test, and Katz Adjustment Scale.	1. No significant differences were found between methylphenidate and placebo condition in any of the outcome measures studied.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

Dymowski et al. (2017) investigated the effects of short-term, 7 wk, methylphenidate administration in patients post TBI compared to a placebo (control). After analyses, it was concluded that there were no significant improvement, or difference between groups for various measures and tests of attention. Speech et al. (1993) conducted a double blind placebo controlled trial evaluating the effects of methylphenidate following closed head injury and arrived at similar conclusions, as the treatment and placebo group did not vary in any measurements of memory, intelligence, or attention. Conversely, Zhang and Wang (2017) used a larger sample size to investigate the effects of long-term (30 wk) methylphenidate use in patients post TBI. While there were no difference between the groups at baseline, the treatment group had improved reaction time, cognitive ability, attention capacity, and depression when compared to the placebo group. The contradictory on methylphenidate use post TBI creates an interesting conflict, as all studies were conducted with high methodological quality and proper controls. The study by Zhang and Wang (2017) however has a larger sample size than the other two studies combined, and thus the results may be more indicative of the true effect of methylphenidate. However, because of the inconclusive results, not conclusive statements can be confidently made regarding the efficacy or methylphenidate use post TBI.

Conclusions

There is conflicting (level 1a) evidence regarding the effectiveness of the administration of methylphenidate following TBI for the improvement of general functioning.

The effectiveness of methylphenidate treatment to improve cognitive impairment following brain injury is unclear. Further studies with larger populations are required.

6.4.2.3 Sertraline

Sertraline, better known under its trade name Zoloft (Pfizer), is a selective serotonin reuptake inhibitor (SSRI) used for the treatment of depression and mood (Khouzam et al., 2003; Jorge et al., 2016). The majority of sertraline TBI research focuses on the prevention or treatment of major depressive symptoms post brain injury. However, recent studies have shifted focus and begun to evaluate the benefits of sertraline at improving cognitive disorders (Banos et al., 2010; Jorge et al., 2016; Lee, 2005). The studies reviewed below investigated the effect of sertraline on cognitive outcomes post TBI.

Table 6.30 The Effect of Sertraline on Executive and General Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
<p>Banos et al. (2010) USA RCT PEDro=9 N=99</p>	<p>Population: TBI. <i>Treatment group (n=49):</i> Gender: Male=39, Female=10; Mean Age=35.3 yr; Mean Time Post Injury=21.5 d; Mean GCS=5.8. <i>Placebo group (n=50):</i> Gender: Male=33, Female=17; Mean Age=34.5 yr; Mean Time Post Injury=19.2 d; Mean GCS=5.8.</p> <p>Intervention: Participants were randomized to either the treatment group which took sertraline daily (50 mg) or placebo. Patients were assessed at 3, 6 and 12 months.</p> <p>Outcome Measure: Wechsler Memory Index (Wechsler Adult Intelligence Scale III), Symbol-Digit Modalities Test, Logical Memory, Trial Making Test and 64-item Wisconsin Card Sorting Test.</p>	<ol style="list-style-type: none"> 1. More subjects in the treatment group dropped out at each time point. 2. Those in the placebo groups at the 6th and 12th month assessment period were older than the control group and had higher GCS. 3. Overall, there were no significant differences between the two groups on any of the cognitive measures.

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

The effect of early administration of sertraline on cognitive functioning was evaluated by Banos et al. (2010) in an RCT. When comparing the sertraline group, who received 50 mg per day, to a control group (placebo), there were no significant between group differences on any of the neuropsychological tests. The assessments examined attention and concentration, speed of processing, memory and executive function at 3, 6 and 12 months. Cognitive functioning was not found to improve following the administration of sertraline. . Of note, more patients in the sertraline group dropped out of the study compared to the control group when this was quantified at all assessment points— indicating the potential side effects associated with the treatment. Combined with the lack of apparent benefit to using the drug, use of sertraline is not currently recommended.

Conclusions

There is level 1b evidence that sertraline does not improve cognitive functioning in individuals who have sustained a moderate to severe TBI.

Sertraline has not been shown to improve cognitive functioning within the first 12 months post TBI, and may be associated with side effects.

6.4.2.4 Amantadine

Amantadine is a non-competitive N-methyl-D-aspartate receptor antagonist and has been used as an antiviral agent, prophylaxis for influenza A, treatment of neurological diseases such as Parkinson’s Disease, and the treatment of neuroleptic side-effects such as dystonia, akinesia and neuroleptic malignant syndrome (Schneider et al., 1999). Amantadine is also thought to work pre- and post-synaptically by increasing the amount of dopamine (in... the synapse? Pre-synaptic junction? Post-synaptic cell?) (Napolitano et al., 2005). Two studies were identified that investigated the effectiveness of amantadine as a treatment for the remediation of learning and memory deficits and cognitive functioning following TBI.

Table 6.31 The Effect of Amantadine on Executive and General Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
Schneider et al. (1999) USA RCT PEDro=5 N=10	<p>Population: TBI; Mean Age=31 yr; Gender: Male=7, Female=3; GCS Score Range=3-11.</p> <p>Intervention: Patients randomized to either amantadine (50-150 mg 2 x/d) or placebo for 2 wk in a crossover design with a 2 wk washout period.</p> <p>Outcome Measure: Battery of Neuropsychological tests, Neurobehavioural Rating Scale.</p>	<ol style="list-style-type: none"> 1. There was a general trend towards improvement in the study sample over the 6 wk. 2. There were no significant between group differences in terms of orientation (p=0.062), attention (p=0.325), memory (p=0.341), executive flexibility (p=0.732) or behaviour (p=0.737).
Kraus et al. (2005) USA Pre-Post N=22	<p>Population: TBI; Mean Age=36 yr; Gender: Male=17, Female=5; Severity of Injury: Mild=6, Moderate=6, Severe=10; Mean Time Post Injury=63.2 mo.</p> <p>Intervention: Positron emission tomography (PET) scan was done and participants received amantadine (10 0mg titrated to up to 400 mg/d over 3 wk). Amantadine was administered 3x/d (200 mg at 8AM, 100 mg at 12PM, and 100mg at 4PM) for 12 wk.</p> <p>Outcome Measure: Trail Making Test part A and B (TMT A, TMT B), Controlled Oral Word Association Test (COWAT), Digit Span, California Verbal Learning Test (CVLT), Rey Osterreith Complex Figure-Immediate (Rey Im) and Delayed (Rey De) recall.</p>	<ol style="list-style-type: none"> 1. Measures of executive function, as indicated by TMT B and COWAT, were significantly improved in patients following treatment with amantadine (t=-2.47; p<0.020). 2. No significant differences were found for attention (TMT A and Digit Span) or memory (CVLT, Rey Im, and Rey De). 3. Correlational analyses with PET scan results suggest that there may be a strong relationship between executive domain improvement and changes in left pre-frontal metabolism (r=0.92; p=0.010) and left medial temporal metabolism (r=0.91; p=0.010).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

In a small sample RCT by Schneider et al. (1999) the effects of Amantadine on cognition and behaviours was assessed. In this six week cross-over study, patients received both placebo and amantadine for 2 weeks each, with a 2 week washout period in between. Although the study found that patients improved over the six week study period, statistical comparison of results evaluating the five subsets of attention, executive/flexibility, memory, behaviour and orientation did not demonstrate any significant effect for the use of Amantadine. Similarly, Kraus et al. (2005) demonstrated that the administration of amantadine over a 12-week treatment period does not improve memory deficits or attention; however, significant improvements in executive functioning were observed. Given the quality and sample size of the current studies, future studies exploring the efficacy of amantadine for learning and memory are warranted.

Conclusions

There is level 2 evidence that Amantadine may not help to improve general functioning deficits in patients post TBI compared to placebo.

Amantadine might not be effective at improving attention and memory deficits post TBI. Its impact on executive functioning should be studied further.

6.4.2.5 Bromocriptine

Bromocriptine is a dopaminergic agonist which primarily exerts its actions through binding and activating D₂ receptors (Whyte et al., 2008). It has been suggested that dopamine is an important neurotransmitter for prefrontal function, an important area of the brain that contributes to cognitive function, memory, intelligence, language, and visual interpretation (McDowell et al., 1998; Siddiqui et al., 2008). In a study looking at the effects of bromocriptine on rats, Kline et al. (2002) noted that the animals showed improvement in working memory and spatial learning; however, this improvement was not seen in motor abilities. Two studies have been identified investigating the use of bromocriptine as an adequate treatment for the recovery of cognitive impairments following TBI.

Table 6.32 The Effect of Bromocriptine on Executive and General Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
McDowell et al. (1998) USA RCT PEDro=4 N=24	<p>Population: TBI; Median Age=32.5 yr; Gender: Male=20, Female=4; GCS Range=3-8; Time Post injury Range=27 d-300 mo.</p> <p>Intervention: In a crossover design, participants were randomly assigned to receive bromocriptine (2.5 mg) then placebo, or receive treatment in the reverse order.</p> <p>Outcome Measure: Dual-task Paradigm (counting and digit span), Stroop Test, Spatial Delayed-response Task, Wisconsin Card Sorting Test (WCST), Reading Span Test, Trail Making Test (TMT), Controlled Oral Word Association</p>	<ol style="list-style-type: none"> Following bromocriptine treatment there were significant improvements on the dual-task counting (p=0.028), dual-task digit span (p=0.016), TMT (p=0.013), Stroop Test (p=0.050), COWAT (p=0.020), and WCST (p=0.041). Bromocriptine had no significant effects on working memory (e.g. spatial delayed-response task and reading span test; p=0.978), or on control tasks (p=0.095).

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
<p>Powell et al. (1996) UK Case Series N=11</p>	<p>Test (COWAT), and Control Tasks.</p> <p>Population: TBI=8, SAH=3; Mean Age=36 yr; Gender: Male=6, Female=5; Time Post Injury Range=2mo-5 yr.</p> <p>Intervention: Patients received bromocriptine (a maximum dose of 5-10 mg/d). Patient assessments included two baseline evaluations (BL1 and BL2), evaluation when stabilized at maximum bromocriptine dose (MAXBROMO), and two post withdrawal evaluations (POST1 and POST2).</p> <p>Outcome Measure: Percentage Participation index (PPI), Spontaneity, Motivation, Card Arranging Reward Responsivity Objective Test (CARROT), Digit Span, Buschke Selective Reminding Test (BSRT), Verbal Fluency, Hospital Anxiety and Depression Scale.</p>	<ol style="list-style-type: none"> 1. Reported PPI ($p<0.0001$), motivation, and spontaneity (both $p<0.005$) increased significantly from BL2 to MAXBROMO. Improvements were seen in CARROT as well ($p<0.0001$). 2. Significant improvements were observed from BL2 to MAXBROMO on the digit span ($p<0.001$), BSRT ($p<0.01$), and verbal fluency ($p<0.001$). Scores on all three tests decreased (non-significant) from MAXBROMO to POST1, scores recovered to near MAXBROMO levels by POST2. 3. Bromocriptine was not associated with improvements in mood state.

PEDro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

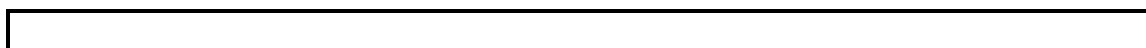
Discussion

The question of whether bromocriptine improves cognitive function in patients with ABI was explored in one RCTs (McDowell et al., 1998; Whyte et al., 2008), and one case series (Powell et al. 1996). In an earlier investigation, low-dose bromocriptine (2.5 mg daily) improved functioning on tests of executive control including a dual task, Trail Making Test, the Stroop test, the Wisconsin Card Sorting Test and the controlled oral word association test (McDowell et al., 1998). However, bromocriptine did not significantly influence working memory tasks. Although McDowell et al. (1998) demonstrated some benefits following administration of bromocriptine, there was only a single administration of bromocriptine and the dose was considerably lower than that given by other studies that did not meet our criteria. Spontaneous recovery may have been a factor leading to the improved abilities in individuals receiving a single dose (2.5 mg daily) of the medication; however, study results did not answer this question. Powell et al. (1996) conducted a multiple baseline design on 11 patients with TBI or subarachnoid hemorrhage who received bromocriptine. Improvements were found on all measures assessed (memory, attention, motivation spontaneity) except mood. In light of the fact that the last RCT investigating the effects of bromocriptine was conducted 20 years ago, new studies are required to build on the promising results of these very early conclusions.

Conclusions

There is level 2 evidence that low-dose bromocriptine may improve cognitive function in patients post TBI.

There is level 4 evidence that bromocriptine may improve motivational deficits in patients post TBI.



Bromocriptine may improve some executive cognitive functions such as dual task performance and motivational deficits. More research is needed before the benefits of using bromocriptine to enhance cognitive functioning are known.

6.4.2.6 Growth Hormone (GH) Replacement Therapy

Following an ABI, it is not uncommon for individuals to be diagnosed with hypopituitarism. It is estimated that as many as 25 to 40% of individuals with a moderate to severe ABI demonstrate chronic hypopituitarism (Bondanelli et al., 2007; Kelly et al., 2006; Schneiderman et al., 2008). Despite this, few patients are screened for GH deficiencies; thus, the link between cognitive impairment and growth hormone deficiencies has not yet been definitively established (High et al., 2010). The benefits of GH replacement therapy on patient’s executive function post TBI will be investigated below.

Table 6.33 The Effect of rh(GH) on Executive and Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro/ N	Methods	Outcome
<p>High Jr et al. (2010) USA PEDro=8 N=23</p>	<p>Population: TBI. <i>Placebo</i> (n=11): Mean Age=39.1 yr; Time Post Injury=5.1 yr. <i>Active rhGH</i> (n=12): Mean Age=36.1 yr; Time Post Injury=11 yr. Intervention: Participants were randomized to either a growth hormone replacement injection (rhGH) group or a placebo injection. Initially the drug was administered at 200 ug, followed by a 200 ug increase every month until the dosage reached 600 ug. Both groups received these injections for one year. Outcome Measure: Wechsler Adult Intelligence Scale-III, Delis-Kaplan Executive Function System.</p>	<ol style="list-style-type: none"> Overall study results did not show great improvements on the majority of assessments between groups. There was a significant improvement on the Finger tapping demonstrated in the treatment group. Processing Speed Index: the treatment group improved significantly over the one year period (p<0.050). The control group showed improvement at the end of the first 6 mo (p<0.010) but this was not seen at the end of the 1 yr. Significant improvement was also noted on the Wisconsin Card Sorting Test (executive functioning) for the treatment group (p<0.010). On the California Verbal learning Test-II improvement was noted for the treatment group on learning and memory.
<p>Moreau et al. (2013) France PCT N=50</p>	<p>Population: TBI. Treatment Group (TG, n=23): Mean Age=37.9 yr; Gender: Male=19, Female=4; Mean Time Post Injury=7.8 yr; Mean GCS=8.1. Control Group (CG, n=27): Mean Age=37.1 yr; Gender: Male=24, Female=3; Mean Time Post Injury=5.5 yr; Mean GCS=9.4. Intervention: Participants were allocated to receive GH therapy (TG, 0.2-0.6mg/d) or no treatment (CG) for 1yr. Outcomes were assessed before (T1) and after (T2) treatment. Outcome Measures: Activities of Daily Living (ADL); Quality of Life Brain Injury (QOLBI); Verbal Memory (VM); Rey</p>	<ol style="list-style-type: none"> Both groups showed significant improvement in instrumental ADL (iADL, p=0.001) at T2, but not personal ADL (pADL). Both groups showed significant improvement in QOLBI total scores (p=0.019) and intellectual (p=0.001), functional (p=0.023), and personal (p=0.044) subscores at T2, but not physical, psychological, and social subscores. Both groups showed significant improvement (p<0.050) in aspects of attention (RT), memory (VM), and visuospatial (RCF) abilities at T2.

	Complex Figure (RCF); Reaction Time (RT).	<ol style="list-style-type: none"> 4. The TG showed significantly greater improvement in QOLBI functional ($p=0.023$) and personal ($p=0.019$) subscores, as well as RCF ($p=0.037$), but no significant difference was found for other outcome measures. 5. There was a significant correlation ($p<0.050$) between QOLBI total and pADL ($r=0.49$). 6. There was a significant negative correlation ($p<0.01$) between attention (RT) and pADL ($r=-0.59$) and iADL ($r=-0.56$).
<p>Reimunde et al. (2011) Spain Cohort N=19</p>	<p>Population: TBI; Gender: Male=19, Female=0. With Growth Hormone Deficiency (GHD) Group (n=11): Mean Age=53.36 yr; Mean Time Post Injury=44.55 mo. Without GHD group (n=8): Mean Age=47.12 yr; Mean Time Post Injury=46.6 mo.</p> <p>Intervention: Those with GHD received recombinant human GH (rhGH), subcutaneously (0.5 mg/d for 20d then 1 mg/d for 5 d). Those without GHD were given a placebo. Cognitive rehabilitation was given to everyone (1 hr/d, 5d for 3 mo).</p> <p>Outcome Measure: Weschler Adult Intelligence Scale (WAIS).</p>	<ol style="list-style-type: none"> 1. Results of the WAIS indicated that the control group improved significantly on the digits and manipulative intelligence quotient ($p<0.050$). 2. For those in the treatment groups improvement was noted in cognitive parameters: understanding digits, numbers and incomplete figures ($p<0.050$) and similarities vocabulary, verbal IQ, Manipulative IQ, and total IQ ($p<0.010$).

PEdro=Physiotherapy Evidence Database rating scale score (Moseley et al., 2002).

Discussion

A 2010 RCT compared the long term (6 mo and 1 yr) effects of rhGH administration to placebo in a TBI population (High Jr et al. 2010). Significant improvements were noted in processing speed, executive functioning (Wisconsin Card Sorting Test), and learning (California Verbal learning test II) for both the rhGH and placebo groups. It is important to note while processing speed also improved in both groups at 6 mo, the improvement was only sustained in the treatment group at 1 yr. Further positive results were reported in a more recent PCT by Moreau et al. (2013). Patient quality of life, instrumental activities of daily living, attention, memory and visuospatial ability improved over the treatment period in both the treatment and control group. However, the treatment group improved significantly more in the functional and personal subscales of quality of life assessments. Reimunde et al. (2011) in a cohort study looking at the benefits of administering rhGH to a group of patients who have sustained either a moderate or severe TBI. Results of the study indicate that those receiving the rhGH improved significantly on the various cognitive subtests such as: understanding, digits, numbers and incomplete figures ($p<0.05$) and similarities vocabulary, verbal IQ, Manipulative IQ, and Total IQ ($p<0.01$). The control group also showed significant improvement but only in digits and manipulative intelligence quotient ($p<0.05$). Of note IGF-I levels were similar between both groups at the end of the study.

Conclusions

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is similar to placebo at improving processing speed (6 mo), executive function and learning in patients post TBI.

There is level 2 evidence that growth hormone (GH) therapy is similar to placebo at improving quality of life, instrumental activities of daily living (iADL), attention, memory, and visuospatial ability in patients post TBI.

There is level 2 evidence that recombinant human Growth Hormone (rhGH) administration improves intelligence and other cognitive subtests in TBI patients with growth hormone deficiency compared to TBI patients without; however, insulin-like growth factor-1 (IGF-1) levels may be the same between groups.

The administration of recombinant human Growth Hormone (rhGH) is likely not different than placebo at improving executive functioning, memory, or learning in patients post TBI; however certain aspects of patient quality of life may be improved.

The administration of recombinant human Growth Hormone (rhGH) might be superior at improving intelligence and cognition in patients with a growth hormone deficiency, versus those who do not, post TBI. Molecular markers of growth however may not be different post treatment between groups.

6.2.4.9 Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors prevent the enzyme acetylcholinesterase from breaking down acetylcholine. This increases the concentration of acetylcholine in synapses. Acetylcholine has been most strongly linked with the hippocampus and memory deficits, however it is also implicated in attentional processing.

Table 6.40 The Effect of Rivastigmine on Executive and General Cognitive Functioning Post ABI

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Silver et al. (2006) USA RCT PEDro=9 N=123	<p>Population: TBI. <i>Rivastigmine</i> (n=80): Mean Age=37 yr; Gender: Male=53, Female=27. <i>Placebo</i> (n=77): Mean Age=37.1 yr; Gender: Male=53, Female=24.</p> <p>Intervention: Participants were randomized to receive either rivastigmine (3-6 mg/d) or placebo. At the end of the first 4 wk, rivastigmine doses were increased to 3.0 mg, 2x/d. If necessary doses were decreased to 1.5 mg or 4.5 mg 2x/d.</p> <p>Outcome Measure: Trails A and B, Hopkins verbal learning test (HVL), Cambridge Neuropsychological Test Automated Battery Rapid Visual Information Processing (CANTAB RVIP A).</p>	<p>5. Results of the CANTAB RVIP A' and HVL found no significant differences between the placebo group and the treatment group.</p> <p>6. Rivastigmine was found to be well tolerated and safe.</p>

Author/Year/ Country/Study design/PEDro Score	Methods	Outcome
Silver et al. (2009) USA Pre-Post N=127	<p>Population: TBI. <i>Ex-Rivastigmine</i> (n=65): Mean Age=36.9 yr; Gender: Male=43, Female=22; Time Post Injury=73.5 mo. <i>Ex-placebo</i> (n=62): Mean Age=38 yr; Gender: Male=42, Female=20; Time Post Injury=100.1 mo.</p> <p>Intervention: Participants were randomized to receive rivastigmine injections (1.5 mg 2x/d to a max of 12 mg/d) or placebo injection.</p> <p>Outcome Measure: Trails A and B, Hopkins verbal learning test (HVL), Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).</p>	<p>7. The mean final dose of rivastigmine was 7.9 mg/day.</p> <p>8. 40% of patients were responders on CANTAB RVIP A' or HVL score at week 38.</p> <p>9. At the end of the study period all (n=98) were seen to improve of the CANTAB RVIP A' (p<0.001), the HVL (P<0.001), and the Trails A and B (p<0.001).</p>

Discussion

In two studies rivastigmine was administered to patients who had sustained a moderate to severe TBI (Silver et al., 2006; Silver et al., 2009). Results from both studies indicate that rivastigmine improved cognitive function and memory impairment, although results were not significant. In Silver’s (2009) follow-up open-label cohort study to their original RCT, participants (n=98) showed significant improvement on the CANTAB RVIP A’, the HVL and the trail A and B scales at the end of 38 week study period; however when further sub-analysis was performed depending on what group the patient previously belonged to, , those in the ex-rivastigmine group to those in the ex-placebo group, the improvements were not significant.

Conclusions

There is conflicting (level 1b and level 4) evidence that rivastigmine may not be effective in improving memory in ABI populations.

Rivastigmine may not be effective in treating memory deficits post-ABI.

6.5 Conclusions

Cognitive interventions target a large variety of cognitive functions and deficits. The rehabilitation of these functions is complicated by the lack of consensus on the definition of attention, cognition, and general and executive functioning.

Comparing the efficacy of various remediation efforts is also complicated by cross-study variability in treatment duration (e.g. from 30 minutes once a day for 5 days to 5 hours, every day for 6 weeks). Severity of injury and time since injury may also fluctuate from study to study. Over the past several years, Cicerone et al. (2000; 2005; 2011) reviewed a series of studies investigating the effectiveness of attentional retraining interventions during rehabilitation following traumatic brain injury and stroke.

Not all patients respond equally to all intervention strategies and no study in the current review indicated whether severity of memory impairment (or memory profile) interacts with a particular external memory aid. Technology has increased the availability of external aids, although some seem more feasible to use than others (e.g., cell phones or hand-held recorders). Unfortunately, the studies reviewed did not specify the length of time subjects required to master compensatory strategies or the nature of the long-term effects. Generally if these electronic appliances are used before the injury, they will be more likely to be used post injury. It was unclear from the studies if any of the participants had had some knowledge of these appliances.

Most studies examined only tasks of word list recall and paired-associate learning suggesting that the mnemonic strategies reviewed may not generalize to other types of information (particularly real-world or functional information outside the laboratory). Errorless learning appears to be one procedure that can be used to enhance learning conditions. One study highlighted the difference between severity of impairment and ability to benefit from internal strategies.

Frequency of intervention has an impact on learning and retention, although the exact parameters of this are unclear at the present time. The optimal duration of a program is also open for speculation. No studies reviewed examined the number of sessions required for memory groups to be effective and only one study evaluated a difference in effectiveness between mild and severely impaired individuals after sessions. Pharmacologic intervention does not appear to be effective in improving learning and memory deficits.

6.6 Summary

There is level 2 evidence that training programs designed to improve attention in general may be effective compared to unstructured stimulation in ABI populations.

There is level 3 evidence that attention processing training may improve attention compared to visual search training in ABI populations.

There is level 2 evidence that dual task training may be effective in improving attention task performance in ABI populations compared to non-specific training.

There is level 2 evidence that neither general nor name brand computer-based rehabilitation intervention may improve attention outcomes compared to usual care in ABI populations.

There is level 4 evidence that attention performance can be improved in ABI populations through repetition of tasks, either through computer-based or virtual reality environments.

There is level 2 evidence that adaptive training is no more effective than non-adaptive training in remediating attention in ABI populations.

There is level 1b evidence that emotional regulation therapy is not effective in treating attentional disorders compared to waitlist controls in ABI populations.

There is level 2 evidence that mindfulness training compared to no intervention may improve an individual's ability to correctly reject inappropriate stimuli post ABI.

There is level 2 evidence to suggest goal management training, when compared to education, may be effective at improving attention in post-ABI individuals. .

There is level 2 evidence that goal management training is more effective in remediating task completion times than motor skill training, however is not more effective in treating attention deficits, in post-ABI individuals.

There is conflicting (level 2) evidence that attentional control or processing training may not significantly improve attention in post-ABI individuals compared to control training.

There is level 4 evidence that summation tasks may be effective at improving attention in individuals post ABI.

There is level 4 evidence that a working memory training program may remediate attention in post-ABI individuals.

There is level 4 evidence that cognitive rehabilitation therapy may not be effective for improving attention post-ABI.

There is level 2 evidence that transcranial direct current stimulation compared to sham stimulation may improve divided attention in individuals post ABI.

There is level 1b evidence that donepezil may improve attention compared to placebo post ABI.

There is conflicting level 1b evidence regarding the effectiveness of methylphenidate following brain injury for the improvement of attention and concentration in individuals post ABI.

There is level 1a evidence that methylphenidate improves reaction time of working memory compared to placebo in individuals post ABI.

There is level 1b evidence that bromocriptine compared to placebo does not improve performance on attention tasks in patients post TBI.

There is level 2 evidence that bromocriptine improves attention, compared to placebo post ABI.

There is level 4 evidence that cerebrolysin may improve attention scores post ABI.

There is level 1b evidence that Rivastigmine compared to placebo may not be effective for improving concentration or attention in individuals post

There is level 4 evidence that the NeuroPage system may increase a patient's ability and efficiency to complete tasks post TBI.

There is level 4 evidence that voice organizer programs are effective at improving recall of goals, and are found to be effective by patients post TBI.

There is level 2 evidence that personal digital assistants (PDAs) are superior to a paper-based schedule book at improving task completion rates post TBI.

There is level 1b evidence that the use of a personal digital assistant (PDA) in combination with conventional occupational therapy is superior to occupational therapy alone at improving memory in patients post TBI.

There is level 1b evidence that use of a personal digital assistant (PDA) after receiving systematic instructions is superior to PDA trial and error learning at improving the number and speed of correct tasks post TBI.

There is level 4 evidence that conventional or touch-screen personal digital assistant (PDA) use are similar at improving memory post TBI.

There is level 1b evidence that reminder text messages sent to patients through their smartphones, whether alone or in combination with goal management training, may improve goal completion post TBI.

There is level 2 evidence that a television assisted prompting (TAP) system is superior to traditional methods of memory prompting (paper planners, cell phones, computers) at improving the amount of completed tasks post TBI.

There is level 1b evidence that the audio-verbal interactive micro-prompting system, Guide, can reduce the amount of support-staff prompts needed for the patient to complete a task post TBI.

There is level 4 evidence that a computerized tracking system that sends reminders to patients when they are moving in the wrong direction reduces the amount of support-staff prompts needed for patients to complete a task post TBI.

There is conflicting (level 2) evidence regarding whether or not the use of a calendar, compared to diary training, is effective for improving memory post ABI.

There is level 2 evidence that the presence of a calendar may not improve orientation post ABI.

There is level 2 evidence that diary training in combination with self-instructional training may be more effective than diary training alone at improving memory and task completion post ABI.

There is level 4 evidence that virtual reality (VR) training may improve learning performance post ABI, although the effect may not be different from non-VR training.

There is level 2 evidence that virtual reality training alone may be promising for improving memory outcomes, and has a positive impact on visual and verbal learning when in combination with exercise.

There is level 1b evidence that hypnosis compared to no treatment may not be effective at improving memory in individuals post ABI.

There is level 1b evidence that the Short Memory Technique may not be more effective than standard memory therapy at improving memory in individuals post ABI.

There is level 2 evidence that participation in a goals training program, followed by an educational program, may be more effective for improving memory in individuals post ABI compared to receiving the treatment conditions in reverse order.

There is level 1b evidence that compensatory memory strategies, self-awareness training, and participation in memory group sessions may be effective for improving memory in individuals post ABI compared to no treatment.

There is level 2 evidence that Strategic Memory and Reasoning Training (SMART) may improve learning and working memory compared to no memory training in individuals post ABI.

There is level 2 evidence that dual-task training may be effective for improving memory in individuals post ABI when presented before the control condition, compared to the reverse.

There is level 2 evidence that both computer-administered and therapist-administered memory training may be more effective than no treatment for improving memory in ABI participants. However, no treatment appears to be better than the other.

There is level 2 evidence that both cognitive remediation and emotional self-regulation may be effective at improving different elements of memory in individuals post ABI.

There is level 1b evidence that attention processing training compared to supportive listening may improve memory in individuals post ABI.

There is level 2 evidence that BrainHQ is not an effective program for improving memory and learning compared to no intervention in individuals post ABI.

There is level 4 evidence that using mental representations and role-playing may not be effective at improving memory in individuals post ABI.

There is level 4 evidence that Cogmed training software may improve working memory performance and occupational performance in individuals post ABI.

There is conflicting (level 4) evidence regarding whether or not Parrot software is effective at improving memory and learning in individuals post ABI.

There is level 4 evidence that mental addition tasks may improve working memory in individuals post ABI.

There is level 1b evidence that cranial electrotherapy stimulation may not improve memory and recall compared to sham stimulation post TBI.

There is level 1b evidence that donepezil improves short-term memory compared to X post ABI.

There is level 4 evidence that donepezil may be effective in improving short-term, long-term, verbal, and visual memory post ABI.

There is conflicting (level 1b) evidence regarding the effectiveness of the administration of methylphenidate compared to X following brain injury for the improvement of memory in patients post TBI.

There is level 1b evidence that sertraline may not improve memory compared to placebo in individuals who have sustained a moderate to severe TBI.

There is level 2 evidence that amantadine may not improve learning and memory deficits in patients post TBI.

There is level 2 evidence that pramiracetam may improve males' memory compared to placebo post TBI.

There is level 1b evidence that oral physostigmine may improve long-term memory compared to placebo in men with TBI.

There is level 2 evidence that low-dose bromocriptine may improve cognitive function, but not working memory in patients post TBI.

There is level 4 evidence that bromocriptine may improve memory in patients post TBI.

There is level 4 evidence that cerebrolysin may improve memory function post ABI.

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is similar to placebo at improving processing speed (6 mo), memory, executive function and learning in patients post TBI.

There is level 2 evidence that growth hormone (GH) therapy is similar to placebo at improving quality of life, instrumental activities of daily living (iADL), attention, memory, and visuospatial ability in patients post TBI.

There is level 1b evidence that rivastigmine may be effective in improving memory in ABI populations.

There is level 1b evidence that targeted hypnosis may transiently improve cognitive function in patients post TBI or stroke.

There is level 1b evidence that an attention remediation intervention is superior to TBI education alone and improving executive function in patients post TBI.

There is level 2 evidence that dual-task training may improve general cognitive functioning compared to a non-specific cognitive program in patients post TBI.

There is level 1b evidence that a comprehensive cognitive treatment strategy may be superior to a computerized training package at improving task initiating and goal achievement post TBI.

There is level 4 evidence that cognitive rehabilitation may increase productivity in everyday functioning, and cerebral blood flow during treatment in patients post TBI.

There is conflicting (level 1b and level 2) evidence as to whether virtual-reality training is or is not superior to conventional cognitive training at improving cognitive and executive function outcomes post TBI.

There is level 2 evidence that computer or smartphone software programs, such as BrainHQ, Parrot Software, ProSolv app, may not be superior to no intervention at improving problem-solving skills and general functioning in patients post TBI.

There is level 2 evidence that goal management training may be superior to motor skills training at improving everyday skills like meal preparation, but not neuropsychological tests or intelligence in patients post TBI.

There is conflicting evidence (level 1b and level 2) as to whether goal orientated group interventions are more than or equally as successful as educational interventions at improving cognitive and executive function in patients post ABI.

There is level 2 evidence that emotional regulation group interventions are effective at improving executive function in patients post TBI.

There is conflicting (level 4) evidence that group cognitive interventions (ie. Metacognitive Strategy Instruction) improves executive function in patients post TBI.

There is level 1b evidence that a remedial occupational therapy intervention may be superior compared to an adaptive occupational therapy intervention at improving general cognitive functioning in patients post TBI.

There is level 4 evidence that a low intensity outpatient cognitive rehabilitation program may improve goal attainment and cognitive impairment in patients post ABI.

There is level 4 evidence that donepezil is effective in improving learning, memory, divided attention, and executive function in patients post TBI.

There is conflicting (level 1a) evidence regarding the effectiveness of the administration of methylphenidate following TBI for the improvement of general functioning.

There is level 1b evidence that sertraline does not improve cognitive functioning in individuals who have sustained a moderate to severe TBI.

There is level 2 evidence that Amantadine does not help to improve general functioning deficits in patients post TBI compared to placebo.

There is level 2 evidence that low-dose bromocriptine may improve cognitive function in patients post TBI.

There is level 4 evidence that bromocriptine may improve motivational deficits in patients post TBI.

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is similar to placebo at improving processing speed (6 mo), executive function and learning in patients post TBI.

There is level 2 evidence that growth hormone (GH) therapy is similar to placebo at improving quality of life, instrumental activities of daily living (iADL), attention, memory, and visuospatial ability in patients post TBI.

There is level 2 evidence that recombinant human Growth Hormone (rhGH) administration improves intelligence and other cognitive subtests in TBI patients with growth hormone deficiency compared to TBI patients without; however, insulin-like growth factor-1 (IGF-1) levels may be the same between groups.

There is conflicting (level 1b and level 4) evidence that rivastigmine is effective in improving memory in ABI populations.

There is conflicting (level 1b and level 4) evidence that rivastigmine may not be effective in improving memory in ABI populations.

6.7 References

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