ERABI EVIDENCE-BASED REVIEW of moderate to severe ACQUIRED BRAIN INJURY

REHABILITATION OF LEARNING & MEMORY DEFICITS

POST ACQUIRED BRAIN INJURY

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Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of moderate to severe Acquired Brain Injury (ERABI) *Rehabilitation of Learning and Memory Deficits Post Acquired Brain Injury.* Through collaboration of researchers, clinicians, administrators, and funding agencies, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Ministry of Health, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and is committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto) and Dr. Shawn Marshall (University of Ottawa) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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Preface

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

Cecilia Flores-Sandoval, PhD, is a clinical research assistant and the coordinator of the Evidence-Based Review of Acquired Brain Injury (ERABI). She completed a master's degree and a PhD in Health and Rehabilitation Sciences, field of Health and Aging. Her research interests include aging and rehabilitation, patient engagement and transitional care for older adults.

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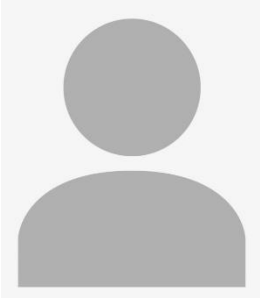
Shannon Janzen, MSc, is a research associate and the project coordinator for the Evidence-Based Review of Acquired Brain Injury (ERABI). Her research interests focus on the integration of best evidence into clinical practice to optimize patient outcomes, with an emphasis on knowledge translation initiatives.

Penny Welch-West has been working as a Speech-Language Pathologist since 1998 and enjoys a very varied practice ranging from Rehabilitation through Complex/Continuing and Palliative Care. This work includes teaching, assessment and treatment in the areas of dysphagia (swallowing), voice, articulation, language, cognitive-communication and Augmentative and Alternative Communication (AAC).

Amber Harnett, MSc, RN, CNF scholar, completed her MSc in pathology and the accelerated BScN program at Western University. Passionate about supporting and advocating for those with acquired brain injuries, she works as a research coordinator to improve healthcare systems through research synthesis, guidelines development, knowledge translation, education, and outreach, in the CORRE lab at Parkwood Institute.



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Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies.

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amyotrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with traumatic brain injury (TBI), diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Brain Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale (GCS). Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the GCS, the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA). Another factor used to distinguish moderate and severe brain injury is evidence of intracranial injury on conventional brain imaging techniques which distinguish severity of injury from a mild or concussion related brain injury.

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–July 2021 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the study population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury (as defined in Table 2), and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality randomized controlled trials (RCTs) (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate and the intensity with which it should be provided, based on their individual patient's needs. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence

allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with the known limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	Prospective Controlled Trial (PCT)	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post Trial	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each RCT was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

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Summary of the Evidence

Intervention	Key Point Level of Evidence
Non-Pharmacological Interventions	
Assistive Devices	Voice organizers may help individuals with ABI remember previously identified goals - *There is level 2 evidence that voice organizers may be an effective memory aid for individuals with ABI* Automated prompting systems, such as Guide (audio-verbal interactive micro-prompting system) and a computerized tracking system, can help individuals with TBI remember to complete tasks, such as attending appointments. - *There is level 1b evidence that the audio-verbal interactive micro-prompting system, Guide, can reduce the number of support-staff prompts needed for the individual to complete a task post TBI.* - *There is level 4 evidence that a computerized tracking system that sends reminders to individuals when they are moving in the wrong direction can aid in increasing attendance to scheduled appointments.* Palmtop computers can assist individuals with ABI with memory dependent activities of daily living. - *There is level 4 evidence that palmtop computers may be an useful memory aid for individuals post ABI* 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. Individuals who have used previous memory aids might benefit from this intervention the most. - *There is level 1b evidence that the use of a personal digital assistant in combination with conventional occupational therapy is superior to occupational therapy alone at improving memory in individuals post TBI.* - *There is level 1b evidence that use of a 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 2 evidence that PDAs are superior to a paper-based schedule book at improving task completion rates post TBI.* - *There is level 2 evidence that PDAs may improve everyday task completion and performance in individuals with TBI.* - *There is level 4 evidence that individuals with ABI who have used memory aids previously may benefit more from the use of PDAs.* The use of a pager may improve the individual's ability to complete tasks post TBI. - *There is level 2 evidence that the NeuroPage system may increase the individual's ability and efficiency to complete tasks post TBI.* A television assisted prompting (TAP) program is useful for improving task completion in individuals with ABI. - *There is level 2 evidence that prospective memory reminders delivered through the television is superior to typical reminder strategies (i.e., paper planners, cell phones, computers) at improving the amount of completed tasks post ABI.* Text message prompts sent to an individual's mobile phone, when used alone or in combination with other memory-improvement therapies, may improve task completion post TBI. However, risk of device dependency exists. - *There is level 1b evidence that reminder text messages sent to individuals through their mobile phones, whether alone or in combination with goal management training, improves goal completion post TBI.*
External Passive Technology or Non-Technology Aids	There are conflicting results about the effectiveness of calendars as a tool for improving memory and task completion post ABI. - *There is conflicting evidence that the use of an electronic calendar is superior to the use of a diary for improving memory in individuals with an ABI.* - *There is level 2 evidence that the presence of a calendar may not improve orientation post ABI.* The use of a diary may help to improve memory and task completion 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 2 evidence that the presence of a diary with or without self-instructional training improves memory following an ABI.*

Computer-Based Software Programs	Some computer-based software programs seem to be effective for improving memory post ABI. - *There is level 1b evidence that a computer-assisted attention program may be more beneficial for individuals with ABI than memory training when compared.* - *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 N-back training compared to virtual search training is not effective for improving memory in those with an 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 2 evidence that non-specific computer-based memory retraining compared, self-paced or otherwise, may not be effective at improving memory in those with an ABI.* - *There is level 4 evidence that Cognitive Pragmatic Treatment, Cogmed, Cogmed QM, and RehaCom software may improve memory and cognitive function in individuals with an ABI.* - *There is conflicting (level 4) evidence regarding the effectiveness of Parrot software at improving memory and learning in individuals post ABI.* - *There is level 4 evidence that a computer assisted cognitive rehabilitation show no significant differences in memory when compared to traditional therapy methods.*
Virtual Reality	Virtual reality programs may enhance the recovery of memory and learning, but there is currently limited evidence supporting the use of virtual reality programs. The evidence is unclear as to which specific VR programs benefit memory rehabilitation and how they compare to manual training therapies. - *There is level 4 evidence that virtual reality (VR) training may improve learning performance post ABI, even in the presence of distractions.* - *There is level 2 evidence that virtual reality training combined with exercise may be promising for improving memory outcomes and has a positive impact on visual and verbal learning when compared to no treatment.*

	- *There is level 2 evidence that virtual reality training may be superior to reading skills training at improving immediate and general components of memory for individuals with an ABI.* - *There is level 2 evidence that the format of route learning (either real or virtual reality based) does not significantly impact any improvements in memory as a result of route learning strategies for those with an ABI.* - *There is level 4 evidence that a virtual reality telerehabilitation program is feasible and safe for cognitive therapy in individuals with TBI.*
Internal Memory Strategies	Internal strategies such as self-imagination, spaced retrieval and rehearsal, and multiple encoding are effective for improving memory following an ABI. - *There is level 1b evidence to support self-imagination as an effective strategy to improve memory compared to standard rehearsal for those with an ABI.* - *There is Level 2 evidence to support that spaced retrieval training is an effective memory strategy when compared to massed retrieval or rehearsal in ABI populations.* - *There is level 2 evidence that strategies that utilize methods of multiple encoding, compared to strategies which only use singular methods, are more superior for improving memory post ABI.* - *There is level 4 evidence that errorless learning is more effective than errorful learning when it comes to improving memory in ABI populations.*
Learning & Memory Training Programs	Memory-retraining programs appear effective, particularly for functional recovery although performance on specific tests of memory may or may not change. Memory training programs are effective. Interventions which include multiple learning techniques such as modelling, observation, verbal instruction, etc. are more effective than interventions which include a singular learning method. - *There is level 1b evidence that individual memory therapy is no more effective than group memory therapy for those with an ABI.* - *There is level 2 evidence that programs involving multiple learning strategies (such as modelling, reciting, verbal instruction, and observation) are more effective than singular strategies for those with an 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 1a evidence that the Categorization Program, and Strategic Memory and Reasoning Training (SMART) may be effective for improving memory compared to standard therapy in individuals*

	with an ABI. - *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 post ABI individuals compared to no treatment.* - *There is level 2 evidence that the Intensive Neurorehabilitation Programme is not effective for improving memory compared to controls in those with an 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.* - *There is level 4 evidence that a cognitive retraining program may improve cognition and memory following moderate to severe TBI.*
Cognitive Pragmatic Treatment	The effectiveness of a Cognitive Pragmatic Treatment (CPT) program on memory in individuals with TBI is unclear. - *There is conflicting level 4 evidence regarding the effectiveness of a Cognitive Pragmatic Treatment (CPT) program on memory in individuals with TBI*.
Time Pressure Management Training	Time Pressure Management may not improve memory in individuals with ABI. - *There is level 2 evidence that time pressure management training is no more effective than concentration training at improving memory for those with an ABI.*
Goal Training	Goal Training may improve memory in individuals with 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 post ABI individuals compared to receiving the treatment conditions in reverse order.*
Emotional Regulation	Emotional self-regulation therapy may be effective for improving specific elements of memory in individuals with ABI. - *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.*
Motor Procedural Training	Motor procedural training may not improve memory in individuals with ABI. - *There is level 2 evidence that motor procedural training, compared to no training, may not be effective for improving memory following an ABI.*

Attention Training Programs	Attention training programs may not be effective for improving memory in individuals with ABI. - *There is level 1b evidence that attention process training may improve memory measurements compared to education alone.* - *There is level 1b evidence that attention training program may not improve memory or learning in individuals with ABI.*
Hypnosis	Hypnosis may not be effective at improving memory in individuals with ABI - *There is level 1b evidence that hypnosis compared to no treatment may not be effective at improving memory in individuals with ABI.*
Dance Therapy	Dance may be beneficial for individuals with moderate to severe TBI and it is a promising intervention to improve short-term and working memory. - *There is level 1a evidence that a dance program is feasible and may improve short-term and working memory in individuals with moderate to severe TBI.*
Brain Stimulation Techniques	Cranial electrotherapy stimulation (CES) is not effective at enhancing memory and recall abilities following TBI. - *There is level 1b evidence that cranial electrotherapy stimulation may not improve memory and recall compared to sham stimulation post TBI.* Transcranial Direct Current Stimulation (tDCS) is not effective at enhancing memory abilities following TBI. - *There is level 1a evidence that transcranial direct stimulation may not improve memory compared to sham stimulation post TBI*
Pharmacological Interventions	
Donepezil	Donepezil likely improves memory following TBI. - *There is level 1b evidence that donepezil improves short-term memory post TBI.* - *There is level 4 evidence that donepezil may be effective in improving long-term, verbal, and visual memory post TBI.*
Methylphenidate	Methylphenidate may not improve memory or learning following an ABI. - *There is level 1a evidence that methylphenidate compared to placebo is not effective for improving memory following brain injury for individuals post TBI.*

Sertraline	Sertraline has not been shown to improve learning, or memory within the first 12 months post TBI and may be associated with side effects. - *There is level 1b evidence that sertraline may not improve memory compared to placebo in individuals who have sustained a moderate to severe TBI.*
Amantadine	Amantadine is not effective for improving learning and memory deficits post TBI. - *There is level 1a evidence that amantadine does not improve learning and memory deficits in individuals with TBI.*
Pramiracetam	Pramiracetam might improve memory in males post TBI; however, additional studies are required. - *There is level 2 evidence that pramiracetam may improve males' memory compared to placebo post TBI.*
Physostigmine	Physostigmine may improve long-term memory in men with TBI; however, additional studies are needed. - *There is level 1b evidence that oral physostigmine may improve long-term memory compared to placebo in men with TBI, however additional studies are needed.*
Bromocriptine	More studies are required to determine the effects of bromocriptine on verbal memory in individuals with TBI. - *There is level 2 evidence that bromocriptine may improve verbal memory in individuals with a TBI, however, more studies are required.*
Cerebrolysin	Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning, including memory in individuals with TBI; however, randomized controlled trials are needed to further evaluate its efficacy. - *There is level 4 evidence that cerebrolysin may improve memory function post TBI.*
Growth Hormone Replacement Therapy	Growth Hormone Replacement Therapy likely does not improve learning and memory following TBI. - *There is level 1b evidence that recombinant human Growth Hormone (rhGH) is similar to placebo for improving memory and learning in individuals with TBI.*
Rivastigmine	Rivastigmine may not be effective in treating memory deficits post TBI. - *There is level 1a evidence that rivastigmine may not effective when compared to placebo for improving memory in individuals with TBI.*
Huperzine A	Huperzine A may not improve memory following TBI.

	- *There is level 1b evidence that Huperzine A may not improve memory following TBI when compared to placebo.*
Hyperbaric Oxygen Therapy	Hyperbaric oxygen therapy may be promising for improving memory following an ABI; however, more controlled studies are required. - *There is level 4 evidence that hyperbaric oxygen therapy may improve memory following an ABI.*

Introduction

Interventions for memory remediation in individuals with TBI have become increasingly important in rehabilitation (Lambez & Vakil, 2021). Memory has been defined as the ability to encode, store and retrieve information (Alessandro et al., 2020). Memory difficulties are very commonly experienced after a TBI, especially by those with more severe injuries (Carlozzi et al., 2019). 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). Compensatory strategies usually include general memory strategies, the use of diaries or notebooks and smartphones (Downing et al., 2018). Conversely, interventions for remediation of memory deficits range from assistive technology to visual imagery. Several studies were identified examining interventions to improve learning and memory following ABI.

Non-Pharmacological Interventions

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 that may be used to support individuals with memory or learning deficits post ABI.

External Technology Aids

External aids, of which there are active or high tech (computers, personal digital assistants (PDAs), and mobile phones) and passive or low technology/no technology (e.g., calendars, diaries, lists, timetables and dictaphones) devices, have been shown to assist with 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. More recently, individuals with TBI that have access to a smartphone may use a variety of functions that facilitate organizational skills and everyday

memory, such as calendar applications and electronic reminders (Wong et al., 2017). Included here are studies which examined how external technology aids, could be used to enhance memory following ABI.

Voice Organizers

TABLE 4 | The Effect of Voice Organizers on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Hart et al. (2002) USA RCT PEDro=5 N=10	**Population:** TBI: Mean Age: 31.5yr; 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).
van den Broek et al. (2000) UK Case Series N=5	**Population:** TBI=1, ABI=4; Age Range: 25-56yr; Gender: male=4, female=1; Time Post Injury: 19-54mo. **Intervention:** The voice organizer was used for a period of 3wk. 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).	1. All patients benefited from the introduction of the Voice Organizer as measured using the message-passing task and the PANAS.

Discussion

Voice organizers have been shown to improve goal execution. 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.

Conclusions

There is level 2 evidence that voice organizers may be an effective memory aid for individuals with ABI (Hart et al., 2002; van den Broek et al., 2000).

KEY POINTS

- Voice organizers may help individuals with ABI remember previously identified goals

Prompting Technology

TABLE 5 | The Effect of Prompting Technology on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
O'Neill et al. (2018) UK RCT PEDro=7 $N_{Initial}$=27, N_{Final}=24	**Population:** TBI=16, Subarachnoid hemorrhage=3, Other=5; Mean Age=45.14yr; Gender: Male=22, Female=2; Mean Time Post Injury=5.53yr; Severity: severe. **Intervention:** Participants were randomly assigned to the 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 caregivers or support workers. Control group participants received rehabilitation as usual. **Outcome Measures:** 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).	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.
Burke et al. (2001) USA Pre-Post N=5	**Population:** TBI=3, SAH=2; Mean Age: 50yr. **Intervention:** Assessing patient's ability to use a patient locator and minder (PLAM) system to assist in their adherence to therapy schedules. Participants 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% ($p<0.005$). 1. Participants arrived on average 1.3 minutes earlier using PLAM – a 6.1-minute improvement over baseline.

Discussion

O'Neill et al. (2018) 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 worker 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., 2018). A computerized tracking system designed to locate individuals and send reminders when they moved in the wrong direction showed efficacy when used to remind individuals to attend appointments at a rehabilitation unit (Burke et al., 2001). By reducing the number of staff prompts needed, these systems can increase independence of individuals and help free-up support personnel for other tasks.

Conclusions

There is level 1b evidence that the audio-verbal interactive micro-prompting system, Guide, can reduce the number of support-staff prompts needed for the individual to complete a task post TBI (O'Neill et al., 2017).

There is level 4 evidence that a computerized tracking system that sends reminders to individuals when they are moving in the wrong direction can aid in increasing attendance to scheduled appointments (Burke et al., 2001).

KEY POINTS

- Automated prompting systems, such as Guide (audio-verbal interactive micro-prompting system) and a computerized tracking system, can help individuals with TBI remember to complete tasks, such as attending appointments.

Palmtop Computers

TABLE 6 | The Effect of Palmtop Computers on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Kim et al. (2000) USA Case Series N=12	**Population:** TBI=11, CVA=1; Age Range: 22-67yr; Gender: male=8, female=4. **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 participants (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. 2. All patients recommended that the computer continue to be used in outpatient brain injury rehabilitation.

Discussion

In a study by Kim et al. (2000), participants were given palmtop computers programmed with scheduling software capable of generating audible reminder cues. Feedback from participants suggested that the use of the palmtop computer was beneficial for their rehabilitation, and over half of the participants continued to use the device even after the conclusion of the study.

Conclusions

There is level 4 evidence that palmtop computers may be an useful memory aid for individuals post ABI (Kim et al., 2000).

KEY POINTS

- Palmtop computers can assist individuals with ABI with memory dependent activities of daily living.

Personal Digital Assistants

TABLE 7 | The Effect of Personal Digital Assistants (PDAs) on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Lannin et al. (2014) Australia RCT PEDro=8 N=42	**Population:** TBI; Mean Age=33.5yr; Gender: Male=26, Female=16; Mean Time Post Injury=9.2yr. **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. **Outcome Measures:** Goal Attainment Scale (GAS), Memory Functioning Questionnaire (MFQ) and Memory Compensation Questionnaire (MCQ).	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).
De Joode et al. (2013) Netherlands RCT PEDro=5 N=34	**Population:** TBI=11; Stroke=12; Mixed stroke/TBI=3; Other=8; Gender: Male=24, Female=10. *Experimental Group (n=21):* Mean Age=42.2yr; Mean Time Post Injury=38.9mo. *Control Group (n=13):* Mean Age=39.4yr; Mean Time Post Injury=65.9mo. **Intervention:** Participants were randomized to either: 1) Control Group: care as usual (paper and pencil aids) aimed at learning skills to support memory, planning and organization, or 2) Experimental Group: participants were trained to use Personal Digital Assistants (PDAs)	1. GAS improved significantly from baseline to T2 for both groups. The experimental group showed a mean increase of 45.2 (p<0.001) and the control a mean increase of 36.7 points (p<0.001); however, the between-group analysis was not significant (p>0.05). 2. None of the other outcome measures differed significantly between groups at T1 or T2 (p>0.05).

	as a cognitive aid to compensate for dysfunctions. After 8hr of training (T1), 16hr of training (T2), and at 5mo follow-up (T3), assessments were conducted. **Outcome Measures:** Goal Attainment Scaling (GAS), Cognitive Failure Questionnaire, Frenchay Activities Index, General perceived Self-Efficacy Scale, Utrecht Coping List.	
Powell et al. (2012) USA RCT PEDro=7 N=29	**Population:** TBI=23, ABI=6; Mean Age=42.31yr; Gender: Male=17, Female=12; Mean Time Post Injury=13.59yr. **Intervention:** Individuals 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). **Outcome Measures:** 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.	1. Those receiving systematic instruction performed significantly more ($p<0.01$) correct tasks at the 30-d follow-up compared to participants receiving the conventional instruction. 2. Those receiving systematic instruction also performed the correct tasks more quickly (16 sec) than the conventional instruction group (41.15 vs 57.73 sec, $p=0.050$). 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 ($p=0.050$). 4. 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.
Dowds et al. (2011) USA RCT PEDro=5 N=36	**Population:** TBI; Mean age: 42.1yr; Gender: male=17, female=19. **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. Participants were randomly assigned to four memory aid conditions (Palm OS, Microsoft OS, Combined Baseline, or paper organizer) in a crossover fashion. **Outcome Measure:** Timely completion rates.	1. 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: $p<0.001$). 2. Results also indicated that those using the Palm OS PDA had a higher completion rate than those using the Microsoft OS PDA ($p<0.0005$).
Waldron et al. (2012) Ireland Pre-Post N=5	**Population:** TBI=3, CVA=1, Tumour=1; Mean Age=48.8yr; Gender: Male=4, Female=1; Mean Time Post Injury=23.2yr. **Intervention:** Participants were given personal digital assistants (PDAs) and a series of seven prospective memory (PM) tasks that they needed to complete. Baseline measures were taken for three weeks, followed by two weeks of PDA condition. More specifically, the PDA was a palmtop computer (Palm IIIe). **Outcome Measure:** Completed tasks.	1. Compared to baseline when internal memory only was used, the use of the PDA significantly improved PM task completion from 59.04% to 90.00% completion ($p<0.05$).

Gentry et al. (2008) Canada Pre-Post N=23	**Population:** TBI; Age Range 18-66yr; Gender: Male=16, Female=7; Time Post-Injury=1-34yr. **Intervention:** Participants were each given a PDA and trained on how to use it by an occupational therapist (OT). **Outcome Measure:** Craig Handicap Assessment and Rating Technique Revised (CHART); Canadian Occupational Performance Measure (COPM).	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 ($p<0.001$).
Wright et al. (2001a) UK Pre-Post N=12	**Population:** TBI=9, SAH=2; Mean Age: 39yr; Gender: male=10, female=2; Mean Time Post-Injury 3yr. **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: 34yr; 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 ($p<0.010$). High frequency users used the keyboard more ($p<0.070$).

Discussion

With advances in technology, organizers such as personal digital assistants (PDAs) have been studied. Individuals accustomed to using memory aids were more likely to make use of computerized organizers (Wright et al., 2001b). No differences were found between groups based on PDA input (physical vs touch-screen keyboard), provided the three core memory aid components of appointment diary, notebook, and to-do list were maintained (Wright et al., 2001a). 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.

Several other studies have also found positive effects for the use of PDAs on memory (De Joode et al., 2013; Gentry et al., 2008; Powell et al., 2012; Waldron et al., 2012). 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.

Conclusions

There is level 1b evidence that the use of a personal digital assistant in combination with conventional occupational therapy is superior to occupational therapy alone at improving memory in individuals post TBI (Lannin et al., 2014).

There is level 1b evidence that use of a PDA after receiving systematic instructions is superior to PDA trial and error learning at improving the number and speed of correct tasks post TBI (Powell et al., 2012).

There is level 2 evidence that PDAs are superior to a paper-based schedule book at improving task completion rates post TBI (Dowds et al., 2011).

There is level 2 evidence that PDAs may improve everyday task completion and performance in individuals with TBI (De Joode et al., 2013; Gentry et al., 2008; Waldron et al., 2012).

There is level 4 evidence that individuals with ABI who have used memory aids previously may benefit more from the use of PDAs (Wright et al., 2001a; Wright et al., 2001b).

KEY POINTS

- 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. Individuals who have used previous memory aids might benefit from this intervention the most.

Paging Systems

TABLE 8 | The Effect of Pagers on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Wilson et al. (2001) UK RCT Crossover PEDro=4 N=143	**Population:** TBI=63, Stroke=36, ABI=44. Mean Age: 38.57yr; Gender: Male=105, female=38; Mean Time Post-Injury: 4.9yr. **Intervention:** After a 2wk baseline, patients were randomized into two groups: Group A received a pager first and Group B was put on a waiting list. After 7wk of treatment the groups crossed-over. Measures were taken during the last 2wk of each treatment period. Patients chose their own tasks in which they wanted to be reminded. **Outcome Measures:** Patients' Ability to Successfully Carry out Everyday Tasks.	1. During the last 2 weeks of the 7-week treatment period, the participants using the pager were significantly more successful in achieving target behaviors than the waiting list group ($p<0.001$).

Wilson et al. (1997) UK Pre-Post N=15	**Population:** TBI=10, Stroke=1; ABI=4; Gender: male=11, female=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 participant ($p<0.050$). 2. Mean success at baseline was 37.08%, during treatment (85.56%) and post-treatment (74.46%).

Discussion

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 a paging 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., 2001). However, the need for a centralized system to send reminders reduces the feasibility of pagers, many people may be able to achieve the same results using other electronic reminder systems.

Conclusions

There is level 2 evidence that the NeuroPage system may increase the individual's ability and efficiency to complete tasks post TBI (Wilson et al., 2001; Wilson et al., 1997).

KEY POINTS

- The use of a pager may improve the individual's ability to complete tasks post TBI.

Television Assisted Prompting

TABLE 9 | The Effect of Television Assisted Prompting on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Lemoncello et al. (2011) USA RCT PEDro=5 N=23	**Population:** *Group A (n=12):* Mean age=47.17yr, mean time post-injury=9yr. *Group B (n=11):* Mean age=47.55yr, Mean time post-injury=12.45yr. **Intervention:** Individuals 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	1. No significant differences were found between groups A or B; therefore, data from the two groups was collapsed. 2. Task completion was significantly better when participants used the TAP condition (72%) versus the TYP condition (43%). 3. In the TAP condition participants completed significantly more experimental tasks compared to either preferred ($p=0.01$) or non-preferred tasks ($p=0.01$).

	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. **Outcome Measures:** Task completion.	

Discussion

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 (i.e., paper planner, cell phones or computers), participants using the TAP system completed significantly more tasks (Lemoncello et al., 2011).

Conclusions

There is level 2 evidence that prospective memory reminders delivered through the television is superior to typical reminder strategies (i.e., paper planners, cell phones, computers) at improving the amount of completed tasks post ABI (Lemoncello et al., 2011).

KEY POINTS

- A television assisted prompting (TAP) program is useful for improving task completion in individuals with ABI.

Mobile Phones

TABLE 10 | The Effect of Mobile Phone Use on Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Text Messages		
Gracey et al. (2017) UK RCT PEDro=6 $N_{Initial}$=74, N_{Final}=59	**Population:** CVA=23, Infection=3, TBI=33, Tumor=10, Missing=1. *Control First (n=34)*: Mean Age=50.18yr; Gender: Male=23, Female=11; Mean Time Post Injury=8.62yr. *Assisted Intention Monitoring (AIM, n=36)*: Mean Age=46.36yr; Gender: males=23, females=13; Mean Time Post Injury=4.89yr. **Intervention:** Participants were randomized to receive AIM or control first. In the AIM-first	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.

	group, participants received goal management training followed by text messages for improving achievement of everyday intentions. Control-first group received brain injury information, Tetris game, and non-informational text messages. After 3wk, participants were crossed over with AIM-first group receiving usual care and control-first group receiving AIM. **Outcome Measures:** 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.	When only comparing group differences at post-intervention phase 1, intention to treat analysis showed no significant difference between groups for proportion of intentions achieved or achievement of goals excluding the phone task.
Fish et al. (2007) UK Case Series N=20	**Population:** Age Range: 19-60yr; Gender: Male=15, Female=5; Condition: TBI=14, Other=6. **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. **Outcome Measure:** Completion of task.	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. 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 time).
Smartphones		
Evald (2018) Denmark Pre-Post N=13	**Population:** Mean age=41.5yr; Gender: Male=11, Female=2; Injury severity: mean GCS=6.6; Mean time post injury=11 yrs. **Intervention:** Each individual received a Windows Phone (version 7.5) for 6-weeks and was asked to use this as their only memory strategy. Five group sessions (1.5 hrs each) were held to help ensure each individual knew how to use the applications on each phone (calendar, reminders, etc.). After the 6-week intervention period a 2-week break was taken to assess all behaviors and then a 6-week follow-up assessment was completed. **Outcome Measures:** Prospective Memory Questionnaire (PMQ), Prospective and Retrospective Memory Questionnaire, Cognitive Failures Questionnaire (CFQ), European Brain Injury Questionnaire (BIQ), Hospital Anxiety and Depression Scale (HADS).	1. Pre- to post-intervention the PMQ ($p=0.005$) and the Prospective and Retrospective Memory Questionnaire ($p=0.014$) revealed a significant decrease in the number of self-reported memory problems. 2. No significant effects were found on common brain injury deficits through the BIQ and CFQ. 3. No significant effects on mood were reported through the HADS or QoL scale. 4. When comparing reports from baseline to 6-week follow-up, significant effects on memory and self-reported errors were seen on PMQ ($p=0.009$), the Prospective and Retrospective Memory Questionnaire ($p=0.014$), and the CFQ ($p=0.000$).
Bos et al. (2017) New Zealand Case Series N=7	**Population:** TBI; Mean Age=51.5yr; Gender: Male=7; Mean Time Post Injury=8.6 yr. **Intervention:** An intervention with either a smartphone alone, or a memory notebook and later a smartphone was conducted. Memory was assessed weekly with memory tasks. The main application of the smartphone was	1. Six of the seven participants (86%) showed improvement in memory tasks when using the smartphone. 2. The performance of three participants declined with the use of the smartphone.

	Google Calendar. **Outcome Measures:** Test of memory malingering (TOMM), Rivermead Behavioural Memory Test-II (RBMT-II), functional memory tasks.	3. Tasks entered in the smartphone's calendar or in the To Do List were better managed by participants.
Evald et al. (2015) Denmark Pre-Post N=13	**Population:** TBI; Mean Age=41.5yr; Gender: Male=11, Female=2; Mean Time Post Injury=11yr; Mean GCS=6.6. **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. **Outcome Measure:** Self-reported measures of overview, memory, stress, and fatigue.	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. There were no negative events reported.

Discussion

The use of mobile health (mHealth) such as smartphones, tablets and mobile applications (apps) has become increasingly popular in recent years, as more people have access to these technologies (Kettlewell et al., 2018). Smartphone reminder apps, such as *ForgetMeNot*, help individuals with ABI to enter reminders with unsolicited prompts (e.g., do you need to set any reminders?), this system allows users to accurately input reminders and it has the potential to assist memory rehabilitation (Jamieson et al., 2017). A number of new smartphone applications have been widely available to people who own a smartphone or tablet, and have the potential to address cognitive difficulties in individuals with TBI, including memory (Juengst et al., 2019). In a recent systematic review, Christopher et al. (2019) found that, while there has been an increasing growth in the use of mHealth for the treatment of various health conditions, there are is a small number of mobile apps for individuals with TBI and limited uptake based on download metrics. In addition, there is limited RTC evidence supporting the benefits of TBI-specific mHealth.

Focusing on those studies targeting ABI, 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 needs 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 prompts more likely to succeed in their goals compared to those not receiving prompts. This effect was not observable once the texts had stopped.

Smartphones are accessible and acceptable devices for individuals with TBI, as they provide valuable memory and organizational aids and other functions that can support communication, social support and community integration (Wong et al., 2017). The most common advantages to smartphones are reminders/alarms and the ability to combine a calendar, tasks list, contacts, mail, and phone on one device. Disadvantages include the loss of battery life and risk of dependency on the assistive device; however, these are minor inconveniences in comparison to the reported benefits and improvement in memory for many individuals (Evald, 2015). On measures such as the Prospective and Retrospective Memory Questionnaire, the use of smartphones was shown to significantly reduce the number of self-reported errors (Evald, 2018). In a case series study, Bos et al. (2017) found that individuals living with TBI who used a smartphone showed improvements in their ability to complete memory tasks.

Conclusions

There is level 1b evidence that reminder text messages sent to individuals through their mobile phones, whether alone or in combination with goal management training, improves goal completion post TBI (Fish et al., 2007; Gracey et al., 2017).

KEY POINTS

- Text message prompts sent to an individual's mobile phone, when used alone or in combination with other memory-improvement therapies, may improve task completion post TBI. However, risk of device dependency exists.

External Passive Technology or Non-Technology Aids

Passive aids are those that do not require specific electronic programming for their use such as paper calendars, notebooks, and planners. A variety of studies have examined the effects of these standard tools on learning and memory; however, the number of studies examining the effect of non-technology aids has been quickly outpaced by those looking at technology given how accessible it has become.

Calendars

TABLE 11 | The Effect of Calendars on Memory and Task Completion Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
McDonald et al. (2011) UK RCT PEDro=5 N=12	**Population:** TBI=4, Stroke=4, Other ABI=3; Mean Age: 47yr; Gender: male=6, female=6. **Intervention:** One of two groups (Group A or Group B). All were asked to complete weekly monitoring forms indicating what activities they	1. Overall, the use of memory aids assisted individuals in completing tasks as opposed to no memory aids.

	would like to complete within the next several 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.	2. Memory performance was greater using the google calendar compared to the standard diary ($p<0.001$). 3. During the Google Calendar intervention phase, there was 40.6% increase in completing their prospective intention compared to the standard diary phase. 4. Overall, 82% of targets were reached using Google calendar but only 55% using the standard diary.
Bergquist et al. (2009) USA RCT PEDro=6 N=14	**Population:** TBI; Mean Age=48yr; Gender: Male=7, Female=7. **Intervention:** Individuals 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. **Outcome Measure:** Neurobehavioural Functioning Inventory (NFI), Community Integration Questionnaire (CIQ), Compensation Techniques Questionnaire (CTQ).	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. 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 $p<0.004$).
Watanabe et al. (1998) USA RCT PEDro=3 N=30	**Population:** TBI=16, ABI=14; Mean Age: 53.4yr; Gender: male=24, female=6. **Intervention:** Participants 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). **Outcome Measure:** Temporal Orientation Test (TOT).	1. Presence of a calendar did not significantly affect TOT scores.

Discussion

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 number of desired tasks, those using the Google calendar had a significant increase in task completion using automated reminders and messages. A second RCT also compared the use of a calendar to diary use; however, no significant between-group differences were found, with both groups reporting positive results on memory (Bergquist et al., 2009). Lastly, Watanabe et al. (1998), found no significant effects of calendar use on a test of orientation, compared to no calendar use when individuals were still inpatients.

Conclusions

There is conflicting evidence that the use of an electronic calendar is superior to the use of a diary for improving memory in individuals with an ABI (Bergquist et al., 2009; McDonald et al., 2011).

There is level 2 evidence that the presence of a calendar may not improve orientation post ABI (Watanabe et al., 1998).

KEY POINTS

- There are conflicting results about the effectiveness of calendars as a tool for improving memory and task completion post ABI.

Notebooks and Diaries

TABLE 12 | The Effect of Notebooks on Memory and Task Completion Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Bergquist et al. (2009) USA RCT PEDro=6 N=14	**Population:** TBI; Mean Age=48yr; Gender: Male=7, Female=7. **Intervention:** Participants 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. **Outcome Measure:** Neurobehavioural Functioning Inventory (NFI), Community Integration Questionnaire (CIQ), Compensation Techniques Questionnaire (CTQ).	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. 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 $p<0.004$).
Ownsworth & McFarland (1999) Australia RCT PEDro=3 N=20	**Population:** Mean Age: 43.1yr; 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).	1. All participants reported significantly fewer problems with memory ($p<0.001$) and lower levels of distress ($p<0.01$) during treatment phase when compared to baseline. 2. There was a significant increase in the degree of strategy use during treatment ($p<0.05$) regardless of type of diary training.

	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 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." **Outcome Measure:** Self report questionnaire on commonly experienced memory problems.	There were no significant differences between the DS and DSIT groups (p>0.05).
Schmitter-Edgecombe et al. (1995) United States RCT PEDro=8 N=12	**Population:** *Notebook Training (N=4):* Mean age=29.9yr; Mean time post-injury=77.7mo. *Supportive Therapy (N=8)*: Mean age=26.8yr; Mean time post-injury=86.8mo. **Intervention:** Individuals were randomly assigned to either a memory notebook use group, or a supportive therapy group (control) for 9 weeks. Participants were assessed at baseline, immediately following treatment, and at 6-months follow-up. **Outcome Measures:** Everyday memory failures (EMFs), laboratory-based memory (Rivermead Behavioral Memory Test), laboratory-based recall (Logical Memory I and II, Visual Reproduction I and II from Wechsler Memory Scale), Everyday Memory Questionnaire (EMQ).	1. Participants did not differ significantly on any baseline measures. 2. There were no significant differences groups on laboratory-based recall, laboratory-based everyday memory, or EMQ scores. 3. Participants in the notebook group experienced significantly fewer EMFs compared to the supportive therapy group (p<0.05). However, this effect was no longer significant at follow-up.

Discussion

In an RCT by Ownsworth and McFarland (1999), diary use was examined alone as well as with the combination of self-instructional training. On self-reported memory scales, all participants reported improvements in memory, as well as 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). Comparing the use of a memory tool (notebook) to generalized supportive therapy, the use of a notebook specifically was shown to result in a greater reduction in memory failures; however, this effect was lost at 6-month follow-up (Schmitter-Edgecombe et al., 1995). In an RCT, Bergquist et al. (2009) compared the use of a calendar to diary use; however, the authors found no significant between-group differences.

Conclusions

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 (Ownsworth & McFarland, 1999) .

There is level 2 evidence that the presence of a diary with or without self-instructional training improves memory following an ABI (Schmitter-Edgecombe et al., 1995).

KEY POINTS

- The use of a diary may help to improve memory and task completion post ABI.

Technological Interventions

Computer-based Interventions

A surge in computer technology in recent years has allowed for the development of computer-based interventions. Computerized cognitive training is a low cost, user-friendly and accessible intervention that may improve cognition in individuals with ABI; additionally, computer interventions can be relatively easy implemented in a clinical setting or a in a home environment (Sigmundsdottir et al., 2016).

TABLE 13 | The Effect of Computer-based Interventions on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Niemann et al. (1990) United States RCT PEDro=7 N=29	**Population:** *Attention Group (N=13)*: Mean age=28.9yr; Mean time post-injury=41mo. *Memory Group (N=13):* Mean age=34.3yr; Mean time post-injury=37.1mo. **Intervention:** Individuals were randomly assigned to either an attention training program or a memory training program. Both programs lasted 9 weeks and had two 2-hour sessions each week. **Outcome Measures:** Attention Test d2, Paced Auditory Serial-Addition Task (PASAT), Divided Attention test (DAT), Trail Making Test-B (TMT-B), Rey Auditory Verbal Learning Test (RAVLT), Block Span Learning Test (BSLT), Ruff 2 & 7 Test, Logical Memory Subtest (Wechsler Memory Scale) (WMS-LM), Ruff-Light Trail Learning Test (RLTLT).	1. There were no significant within-group differences on the Test d2, PASAT, DAT, RAVLTBSLT, Ruff 2 & 7 Tests, WMS-LM, or the RLTLT. 2. Significant within group differences were seen on the TMT-B for both the attentional ($p<0.01$), and memory ($p<0.01$) groups. 3. The attention group improved significantly more on the TMT-B compared to the memory group ($p=0.05$). 4. The attention group improved significantly more than the memory group on the Attention Test d2 ($p=0.02$). 5. No other significant differences were found.
Dou et al. (2006) China RCT PEDro=5	**Population:** TBI; Mean Age=38.07yr; Gender: Male=27, Female=10; *Computer Assisted Memory Training Group (CAMG; n=13):* Mean Time Post Injury=270.15 d. *Therapist Administered Memory Training Group (TAMG; n=11):* Mean Time Post Injury=161.27 d. *Control Group (n=13)*: Mean Time Post Injury=226.77 d.	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 ($p=0.256$).

Author Year Country Study Design Sample Size	Methods	Outcome
N=37	**Intervention:** Participants 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). **Outcome Measure:** Neurobehavioural Cognitive Examination (NCSE), Rivermead Behavioural Memory Test (RBMT), Hong Kong List Learning Test.	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. 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).
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. **Intervention:** Computerized training. 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.	1. 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). 2. 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. 3. 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.
O'Neil-Pirozzi and Hsu (2016) PCT $N_{Initial}$=14 N_{Final}=12	**Population:** TBI=4, CVA=2, Brain tumor=1; Severity: moderate/severe. *Experimental Group (n=7)*: Mean Age=51.3yr; Gender: Male=5, Female=2; Mean Time Post Injury=20.9yr; Etiology: TBI=5, CVA=2. *Control Group (n=7):* Mean Age=46.9yr; Gender: Male=7; Mean Time Post Injury=25.0yr. **Intervention:** 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 Measures:** Number/percentage of sessions completed, Number/percentage of sessions initiated by participants, Number/percentage of sessions	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. 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.

Author Year Country Study Design Sample Size	Methods	Outcome
	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.	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. 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. 5. Compared to baseline, control group did not show significant differences post-intervention for WCST, HVLT, TMT A or B, or SWL. 6. 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 were found for changes in WCST, HVLT-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.
Hellgren et al. (2015) Sweden Case Series N=48	**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=51.2 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 5-7wk, 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, Canadian Occupational Performance Measure (COPM performance and satisfaction), EuroQol descriptive (EQ-5D Index), EuroQol Visual Analogue Scale (EQ-VAS), Working Memory Index (WM Index).	1. 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. 2. Compared to baseline, all participants significantly improved their WM Index at 20 wk 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 for ≤18 mo since injury exhibiting more improvement than >18 mo in terms of WM index difference ($p<0.050$), COPM performance improvement ($p<0.050$), and COPM satisfaction improvement ($p<0.050$).

Author Year Country Study Design Sample Size	Methods	Outcome
Lesniak et al. (2020) Poland Pre-Post N= 15	**Population:** TBI; Mean Age= 26.2yr; Gender: Male=11, Female=4; Mean time post injury= 11.6mo; Severity: Severe=10, Moderate=5. **Intervention:** Cognitive rehabilitation therapy program focused on memory and attention. The individual therapy program was cognitive training conducted with computer software (RehaCom) and supervised by a psychologist. Group sessions were run by a neuropsychologist and focused on internal memory strategies and external aids. Participants had 15 group session (45 min, 5d/wk) and 15 individual therapy sessions (45min, 5 d/wk). Assessments were conducted at baseline (3wk prior to start), pre-treatment, posttreatment and at 4mo follow-up. **Outcome Measures:** Cambridge Neuropsychological Test Automated Battery (CANTAB), Pattern Recognition Memory Test, Rey's Auditory Verbal Learning Test (RAVLT), Spatial Span Test (SSP), Paced Auditory Serial Addition Test (PASAT), Rapid Visual Information Processing, European Brain Injury Questionnaire (EBIQ).	1. From baseline to preintervention only the PASAT changed significantly (p=0.047). 2. From baseline to post-intervention there were no significant changes in short-term verbal memory (RAVLT; p=0.242), short-term visual memory (PRM; p=0.172) or visuospatial working memory (SSP; p=0.24). 3. From baseline to post-intervention RVP attention test (p=0.002) and PASAT (p=0.005) showed significant improvement. 4. Pre to Post intervention significant improvements were found for PRM (p=0.022), RVP (p=0.002) and PASAT (p=0.012). 5. Post-intervention, patients reported less everyday cognitive problem than at baseline (EBIQ). No significant differences were found between post-intervention and follow-up.
Li et al. (2015) USA Pre-Post $N_{Initial}$=13, N_{Final}=12	**Population:** Stroke=5, TBI=5, Brain tumor=2; Mean Age=61yr; Gender: Male=10, Female=2. **Intervention:** 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 Measures:** Montreal Cognitive Assessment (MoCA overall, attention, memory), Medication-box Sorting Task.	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.
Li et al. (2013) USA Pre-Post N=11	**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).	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).

Author Year Country Study Design Sample Size	Methods	Outcome
Johansson & Tornmalm (2012) Sweden Pre-Post N=18	**Population:** TBI=5, Brain Tumor=6, Stroke=7; Mean Age=47.5yr; Gender: Male=13, Female=5; Mean Time Post Injury=7yr. **Intervention:** All participants received a working memory training program (WMTP) using computerized training software (Cogmed QM), coaching, education, and peer support. This consisted of visual and auditory working memory tasks. Training ranged from 20-25 sessions. **Outcome Measures:** Cognitive Failures Questionnaire (CFQ), Canadian Occupational Performance Measure (COPM), CogMed QM tasks.	1. A significant reduction in cognitive problems was found through self-rating on the CFQ (median change 5, p=0.018). 2. A significant improvement on self-rating scores on the COPM were found for performance (median change=1.4, p=0.008) and satisfaction with performance (median change=1.8, p=0.010). 3. Significant improvements were noted on Cogned QM tasks (p<0.001).
Fernandez et al. (2012) Cuba Pre-Post N=50	**Population:** TBI =29, Stroke=21; Age range= 20-36yr, Gender: Male = 34, Female=16. **Intervention:** A psychologist administered attention and memory tests before and after training with RehaCom software. Participants received 60 training sessions over 12 weeks, 50-min per session, five days a week. **Outcome Measures:** Mini-Mental State Examination, Wechsler Memory Scale and Trail Making Test (Parts A and B).	1. Significant improvements were found in logical memory, visual memory, and overall memory measures. 2. Participants showed a substantial increase in Wechsler memory Scale scores. 3. RehaCom software was found to be accessible and an effective intervention for individuals with TBI with memory difficulties.
Tam & Man (2004) China PCT N=32	**Population:** TBI. *Self-Pace Group (n=6)*: Mean Age=40.5yr; Gender: Male=4, Female=2. *Feedback Group (n=6)*: Mean Age=33.3yr; Gender: Male=4, Female=2. *Personalized Group (n=6)*: Mean Age=32.6yr; Gender: Male=3, Female=3. *Visual Representation Group (n=6)*: Mean Age=39.8yr; Gender: Male=3, Female=3. *Control Group (n=8)*: Mean Age=45yr; Gender: Male=4, Female=4. **Treatment:** Participants were randomly assigned into one of four parallel computer-assisted retraining groups: 1) self-paced, 2) feedback (i.e., immediate feedback), 3) personalized (in actual living environment), or 4) visual presentation (colourful, bright, and attractive presentation). There was a total of 10 sessions, each lasting 20-30min. The control received no computerized retraining. **Outcome Measure:** Rivermead Behavioural Memory Test (RBMT).	1. After intervention, all groups receiving the computer-assisted memory programs performed significantly better in memorizing and remembering 'drilled content' (p<0.05). 2. No significant differences were found between pre- and post-RBMT scores in any of the treatment groups. 3. All memory-training conditions showed a positive trend in the treatment group as compared to the control group although there were no statistical differences between measures.
Chen et al. (1997) USA Case-Control	**Population:** TBI; Age=18+yr; Gender: Male=27, Female=13. **Intervention:** Divided retrospectively into computer-assisted rehabilitation (CACR) and traditional therapy groups.	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

Author Year Country Study Design Sample Size	Methods	Outcome
N=40	**Outcome Measures:** Neurophysiological Test Scores (WAIS-R; WMS).	significant gains on seven measures ($p<0.005$). 2. No significant difference was found between groups for post-treatment gains.

Discussion

In a prospective cohort study, Johansson and Tornmalm (2012) examined the benefits of 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 6-month follow up. 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). RehaCom software has been evaluated in two studies (Fernández et al., 2012; Lesniak et al., 2020). Fernandez et al. (2012) found that individuals significantly improved on the Wechler Memory Scale for logical memory, visual memory, and overall memory, as well as on measures of attention (Fernández et al., 2012). Lesniak et al. (2020) also examined the effectiveness of RehaCom software, and found improvements in memory; however, the results did not persist past follow-up.

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 (K. 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 (K. Li et al., 2015).

Some authors examined the effect of computerized interventions on memory in individuals with ABI. Tam and Man (2004) found no significant differences between groups when using a computer-assisted memory retraining program; however, the authors found a positive trend in the treatment group. Hellgren et al. (2015), found that a computerized memory training program was successful in enhancing working memory in both tasks trained in the program, and in other working memory tasks that emerged in neuropsychological tests. Participants' everyday working memory related activities showed improvement as well. Lindelov et al. (2016) compared N-back computerized training with visual search training. The authors found that neither group demonstrated transfer to untrained tasks, and that computerised training may improve specific skills rather than high-level cognition in individuals with ABI and the control group.

In one RCT Dou et al. (2006) demonstrated that computer assisted memory training may not be superior

to therapist administered memory training as both groups improved on measures of memory over time compared to a no-treatment control group but did not significantly differ from each other. 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 in terms of cognitive gains, including memory (Chen et al., 1997). When comparing a non-specified memory training program and an attention training program, Niemann et al. (1990) found that neither program actually improved measures of memory.

Cumulatively, by observing studies from across a period of nearly 20 years, the literature reveals that several computer software programs were examined; therefore, limited conclusions can be made on their efficacy compared to therapist administered therapy or to each other. A recent systematic review and meta-analysis Fernandez-Lopez and Antoli (2020) examined computer-based cognitive interventions for individuals with ABI and stroke, and found that computer-based interventions may be beneficial for both verbal and visual memory; however, they may not have effect on other cognitive domains (e.g., attention, reasoning). The authors suggested that more high-quality RCTs are needed, as well as long-term and daily-living measures.

Conclusions

There is level 1b evidence that a computer-assisted attention program may be more beneficial for individuals with ABI than memory training when compared (Niemann et al., 1990).

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 (Dou et al., 2006).

There is level 2 evidence that N-back training compared to virtual search training is not effective for improving memory in those with an ABI (Lindelov et al., 2016).

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 (O'Neil-Pirozzi & Hsu, 2016).

There is level 2 evidence that non-specific computer-based memory retraining compared, self-paced or otherwise, may not be effective at improving memory in those with an ABI (Tam & Man, 2004).

There is level 4 evidence that Cognitive Pragmatic Treatment, Cogmed, Cogmed QM, and RehaCom software may improve memory and cognitive function in individuals with an ABI (Fernández et al., 2012; Hellgren et al., 2015; Johansson & Tornmalm, 2012; Lesniak et al., 2020).

There is conflicting (level 4) evidence regarding the effectiveness of Parrot software at improving memory and learning in individuals post ABI (K. Li et al., 2015; Li et al., 2013).

There is level 4 evidence that a computer assisted cognitive rehabilitation show no significant differences in memory when compared to traditional therapy methods (Chen et al., 1997).

KEY POINTS

- Some computer-based software programs seem to be effective for improving memory post ABI.

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 training has advantages over conventional therapies, as it has the potential to simulate real-life or imaginary circumstances in a safe environment (Alashram et al., 2019). In addition, VR systems provide the option to adjust the task complexity according to individual skills and goals (Brassel et al., 2021). 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. On observational study by Canty et al. (2014) demonstrated that VR might also be potentially helpful as an assessment tool.

TABLE 14 | The Effect of Virtual Reality Exercises on Learning & Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Yip & Man (2013) Hong Kong RCT PEDro=5 N=37	**Population:** ABI. *Treatment Group (TG, n=19):* Mean Age=37.83yr; Gender: Male=12, Female=7; Mean Time Post Injury=145.13d. *Control Group (CG, n=18):* Mean Age=38.53yr; Gender: Male=12, Female=6; Mean Time Post Injury=167.53d. **Intervention:** Participants were randomized to receive virtual-reality prospective memory training (VRPM) 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 reading and games. Both were received in 30min sessions 2/wk for a total of 6wk. Outcomes were assessed at baseline and after treatment. **Outcome Measures:** VR-based PM test (VRPMT), Real life behavioural PM test	1. 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. 2. In the TG, RLPMT showed significant improvements after treatment in event-based ($p<0.01$) and time-based ($p<0.01$) tasks, but not ongoing tasks, compared to baseline. 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. 4. In the CG, no significant difference was found after treatment on any outcome measure compared to baseline.

	(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).	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.
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: participants were allocated to a 4-week intervention of receiving 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 Pre-Post $N_{Initial}$=21 N_{Final}=15	**Population:** CVA=6, TBI=5, Tumor=2, Anoxia brain injury=2; Mean Age=40.3yr; Gender: Male=12, Female=3. **Intervention:** 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. **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).	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. 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. 3. No significant differences from session 1 to session 8 were found for all pair cancellation subtest scores. 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.
De Luca et al. (2020) Italy Post-Test N=20	**Population*****: TBI; Patients (n=10):*** Mean Age=45.7yr; Gender: Male=5, Female=5; Mean GCS<8. ***Caregivers (n=10):*** Mean Age=43.7yr; Gender: Male=6, Female=4. **Intervention:** Participants with severe TBI and their caregivers were recruited and trained by telemedicine operators for proper use of the Tele-rehabilitation virtual reality rehabilitation system (VRRS). The VRRS device incorporates exercises that improve attention, memory, and visuospatial and reasoning tests. Both participants and their caregivers were trained for 60 minutes, 3 days per week for two weeks. **Outcome Measures:** Intrinsic Motivation Inventory (IMI), System Usability Scale (SUS).	1. The motivation experienced by all participants was positive, as reflected by the median IMI score of 198.5 points for patients, and 217 for caregivers. 2. Participants presented positive usability scores: the median SUS score was 65.0 for patients and 70 for caregivers. 3. Notably, younger TBI participants had higher usability scores than older adult participants. 4. No significant differences emerged between the two groups for the other IMI scales or SUS.

Sorita et al (2013) France PCT N=27	**Population:** TBI. *Treatment Group (TG, n=14):* Mean Age=31.1; Gender: Male=12, Female=2; Mean Time Post Injury=4.67yr; Mean GCS=5.8. *Control Group (CG, n=13)*: Mean Age=31.1; Gender: Male=13, Female=0; Mean Time Post Injury=6.77yr; Mean GCS=6.7. **Intervention:** Participants engaged in the same route-learning task in either a real urban environment (CG) or a virtual simulation of that environment (TG). After a learning phase, participants repeated the task twice in a row and >24h later. Outcomes were assessed after each repetition and a series of tests was completed after the last repetition. **Outcome Measures:** Route-learning task; Sketch map test; Map recognition test; Scene arrangement test.	1. On the task, mean error rates for immediate and delayed recall were higher in the TG than in the CG, but this difference was not significant (p=0.42). 2. On the task, mean scores were higher on the second (immediate) recall and the third (delayed) recall compared to the first (immediate) recall in both groups (p<0.001). 3. On the task, mean scores were higher on the second recall than on the third recall in both groups, but the difference was not significant (p=0.44). 4. No significant interactions between recall and environment were found. 5. Mean scores on the scene arrangement test were significantly higher in the CG than in the TG (p=0.01). 6. Mean scores on the sketch mapping test were higher in the CG than in the TG, but this difference was not significant (p=0.07). 7. Mean scores on the map recognition test were the same in both groups (p=0.83).

Discussion

The use of a VR rehabilitation program as cognitive therapy is feasible and safe for individuals with TBI (De Luca et al., 2020). In an RTC, Yip and Man (2013) found that those who received virtual reality memory training showed a significant improvement in immediate recall of tasks and event-based performance. Although the control group saw no improvements on items of memory evaluation there were no significant differences between groups on measures of community integration (Yip & Man, 2013). 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. Dahdah et al. (2017) also found that multiple Stroop tasks in VR environments resulted in improved performance on parts of those tasks. VR has been found to improve more than just memory as well, in an older RCT by Grealy et al. (1999), not only did individuals receiving VR exercise significantly improve on visual learning abilities, they also improved on reaction time.

In a recent systematic review, Alashram et al. (2019) indicated that VR may improve cognitive functions such as memory and executive function; however, larger sample sizes and randomized controlled trials with a higher PEDro score are needed to verify these findings. Other aspects such as cost, care equity and accessibility (Maggio et al., 2019) , as well as the potential for cybersickness (disorientation, nausea, dizziness) (Moraes et al., 2021) must also be considered when using VR to improve cognitive functions in individuals with moderate to severe TBI. Finally, despite the potential of VR to assist ABI rehabilitation, there is limited evidence on how to design and implement a VR tasks specific to TBI (Brassel et al., 2021).

Conclusions

There is level 4 evidence that virtual reality (VR) training may improve learning performance post ABI, even in the presence of distractions (Dahdah et al., 2017).

There is level 2 evidence that virtual reality training combined with exercise may be promising for improving memory outcomes and has a positive impact on visual and verbal learning when compared to no treatment (Grealy et al., 1999).

There is level 2 evidence that virtual reality training may be superior to reading skills training at improving immediate and general components of memory for individuals with an ABI (Yip & Man, 2013).

There is level 2 evidence that the format of route learning (either real or virtual reality based) does not significantly impact any improvements in memory as a result of route learning strategies for those with an ABI (Sorita et al., 2013).

There is level 4 evidence that a virtual reality telerehabilitation program is feasible and safe for cognitive therapy in individuals with TBI (De Luca et al., 2020).

KEY POINTS

- Virtual reality programs may enhance the recovery of memory and learning, but there is currently limited evidence supporting the use of virtual reality programs. The evidence is unclear as to which specific VR programs benefit memory rehabilitation and how they compare to manual training therapies.

Internal Memory Strategies

The following studies examined how different cognitive strategies could be used to enhance learning and memory following an ABI. Internal memory strategies assist individuals to direct their attention to new information and to elaborate in a meaningful way upon it, to facilitate subsequent retrieval (Velikonja et al., 2014). Internal memory strategies, also known as mnemonic strategies, refer to behaviours or techniques (e.g., visual imagery, forming acronyms) that help an individual gain control over their learning and memory ability, by encouraging a deeper level of processing and facilitating the integration of isolated information, as well as providing built-in retrieval cues (O'Neil-Pirozzi et al., 2016).

TABLE 15| The Effect of Internal Strategies on Learning & Memory Post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Grilli & McFarland (2011) United States RCT Crossover PEDro=4 N=12	**Population:** Mean age=49.42yr; Gender: Male=5, Female=7. **Intervention:** Participants were either instructed to self-imagine participation in a memory trivia game or rehearse the information they wanted to remember out loud during memory training trials. **Outcome Measures:** Prospective memory, neuropsychological functioning (executive functioning).	1. There was a significant between groups difference, where self-imagination instruction improved prospective memory ($p<0.01$). However, the proportion of questions answered correctly did not differ significantly between groups. 2. A Pearson correlations test showed that performance in the self-imagination condition was not significantly correlated to memory or executive functioning.
Bourgeois et al. (2007) USA RCT PEDro=2 N=38	**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 Measures:** Goal Mastery, Cognitive Difficulties Questionnaire (CDS).	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 significantly 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 ($p>0.05$).
Kaschel et al. (2002) Germany RCT PEDro=6 N=27	**Population:** *Pragmatic Group (N=15)*: Mean age=36.6yr; Gender: Male=12, Female=3. *Imagery Group (N=11):* Mean age=41.9yr; Gender: Male=9, Female=2. **Intervention:** Individuals were assigned to either imagery-based training (experimental), or pragmatic-based training (control) for 10 weeks, 3 times a week. Individuals were assessed at baseline, immediately following treatment conclusions, and at 3-months follow-up. **Outcome Measures:** Concentration endurance, Wechsler Memory Scale (WMS), Rivermead Behavioral Memory Test (RBMT), Appointments test, Memory Assessment Clinics Rating Scales (MAC).	1. There was a significant effect of time for the assessment of concentration endurance with both groups significantly improving over time ($p<0.05$). No other significant measures were found for concentration endurance. 2. There were no significant differences between groups on the WMS. 3. For the RBMT, only a significant effect of time was observed ($p<0.05$). A specific subset of the RBMT for logical memory showed a significant group ($p<0.01$) and interaction effect ($p<0.05$) indicating that those in the imagery condition had improved logical memory. 4. When assessing ability to recall multiple appointment times, a significant effect of group ($p<0.05$), and time ($p<0.01$) was observed with individuals in the imagery performing better. 5. On the MAC scale for relative's rating of memory problems, there were significant interactions at all time points ($p<0.05$), and a significant effect of time ($p<0.05$) indicating that the self-imagery group had greater gains in memory according to relative's ratings compared to the pragmatic group.
Milders et al. (1995) Netherlands RCT	**Population:** Closed Head Injury (CHI); *Strategy Group (n=15)*: Mean Age=42.4yr; Mean Time Post-Injury=10.4yr; *Pseudo Group (n=8)*: Mean	1. Standardized memory sum scores at long-term follow-up were significantly lower in the three

PEDro=5 N=31	Age=35.6yr; Mean Time Post-Injury=12.4yr; *No-Treatment Group (n=8)*: Mean Age=37.7yr; Mean Time Post-Injury=12.9yr; *Healthy Control (n=13)*: Mean Age=41.1yr **Intervention:** 4yr follow-up to Berg et al. (1991). **Outcome Measures:** Four-choice Reaction Time Task, Distraction Reaction Time Task, 15-Words Test, Face-Name Learning, Shopping Lists.	patient groups than in the normal control group ($p<0.05$). 2. Pseudo-rehab group improved significantly ($p<0.05$) in memory from post-training to long-term follow-up; such improvements were not seen in any other groups. 75% of patients in the pseudo group improved compared to 20% in the strategy group and 37.5% in the no-treatment group. 3. Reaction time scores did not differ significant between groups at follow-up (P=0.08).
Twum and Parente (1994) USA RCT PEDro=3 N=60	**Population:** TBI; Mean Age=21yr; Time Post Injury>6mo. **Intervention:** Participants 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. **Outcome Measure:** VerPA and VisPA tasks.	1. MANOVA analysis revealed an overall significant main effect of mental imagery instructions ($p<0.0001$) and a main effect of verbal labeling instructions on the VisPA ($p<0.0001$).
Berg et al. (1991) Netherlands RCT PEDro=5 N=39	**Population:** Closed Head Injury (CHI); *Strategy Group (n=17)*: Mean Age=36yr; Mean Time Post Injury=5.3yr. *Pseudo Group (n=11)*: Mean Age=33yr; Mean Time Post Injury=6.3yr. *No-Treatment Group (n=11)*: Mean Age=35yr; Mean Time Post-Injury=6.8yr. **Intervention:** Individuals were randomly assigned to one of three groups: strategy rehabilitation, pseudo-rehabilitation, or no-treatment. The strategy rehabilitation group had individualized training targeting to the identified memory problems (1hr, 3x/wk for 6wk). Daily homework was administered to augment the benefits of rehabilitation. The pseudo-rehabilitation ("drill and practice") group participated in sessions consisted of memory tasks and games that were practiced in the laboratory and at home. The no-treatment group received no training. **Outcome Measures:** Four-choice Reaction Time Task, Distraction Reaction Time Task, 15-Words Test, Face-Name Learning, Shopping Lists.	1. No single effect of strategy training was found with respect to reaction time tasks post-training. 2. While no significant effect of pseudo-training was found, strategy training had significant positive effects on all memory performance measures (memory sum score: p=0.011; acquisition score: p=0.038; delayed recall score: p=0.004), particularly at the final follow-up.
Raskin et al. (2019) USA PCT N=40	**Population:** *TBI Group (N= 20):* Mean Age=42.11±13.21yr; Gender: Male=12, Female=8; Mean time post injury=217.19±198.45d; Mean GCS=7.25±3.89. *Control Group (N= 20)*: Healthy controls; Mean Age=39.15±14.21yr; Gender: Male=10, Female=10. **Intervention:** AB-BA study design where participants with TBI underwent prospective	1. All participants with TBI showed an increase in the time they could recall the prospective memory task (mean increase 2.51±1.85min. 2. There was a significant interaction ($p<0.001$) explained by pre-post difference for the PM training using a metacognitive technique but not the other PM training. 3. Within the TBI group, there was significant improvement on the MIST test (summary, total

	memory (PM) training using a metacognitive technique involving visual imagery under the conditions of rote repetition and spaced retrieval (1hr sessions, 1-2/wk, for 6mo) or the control condition, then switched. The control condition was the same frequency but used a PM training that had been proven to be ineffective. Participants were assessed at baseline, post-treatment, and at 1yr follow-up. Healthy controls were used to control for the effects of re-testing are not reported on here. **Outcome Measures:** Memory for Intentions Test (MIST), Trail Making Test, the Brief Test of Attention, and the Hopkins, Verbal Learning Test, Prospective Memory Questionnaire (PMQ), Everyday Memory Questionnaire (EMQ), World Health Organization-Quality of Life-Bref (WHO-QoL-BREF), participant diary recording.	errors, PM errors), EMQ, diary recording scoring, brief test of attention, and trail making part B, from pre to post test for cognitive rehabilitation therapy ($p<0.05$).
O'Neil-Pirozzi et al. (2010b) USA PCT N=94	**Population:** TBI; *Experimental Group*: Mean Age=47.3yr; Mean Time Post-Injury=11.8yr; *Control Group*: Mean Age=47.0yr; Mean Time Post-Injury=13.4yr **Intervention:** Participants in the experimental group were trained to use Internal Memory Strategies (I-MEMS; n=54); the intervention consisted of 12 90-min sessions, held 2×/wk for 6 wk. It included memory education and emphasized internal strategy acquisition to improve memory function from encoding, storage, and retrieval perspectives; the control group (n=40) consisted of a convenience sample. **Outcome Measure:** Hopkins Verbal Learning Test-Revised (HVLT-R), Rivermead Behavioural Memory Test II (RBMT II). Patients were assessed on Week 1 (pretest), Week 7 (posttest 1), and Week 11 (posttest 2).	1. Pretesting revealed a significant difference between experimental and control groups on the HVLT-R only ($p=0.02$). 2. Individuals who had a severe TBI performed more poorly on the HVLT-R than those with moderate injuries. 3. Although those with a severe injury did not improve as much as those with a mild or moderate injury, they did improve more than those in the control group at both posttest 1 ($p=0.0002$) and posttest 2 ($p<0.0001$). 4. Similar to what was found with HVLT-R assessments, severe injury predicted worse RMBT II scores than moderate injury. 5. RBMT II scores in the I-MEMS groups revealed significant improvements at both posttest 1 ($p=0.045$) and posttest 2 ($p=0.0013$) relative to control. 6. Overall memory performance was improved for all those in the experimental group compared to the control group.
Manasse et al. (2005) USA Case Series N=5	**Population:** TBI: Age Range: 29-48yr; Gender: male=3, female=2; Time Post-Injury: 1-29yr. **Intervention:** participants were shown pictures of individuals they interacted with daily and asked to identify them. **Traditional treatment**: To assist participants in memory recall, pictures were paired with an imagery statement. There were 9 (3 weeklies 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	1. **Traditional treatment:** results indicate that 2 of the 5 participants mastered 6 names during treatment, 1 of the 5 mastered 3 names and 4 of the 5 mastered one of the names. 2. **Real-world treatment:** During the real-world cueing condition only 2 names were consistently used by each participant. 3. Improved name learning was seen regardless of the cueing strategy.

	the interactions. Researchers recorded the participants' spontaneous use and knowledge of the staff's name. **Outcome Measures:** Name recall.	
Tailby & Haslam (2003) Australia Pre-Post N=24	**Population:** Head Injury=12, CVA=6, Hypoxia=3, Other=3. *Severe memory impairment group (n=8)*: Mean Age=43yr. *Moderate memory impairment group (n=8)*: Mean Age=43.8yr. *Mild/no memory impairment group (n=8)*: Mean Age=37.5yr. **Intervention:** 3 groups were formed based on Verbal Memory Index (VMI) on the Wechsler Memory Scale-III. All participants were tested in 3 conditions: errorful (EF), standard errorless (examiner-generated; EL-E) and self-generated errorless (EL-S). For training, 96 words of 5-6 letters were used over 2 sessions. Following the learning tasks, memory was tested explicitly and implicitly 5 and 30 min after the study phase, generating 6 scores for each learning condition. **Outcome Measures:** Verbal Memory Index (VMI).	1. Cued recall performance following EL-S learning was significantly better than standard errorless learning (EL-E) conditions ($p<0.0001$). 2. Level of priming did not differ significantly between groups ($p>0.05$). 3. Memory performance was significantly better following EL-E activity ($p<0.0001$) compared to EF. 4. A significant effect of severity was found ($p<0.005$) for the standard EL-E conditions; mild and moderate groups performed significantly better than severe group (defined by VMI: $p<0.0001$); significant effect of severity was also found for the EF condition ($p<0.001$).
Sumowski et al. (2014) USA Pre-Post N=10	**Population:** Severe TBI=10; Mean Age=42.8 yr; Gender: Male=6, Female=4; Mean Time Post Injury=8.4 yr. **Intervention:** Participants studied 48 verbal paired associates (VPAs) divided into 3 learning conditions: massed restudy (MR), spaced restudy (SR), and retrieval practice (RP). MR is similar to cramming, whereas SR is distributed learning. RP was similar to SR; however, re-exposure trials were framed as cued recall tests. Recall of VPAs was done at 30 min post intervention, and at 1 wk. Participants performed all 3 methods of learning. **Outcome Measure:** Recall of VPAs.	1. Participants recalled 46.3% of VPAs learned through RP compared with 12.5% through MR ($p<0.0001$), and 15% through SR ($p=0.002$). 2. SR did not result in better memory than MR ($p=0.0555$). 3. At 1wk, participants recalled 11.3% in the RP group compared to 0.0% in the MR ($p=0.004$), and 1.3% in SR ($p=0.011$). Again, SR and MR did not differ from each other ($p=0.343$).
Potvin et al. (2011) Canada PCT N=30	**Population:** TBI; *Rehabilitation Group (n=10)*: Mean Age=35yr; Gender: Male=7, Female=3. *Control Group (n=20)*: Mean Age=30.90yr; Gender: Male=11, Female=9. **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. **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	1. The experimental group performed significantly better on the TEMP post PM training than the control group ($p<0.05$). 2. During the learning phase, cued recall improved for those in the experimental group, although this improvement was not found to be significant. 3. Participants who took part in the rehabilitation program improved their performance on the PM experimental task ($p<0.05$). 4. No significant group effects were found for any neuropsychological tests, except with the digit symbol test ($p<0.05$). 5. Self-evaluated PM failures was significantly lower post-test in the rehabilitation group ($p<0.05$) but not the control group.

	Test, Brief Visuospatial Memory Test, Semantic Verbal Fluency, Mazes, Stroop Interference and Flexibility, CAPM (relative and participant versions).	
Grilli & Glisky (2013) USA Pre-Post N=30	**Population:** *Patient Group*: TBI=13, ABI=2; Mean Age=51.3yr; Gender: Male=7, Female=8. *Healthy Control (n=15):* Mean Age=50.7yr; Gender: Male=7, Female=8. **Intervention:** Participants were exposed to five intentional coding conditions over two days. Controls did all five in one day. For each trial a word was on the screen for 10sec. A sentence specifying the task (condition) would appear above the target word. The conditions were: baseline, semantic elaboration, semantic self-referential processing, episodic self-referential processing, and self-imagining. **Outcome Measure:** Immediate free-recall test.	*Only results for the TBI group are reported 1. For the patient group, self-imagining showed better free recall than baseline ($p<0.001$), semantic elaboration ($p<0.001$), episodic self-referential processing ($p<0.001$), and semantic self-referential processing ($p<0.05$). 2. Self-referential processing enhanced free recall more than episodic self-referential processing ($p<0.05$). 3. Semantic elaboration and episodic self-referential processing showed better free recall than scores attained at baseline ($p<0.05$, $p<0.01$, respectively). 4. Self-descriptive trait adjectives were recalled more than non-self-descriptive trait adjectives among only those in the self-imagining ($p<0.05$) and semantic self-referential processing conditions ($p<0.05$).
Sumowski et al. (2010) USA Case-Control N=28	**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 Measures:** Delayed cue recall test.	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 ($p<0.001$, $p=0.23$).
Schefft et al. (2008) USA PCT N=20	**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.	**Study 1**: 1. Self-generation encoding procedures improved recognition memory test performance, but not free recall, compared with the didactic presentation. **Study 2**: 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.

	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.	
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 Measures:** 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).
Milders et al. (1998) Netherlands PCT N=26	**Population:** Closed Head Injury (CHI)=13; Healthy Controls=13. *CHI Group*: Mean Age=39yr; Mean Time Post Injury=5yr. **Intervention:** Individuals with TBI completed exercises with standardized instructions that help make the new name more meaningful to the learner (8, 60-90min sessions over 4mo). Participants were assessed at baseline (3x) and 1wk and 6mo after training. **Outcome Measures:** Name Learning Test, Name-Occupation-Town Learning Test, Famous Faces Naming Test, Digit Span Forwards, Auditory Verbal Learning Task.	*Only results for the TBI group are reported 1. A main effect for the patient's group was found for the Name-Occupation Town Test (p<0.001). 2. Performance on the name learning test for the patient's group from pre-to post training (meaningful names= 12.8±4.6 to 14.0±3.6; meaningless names=11.6±3.9 to 11.7±3.2). 3. There were improvements on the Name-Occupation-Town Learning Test in the patient group (names= 16.8±7.7 to 21.6±7.2; Occupations + town= 22.4±9.4 to 23.5±8.2).
Thoene & Glisky (1995) Germany PCT N=12	**Population:** Mean age=45.58yr; Gender: Male=6, Female=6; Mean time post-injury=7.38yr. **Intervention:** Individuals attempted to learn the names associated with 4 faces in 3 conditions (mnemonic, vanishing cues, and video). Mnemonic trials consisted of associating a face with an elaborate verbal association. The video condition consisted of the 'face subject' introducing themselves via video to the	1. There as a significant effect of condition where the only condition to reach the criterion threshold was the mnemonic condition (p=0.001). Post hoc tests confirmed that individuals required fewer trials in the mnemonic condition to reach criterion (p=0.017). 2. While participating in the vanishing cues condition, individuals required less cues to remember target names over time.

	participant. The vanishing cues condition consisted of cueing the individual to remember the name during training sessions by cueing them with letters from the target name. **Outcome Measures:** Naming errors: Omission errors, other-set intrusions (information from another condition), same-set intrusions, other errors in naming, reaching criterion threshold, incidental recall (information not related to names).	3. There were significant differences between conditions for omission made, with the mnemonic group making significantly less (p=0.000). 4. There were significantly fewer other-set intrusions in the mnemonic group, compared to the other groups (p=0.04). 5. There were significantly fewer same-set intrusions in the mnemonic condition than other conditions (p=0.01). 6. The incidental recall of the target's professions was significantly higher in the video condition compared to other conditions (p=0.04).

Discussion

A variety of internal memory strategies exist which attempt to remediate memory deficits following an acquired brain injury. As a result of the breadth of strategies attempted and evaluated, few studies overlap in methodology and protocol limiting the conclusions that can be made about each intervention.

Potvin et al. (2011) used one of the more common strategies; visual imagery techniques. Following visual imagery instruction, the scores on the Test Ecologique de Memoire Prospective significantly improved for those in the visual imagery group, this group also reported significantly fewer prospective memory errors and depression. Prospective memory is an area that has been found to be positively affected by more than one imagery technique. Another RCT found that self-imagery significantly improved prospective memory compared to information rehearsal (Grilli & McFarland, 2011). Imagery techniques in general have been found to be effective for improving general memory (Twum & Parente, 1994), as well as specific areas of memory like logical memory (Kaschel et al., 2002). Overall, there is strong evidence to support the use of imagery techniques to improve memory. One study used self-imagery in combination with a variety of other encoding techniques to determine its efficacy against other encoding strategies such as semantic elaboration (Grilli & Glisky, 2013). The authors found that those in the self-imagining condition showed better free recall than the control condition, but also recalled more self-descriptive adjective words than the other control and experimental conditions (Grilli & Glisky, 2013).

Another common memory strategy is retrieval practice. A variety of different retrieval strategies have been studied, such as spaced retrieval, massed retrieval, and cued retrieval (Sumowski et al., 2014). The use of retrieval strategies has been shown to significantly improve goal mastery (Bourgeois et al., 2007), delayed recall (Hillary et al., 2003; Raskin et al., 2019; Sumowski et al., 2010), and immediate recall (Hillary et al., 2003; Raskin et al., 2019). Bourgeois et al. (2007) found that compared to didactic strategy instruction, spaced retrieval significantly improved goal mastery; however, both groups achieved significant improvements in memory and memory errors. In a follow-up study to Berg et al. (1991), which found significant improvements on all memory measures as a result of individual strategies, Milders et al. (1995) found that at four-year follow-up the group which experienced 'drill and practice" retrieval strategies had the best long-term memory outcomes. Although a general trend has shown spaced

retrieval and cued retrieval to be effective, it should be noted that the highlighted studies did not overlap in terms of their application of this strategy. Multiple studies have shown that massed retrieval or "cramming" is not an effective strategy for improving memory (Hillary et al., 2003; Sumowski et al., 2010).

Strategies which use multiple encoding techniques have also been found to be effective. Milders 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). This was shown to improve memory and recall (Milders et al., 1998). Also, learning procedures were more effective on one task (where participants were required to learn the name-occupation-and town) compared to the other two tasks (famous-faces or name learning). Twum and Parente (1994) randomly assigned 60 individuals with a TBI into one of four groups (one control and three mnemonic strategy groups) counterbalanced. The research demonstrated improved performance for participants who were taught a strategy (either verbal labeling or visual imagery, or both) while learning paired-associations. Treatment groups showed greater efficiency in learning and greater delayed recall information. This conclusion is supported by other studies which have found general improvements in memory when combining multiple encoding cues such as visual imagery and verbal/written cues (Manasse et al., 2005). In a final study examining encoding, individuals were taught word association pairs and found that when primed with the first word of the pair, individuals were able to recall the second word more effectively (Schefft et al., 2008).

The remaining interventions have been explored in limited studies. 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. A pre-post study examined the type of errorless learning to take place (self-generated or examiner generated) and found that self-generated errorless learning resulted in significantly higher recall (Tailby & Haslam, 2003). However, examiner errorless learning was observed to be better than errorful learning. Lastly, an interaction effect was seen with regard to injury severity such that those of a mild to moderate ABI responded better to treatment than those with a severe injury (Tailby & Haslam, 2003). A combination of internal memory strategies was also found to be effective for improving memory compared to a convenience sample of controls (O'Neil-Pirozzi et al., 2010a). Similarly, it was seen that those with mild to moderate ABIs gained the most from treatment, while those with a severe injury were not able to perform as well over all (O'Neil-Pirozzi et al., 2010a).

Internal memory strategies can be effective in individuals who have appropriate executive function, motivation and self-awareness to be able to identify a situation where they need to apply memory strategies and use them properly; therefore, it may depend on the severity of the injury (Velikonja et al., 2014). Individuals who experience memory difficulties following ABI may benefit from internal memory strategy training; however, more evidence is needed to understand the immediate and long-term impact on decontextualized and functional outcomes, as well as to define and compare participant profiles

(O'Neil-Pirozzi et al., 2016).

Conclusions

There is level 1b evidence to support self-imagination as an effective strategy to improve memory compared to standard rehearsal for those with an ABI (Grilli & McFarland, 2011; Kaschel et al., 2002; Twum & Parente, 1994).

There is Level 2 evidence to support that spaced retrieval training is an effective memory strategy when compared to massed retrieval or rehearsal in ABI populations (Berg et al., 1991; Bourgeois et al., 2007; Milders et al., 1995; Raskin et al., 2019).

There is level 2 evidence that strategies that utilize methods of multiple encoding, compared to strategies which only use singular methods, are more superior for improving memory post ABI (Milders et al., 1998; Schefft et al., 2008).

There is level 4 evidence that errorless learning is more effective than errorful learning when it comes to improving memory in ABI populations (Tailby & Haslam, 2003).

KEY POINTS

- Internal strategies such as self-imagination, spaced retrieval and rehearsal, and multiple encoding are effective for improving memory following an ABI.

Learning and Memory Training Programs

Following a brain injury, one of the most persistent problems are memory deficits (Hasegawa & Hoshiyama, 2009). Although the literature examining the efficacy of memory programs is limited, there is some support for training that stresses external memory strategies.

TABLE 16 | The Effect of Memory Retraining Programs on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
das Nair et al., (2019) UK RCT PEDro=8 $N_{Initial}$=328, N_{Final}=234	**Population:** TBI=328; *Treatment Group (n=171):* Mean Age=45.8±11.5yr; Gender: Male=123, Female=48; Median Time Post Injury=46mo; Severity: Moderate-to-Severe. *Control Group (n=157):* Mean Age=45.1±12.5yr; Gender: Male=116, Female=41; Median Time Post Injury=58mo; Severity: Moderate-to-Severe. **Intervention:** Participants were randomized to receive group memory rehabilitation plus usual care (treatment group) or usual care alone (control). Participants completed 10 group sessions once wk. Outcome measures were assessed at 6 and 12mo post randomization. **Outcome Measures:** Everyday Memory Questionnaire – Patient Version and Relative Version (EMQ-P/R), General Health Questionnaire 30 (GHQ-30), Rivermead Behavioural Memory Test General Memory Index (RBMT-3 GMI), European Brain Injury Questionnaire-Patient and Relative Version (EBIQ-P/R), Short- and Long-term Goal Attainment, Health Economic Analysis.	1. No significant differences in EMQ-P/R, memory ability (RBMT-3 GMI), mood (GHQ-30) or experience of brain injury (EBIQ-P/R) were observed between groups at 6 or 12mo post randomization (p>0.05). 2. Short- and long-term goal attainment scores improved with the intervention program at both 6 (short-term 95% CI 0.6(0.3 to 0.9); long-term 95%CI 0.5(0.2 to 0.7)) and 12mo (short term 95% CI 0.3(0.0 to 0.5); long term 95%CI 0.4(0.1 to 0.6)). 3. Health economic analysis suggested that the intervention was unlikely to be cost effective compared to the control.
Lesniak et al. (2018) Poland RCT PEDro=7 N=65	**Population:** *Group Therapy (N=18):* Mean age=41.3yr; Gender: Male=11, Female=7; Mean time post-injury=15.2mo. *Individual Therapy (N=23):* Mean age=39.6yr; Gender: Male=17, Female=6, Mean time post-injury=11.6mo. *No Therapy (N=20):* Mean age=42.2yr; Gender: Male=13, Female=7; Mean time post-injury=10mo. **Intervention:** Participants were assigned to either the individual therapy group (IT), the group therapy group (GT), or the no therapy group (NT). Individuals were assessed pre-treatment, immediately post treatment (3 weeks), and at 4-month follow-up. **Outcome Measures:** Cambridge Neuropsychological Test Automated Battery (CANTAB), Rivermead Behavioral Memory Test (RBMT)	1. All groups saw a significant improvement over time on the RBMT (p<0.05). There were no significant differences between posttreatment and follow-up in any group. Only the GT group saw a significant difference between pretreatment and follow-up (p<0.05). 2. On the Pattern Recognition Memory subset of the CANTAB both the IT and the NT groups has significantly higher scores (p=0.016, p=0.015) respectively. Only the IT group maintained this difference at follow-up (p=0.002). 3. The IT group was the only group to see a significant difference on the spatial span (p=0.031) and rapid visual processing (p=0.024) subsets of the CANTAB. 4. No other significant differences were found.
Chiaravalloti et al. (2016) USA RCT PEDro=9 $N_{Initial}$=69 N_{Final}=53	**Population:** TBI. *Treatment Group (TG, n=35):* Mean Age=37.17 yr; Gender: Male=27, Female=8; Mean Time Post Injury=120 mo; Mean GCS=4.83. *Control Group (CG, n=34):* Mean Age=40.68 yr; Gender: Male=24, Female=10; Mean Time Post Injury=102 mo; Mean GCS=5.0. **Intervention:** Participants were randomized to receive the modified Short Memory Technique (TG) or conventional therapy (CG) in 10 sessions over 5 weeks.	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).

Author Year Country Study Design Sample Size	Methods	Outcome
	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. **Outcome Measures:** California Verbal Learning Test (CVLT); Memory Assessment Scales, Prose Memory (MAS-PM); Rivermead Behavioural Memory Test (RBMT).	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).
Sandry et al. (2016) USA Post Hoc Analysis: Chiaravalloti et al. (2016) N=69	**Population:** See above. **Intervention:** See above. **Outcome Measures:** Working memory capacity (WMC); Long-term memory percent retained (LTMPR).	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). 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).
Shum et al. (2011) Australia RCT PEDro=7 N=45	**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 compensatory PM training. All interventions involved 8 weekly attendances (1.5 hr each). Participants were assessed at baseline and after intervention. **Outcome Measure:** Cambridge Prospective Memory Test (CAMPROMPT); number of valid diary entries; Comprehensive Assessment of Prospective Memory (CAPM); Sydney Psychosocial Reintegration Scale (SPRS).	1. All 4 groups showed no significant differences on the CAMPROMPT during the pre-intervention phase. 2. Following intervention, those with a self-awareness training component were not significantly different from those without on the change scores. 3. Groups with a compensatory training component were found to have a significantly larger change score than those without (p=0.007). 4. There was a significant increase in the number of participants who took notes (p=0.008). 5. Post intervention the groups with a compensatory training component were found to have larger change scores than those without (p<0.017). 6. Scores on the CAPM and SPRS were not significantly different among the 4 groups pre- or post-intervention.
Vas et al. (2011) USA	**Population:** TBI: *Strategic Memory and Reasoning Training (SMART) Group* (n=14): Mean Age=39 yr;	1. The SMART group had significantly greater TOSL scores compared to the control group

Author Year Country Study Design Sample Size	Methods	Outcome
RCT PEDro=6 N=28	Gender: Male=9, Female=5; Mean Time Post Injury=16.71 yr. *Brain Health Workshop Group* (n=14): Mean Age=47 yr; Gender: Male=7, Female=7; Mean Time Post Injury=16.35 yr. **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 6-month follow-up. **Outcome Measure:** Test of Strategic Learning (TOSL); Working memory listening span task; Community Integration Questionnaire (CIQ); Wechsler Adult Intelligence Scale III (WAIS III).	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.
Zlotowitz et al. (2010) UK RCT PEDro=6 N=16	**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 Measures:** Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Patients' recall of sequences.	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).
Thickpenny-Davis & Barker-Collo (2007) New Zealand RCT PEDro=5	**Population:** Mean age=32.75yr; Gender: Male=12, Female=2; Mean GCS=6.6. **Intervention:** Individuals were assigned to either a memory rehabilitation program or a waitlist control group. The memory program consisted of 8 sessions.	1. Immediately following rehabilitation, the memory rehabilitation group had significantly improved scores on the CVLT-long delay free subtest (p=0.007), WMS-LM delayed recall (p=0.009), used significantly

Author Year Country Study Design Sample Size	Methods	Outcome
N=14	Measures were taken at baseline, immediately following intervention, and at 1-month follow-up. **Outcome Measures:** California Verbal Learning Test (CVLT), Wechsler Memory Scale-Logical Memory (WMS-LM), visual paired associates (VPA), Integrated Visual and Auditory Continuous Performance Test (IVA-CPT), Memory in Everyday Life and Use of Aids and Strategies Questionnaire, Behavioral indicators of memory impairment checklist, Memory Quiz, participant feedback questionnaire.	more memory aids (p=0<0.001), and had significantly higher memory quiz scores (p<0.001). 2. When comparing immediately after rehabilitation to follow-up, there was a significant difference in VPA delayed recall scores (p=0.048). 3. Comparing baseline to 1-month follow-up scores there was a significant difference
Eakman & Nelson (2001) United States RCT PEDro=5 N=30	**Population:** Mean age=29.6yr: Gender: Male=30, Female=0; Mean time post-injury=53.5 mo. **Intervention:** Participants were randomly assigned to receive either hands-on meatball making training, or verbal instruction only meatball making training, which consisted of a 10-step instruction process. **Outcomes:** Memory of steps involved in making meatballs.	1. The hands-on meatball group remembered significantly more steps for making meatballs than the verbal instruction group (p<0.001).
Afsar et al. (2021) India Pre-Post N=12	**Population:** TBI; Moderate-Severe=12; Mean Age=32.33yr; Gender: Male=9, Female=3; Mean Time Post Injury=11.37mo. **Intervention:** Participants underwent a hospital-based cognitive retraining (CR) intervention for three days per week for two months. The CR intervention included five tasks and aimed at enhancement of impaired cognitive functions through repetitive practice and drills. Outcome assessments were measured at baseline and post-intervention. **Outcome Measures:** Visual Analogue Scale (VAS), Perceived Stress Scale (PSS), Rivermead Post-Concussion Symptoms Scale (RPCSS), World Health Organization Quality of Life Scale-Brief (WHOQLS-Brief), Digit Symbol Substitution Test (DSST), Complex Figure Test-Copy (CFT-Copy), Complex Figure Test-Delayed Recall (CFT-Delayed Recall), Rey's Auditory Verbal Learning Test-Total Learning (AVLT-Total Learning).	1. Patients exhibited significant changes at post intervention in the domains of processing speed (DSST), working memory (Spatial Span), planning (Tower of London), visuo-spatial construction (CFT-Copy), visual memory (CFT-Delayed Recall), and verbal memory (AVLT-Total Learning). 2. AVLT-Total Learning scores represented the individual's capacity to learn information over trials and is considered as the measures of memory encoding, whereas Recall trials are considered as the measures of memory retention. 3. At post-intervention, the patients exhibited significantly lower amounts of perceived stress (PSS), lower levels of post-concussive symptoms (RPCSS), and higher levels of psychological quality of life (WHOQLS-Brief).
Holleman et al. (2018) Netherlands PCT N=75	**Population:** *Experimental Group (N=42):* Mean age=43.3yr; Gender: Male=27, Female=15; Mean time post-injury=7.9yr. *Control Group (N=33)*: Mean age=40.7yr; Gender: Male=20, Female=13; Mean time post-injury=6.9yr. **Intervention:** Participants were either assigned to the Intensive NeuroRehabilitation programme or the control group. The programme took place over the course of 16 weeks and consisted of 2 groups of 7 weeks of training with a 2-week break in between. Individuals had 5 hours of training 4 days a week in a group setting.	1. There were no significant between group differences pre-intervention on any measures. 2. Following the intervention, the experimental group had significantly lower SCL scores indicating a reduction in overall symptoms (p=0.005). 3. On measures of neuropsychological functioning, the experimental group reported significantly lower scores on the BDI-II (p=0.001), HADS (p<0.01), and ZBV-

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcomes: Symptom checklist (SCL), Beck Depression Inventory-II (BDI-II), Hospital Anxiety and Depression Scale (HADS), Zelfbeeldenvragenlijst-trait (ZBV), Quality of Life in Brain Injury (QOLIBRI), Trail making test Part A, Stroop test, Wechsler Adult Intelligence Scale-III (WAIS-III), Rey Auditory Verbal Learning Test, Rivermead Behavioural Memory Test, Groninger Intelligentie Test 2, Trail making test Part B.	trait (p=0.002) showing improvement on these neuropsychological measures. 4. The experimental group reported significantly higher scores for quality of life on the QOLIBRI (p<0.05). 5. On measures of cognitive functioning no significant differences were seen for any outcome measures.
Raskin et al. (2012) United States PCT N=18	**Population:** *Brain injury (N=8):* Mean age=41.75yr; Gender: Male=4, Female=4; Mean GCS=8.5; Mean time post-injury=84.22mo. *Healthy Adult (N=10):* Mean age=45yr; Gender: Male=2, Female=8. **Intervention:** Participants with a brain injury were given a memory intervention which included behavioral interventions, metacognitive strategies, and restorative approaches and compared to healthy controls. **Outcomes:** Assessment of Intentional Memory (AIM), Community Integration Questionnaire (CIQ), Prospective Memory Questionnaire (PMQ), Everyday Memory Questionnaire (EMQ), Diary Study.	1. All participants increased the time between recall on the ProM tasks. 2. Both groups improved scoring on the AIM with the 2-min time delay assessment, but the BI group had lower scores when the delay was pushed to 15 mins. 3. Individuals in the brain injury group showed significant improvement in total AIM scores (p<0.05), and a significant reduction in the number of errors made (p<0.05). 4. There were no significant improvements on the CIQ, or PMQ. 2. The BI group had a significant decrease in EMQ scores (p<0.05). And a significant increase in memory scores related to the Diary Study (p<0.05).
Constantinidou et al. (2008) RCT PEDro=8 N=35	**Population:** TBI; Mean age=32.1, Age range=19 to 54yr; time since injury=9.74 months. **Intervention:** participants were enrolled in a categorization program (CP). Tasks included (1) recognition and categorization of everyday objects, and (2) new category learning. **Outcomes:** Wechsler Abbreviated Scale of Intelligence, Perception and discrimination, organization and reasoning scales – Scales of Cognitive Ability for Traumatic Brain Injury, Rey Complex Figure Test, Trail Making Test A and B, Digit Span – Wechsler Memory Scale III, Californian Verbal Learning Test II, Wisconsin Card Sorting Test, The Booklet Category Test, Symbol Digits Modalities Test, Control Oral Word Association, Woodcock-Johnson III, Mayo-Portland Adaptability Inventory III (MPAI-3), Community Integration Questionnaire (CIQ).	1. There was no difference at baseline between the two groups of participants with TBI on their CP test 1 performance, t(32)=0.804, P=.427. 2. Analysis of the pre- and post-performance of the two groups revealed that performance on the CP test 1 improved with therapy (P=.0001). Participants in the CP experimental group performed significantly better on the posttest compared to the control group (P=.039). 3. Participants in both groups showed significant improvements on the CIQ and the MPAI-3. 4. The CP Test 2 (pretest) scores were significantly correlated with all measures, except the Memory Composite.
Serino et al. (2007) Italy Case Series N=9	**Population:** TBI: Age range=16-57 yr; Gender: male=6, female=3; Time since injury=6-78 months. **Intervention:** A long sequence of numbers was 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	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<0.460) after GST.

Author Year Country Study Design Sample Size	Methods	Outcome
	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. **Outcome Measure:** Working memory training (WMT), Paced Auditory Serial Addition Test (PASAT), Months task	3. Working memory ($p<0.050$), divided attention ($p<0.050$), executive function ($p<0.050$), and long-term memory ($p<0.050$) for participants 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.
Hewitt et al. (2006) United Kingdom PCT N=30	**Population:** *Control Group (N=15):* Mean age=33.13yr; Gender: Male=10, Female=5; Mean time post-injury=7yr. *Experimental Group (N=15):* Mean age=38.47yr; Gender: Male=10, Female=5; Mean time post-injury=5.3yr. **Intervention:** Both groups completed sessions where they were asked to describe procedures for completing everyday tasks. The experimental group underwent additional procedural training which included memory retrieval prompts. **Outcomes:** Effectiveness of memory plan, number of steps remembered in procedures, number of specific memories, Rivermead Behavioral Memory Test (RBMT).	1. There was a significant between groups difference post-intervention for the effectiveness of memory strategies with the experimental group showing improved scores ($p<0.01$). 2. The experimental group were able to communicate significantly more steps on procedures post-intervention compared to the control group ($p<0.03$). 3. There was a significant within-participants effect for the number of specific memories recalled post-intervention compared to pre-intervention ($p<0.01$). 4. There were significant correlations between the number of specific memories produced and the effectiveness of the plan ($p<0.01$), and the number of steps ($p<0.01$). 5. RBMT scores were significantly associated with the difference in the number of specific memories between pre- and post-intervention ($p<0.02$), but not for effectiveness of plan used, of the number of relevant steps in the procedure.
Quemada et al. (2003) Spain Pre-Post N=12	**Population:** Mean Age: 33.1yr; Gender: male=6, female=6; GCS Score=5.7; Condition: TBI. **Intervention:** Individualized treatment using Wilson's Structured Behavioral Memory Program in 50-minute sessions daily for 6 months. **Outcome Measures:** Rey-Osterrieth Complex Figure Test (REY), California Verbal Learning Test (CVLT), Rivermead Behavioural Memory Test (RBMT), Memory Failures in Everyday Memory Questionnaire (MFE) Tests.	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 ($p=0.030$, $p=0.090$, $p=0.050$).
Laatsch et al. (1999) USA Case series N=5	**Population:** TBI; Age=18-65yr; Time Post-Injury=2-48 months. **Intervention:** Cognitive rehabilitation therapy (CRT) programme in a longitudinal protocol involving a resting SPECT and neuropsychological evaluation are	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 ($p<0.050$).

Author Year Country Study Design Sample Size	Methods	Outcome
	pre-treatment, post-treatment and post non-treatment intervals. **Outcome Measures:** Neuropsychological Measures.	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=32yr; 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 Measures:** 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 ($p<0.050$).
Jennett & Lincoln (1991) United Kingdom PCT N=18	**Population:** Mean age=52.3yr; Gender: Male=11, Female=8; Mean time post-injury 2-111mo. **Intervention:** Individuals were randomly assigned to participate in a memory strategy program in a group setting or be put on a waitlist. **Outcomes:** Rivermead Behavioral Memory Test (RBMT), Subjective Memory Questionnaire (SMQ), number and intensity of memory problems bothering individuals, use of memory aids.	1. There were no significant differences on the RBMT, or the SMQ. 2. There was no significant difference in the number of items individuals reported being bothered by, however the intensity to which they were bothered by them significantly decreased ($p=0.03$). 2. There was a significant decrease in the number of memory aids used by the experimental group ($p<0.05$).

Discussion

Similar to internal memory strategies, many potential interventions have been studied, with little overlap between studies themselves in terms of methodology. A variety of trademarked cognitive programs have been evaluated to improve learning and memory following an ABI. Constantinidou et al. (2008) evaluated the Categorization Program (CP) for 13 weeks in an RCT and found that, although individuals who received the program performed better on measures of executive function, there were no significant improvements seen in learning or memory. 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 (Sandry et al., 2016). Asfar et al., (2021) found that cognitive retraining may significantly improve cognitive domains such as processing speed, working memory, visual memory, and verbal memory.

Several specific non-computerized learning and memory interventions have also been evaluated in singular studies. 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 group 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. In contrast, das Nair et al. (2019) examined the effects of a 10-hour group memory rehabilitation program versus usual care and found no significant improvements in memory. Additionally, the authors performed a health economic analysis, which found the intervention was unlikely to be cost effective.

In another RCT, 45 individuals were randomly assigned into one of four treatment groups (Shum et al., 2011). The treatment groups consisted of four 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 CAMPROMPT 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 finished.

Another unique intervention aimed at improving memory following an ABI was an RCT evaluating meatball making (Eakman & Nelson, 2001). Individuals received either hands-on or verbal instructions for making meatballs and were required to reproduce the meatballs at a later time. In this instance meatballs were used as an example to explore the benefits of modelling compared to verbal instruction only on memory consolidation. It was found that the hands-on meatball making group remembered significantly more steps in the making process compared to the verbal instruction only group (Eakman & Nelson, 2001) suggesting that modelling may be more effective than verbal instruction alone. Another study which compared the type of instruction given showed that asking individuals to describe procedures in detail and providing retrieval prompts was significantly more beneficial for recall than individuals training by describing procedures alone (Hewitt et al., 2006). These studies support the use of a combination of modelling and instructional techniques to improve memory.

Thickpenny-Davis and Barker-Collo (2007) randomly assigned 14 individuals to either the treatment or control group. 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 1-month follow-up time period. 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 individuals with TBI and their family members report meaningful functional gains (self-report and observed behaviour in everyday functioning).

Only one study (Serino et al., 2007) described a specific task that was successful in improving memory. This cognitive task involved mental addition in combination with two other standardized tasks and was an effective strategy for improving working memory. Changes on the Claeson-Dahl Memory test did not increase pre to post to 3-month follow-up. The findings of the previous study support 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.

Lesnaik et al. (2018), compared the effects of individual versus group therapy on memory and found that although both groups improved over time, there were no significant differences between groups. In a prospective controlled trial, a formal protocol for the Intensive Neurorehabilitation Programme showed no significant effects on the Rivermead Behavioral Memory Test, however depression and anxiety were seen to be significantly reduced (Holleman et al., 2018). One study demonstrated that a memory program which included all of these components elevated memory scores in individuals with an ABI similar to that of healthy controls (Raskin et al., 2012). A small 1991 RCT also provides support that memory programs which include memory strategies can also significantly decrease dependence on memory aids for those with an ABI (Jennett & Lincoln, 1991).

Conclusions

There is level 1b evidence that individual memory therapy is no more effective than group memory therapy for those with an ABI (das Nair et al., 2019).

There is level 2 evidence that programs involving multiple learning strategies (such as modelling, reciting, verbal instruction, and observation) are more effective than singular strategies for those with an ABI (Eakman & Nelson, 2001).

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 (Chiaravalloti et al., 2016).

There is level 1a evidence that the Categorization Program, and Strategic Memory and Reasoning Training (SMART) may be effective for improving memory compared to standard therapy in individuals with an ABI (Constantinidou et al., 2008; Vas et al., 2011).

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 post ABI individuals compared to no treatment (Shum et al., 2011).

There is level 2 evidence that the Intensive Neurorehabilitation Programme is not effective for improving memory compared to controls in those with an ABI (Holleman et al., 2018).

There is level 4 evidence that mental addition tasks may improve working memory in individuals post ABI (Serino et al., 2007).

There is level 4 evidence that the Wilson's Structured Behavioral Memory Program is not effective for improving memory post ABI (Quemada et al., 2003).

There is level 4 evidence that a cognitive retraining program may improve cognition and memory following moderate to severe TBI (Asfar et al., 2021).

KEY POINTS

- Memory-retraining programs appear effective, particularly for functional recovery although performance on specific tests of memory may or may not change.
- Memory training programs are effective
- Interventions which include multiple learning techniques such as modelling, observation, verbal instruction, etc. are more effective than interventions which include a singular learning method.

Cognitive Pragmatic Treatment

TABLE 17 | The Effect of Cognitive Pragmatic Treatment on Memory Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Bosco et al. (2018) Italy Pre-post N=19	**Population:** Severe TBI: Mean age=38.5yr; Gender: Male=16, Female=3; Mean time post-injury=99.4 months; GCS<8. **Intervention:** Groups of 5-6 participants met twice a week for 12 weeks for a total of 24 Cognitive Pragmatic Treatment (CPT) sessions. Participants were assessed at four time points, 3-months pre-treatment, immediately before treatment, immediately following treatment, and 3-months post-treatment. **Outcome Measures:** Assessment Battery for Communication (ABaCo), Communications Activities of Daily Living (CADL), Aachener Aphasie test, Attentional Matrices, Trail Making test, Verbal Span, Corsi's Block-Tapping test, immediate and deferred recall test, Tower of London test, Modified Card Sorting test, Raven Colored Progressive Matrices, Sally & Ann, Strange Stories.	1. There was a significant difference in scores on the ABaCO between pretreatment and posttreatment scores (p<0.001). There were no significant differences between the two initial time points, or the two posttreatment timepoints. 2. Similar results were seen for the CADL, with individuals showing a significant improvement in their functional communication skills following treatment (p=0.024). 3. Between immediate pretreatment scores and immediate post-treatment scores significant differences were only seen on the Verbal Span (p=0.045), and the Modified Card Sorting test (p=0.004).
Gabbatore et al. (2015) Italy Pre-Post $N_{Initial}$=20 N_{Final}=15	**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 Cognitive pragmatic treatment (CPT) program focused on mental representations underlying one's behaviors (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 Measures:** 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).	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).

Discussion

Bosco et al. (2018) evaluated a Cognitive Pragmatic Treatment (CPT) program over the course of 24 sessions with participants being assessed at four different time points. The results showed strong effects

on communication and activities of daily living; however, differences in other cognitive domains, such as memory, were not significant (Bosco et al., 2018). Gabbatore et al. (2015) implemented a Cognitive Pragmatic Treatment (CPT) program for individuals post TBI and found significant improvement on the Immediate and Deferred Recall test for long-term verbal memory and the Wisconsin Card Sorting test. The authors suggested that higher scores in long-term verbal memory tests should be interpreted with caution, given that these tests are frequency used, resulting in a potential learning effect (Gabbatore et al., 2015).

Conclusions

There is conflicting level 4 evidence regarding the effectiveness of a Cognitive Pragmatic Treatment (CPT) program on memory in individuals with TBI (Bosco et al., 2018; Gabbatore et al., 2015).

KEY POINTS

- The effectiveness of a Cognitive Pragmatic Treatment (CPT) program on memory in individuals with TBI is unclear.

Time Pressure Management Training

TABLE 18 | The Effect of Attention Training on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Fasotti et al. (2000) Netherlands RCT PEDro=5 N=22	**Population:** TBI; *Experimental Group (n=12)*: Mean Age=26.1yr; Gender: Male=8, Female=4; Mean Time Post Injury=9.8mo. *Control group (n=10)*: Mean Age=30.1yr; Gender: Male=7, Female=3; Mean Time Post Injury=8.3mo. **Intervention:** Participants 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	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.

Author Year Country Study Design Sample Size	Methods	Outcome
	Test, Paced Auditory Serial Addition Task, Visual Choice Reaction Time Task.	

Discussion

Fasotti et al. (2000) examined the effects of Time Pressure Management (TPM) on cognitive function in individuals with ABI. TPM can be used to help individuals with ABI to deal with time pressure in a task that involves processing information. The authors did not find significant improvements in memory outcomes compared to the control group (Fasotti et al., 2000).

Conclusions

There is level 2 evidence that time pressure management training is no more effective than concentration training at improving memory for those with an ABI (Fasotti et al., 2000).

KEY POINTS

Time Pressure Management may not improve memory in individuals with ABI.

Goal Training

TABLE 19 | The Effect of Goal-Oriented Attentional Self-Regulation Training on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Novakovic-Agopian et al. (2011) USA RCT Crossover PEDro=5 N=16	**Population:** TBI=11, Stroke=3, Other=2: Mean Age=50.4yr; Gender: Male=7, Female=9; Time Post Injury Range=1-23 yr. **Intervention:** Participants were randomized to 5wk 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 Measures:** Auditory Consonant Trigrams,	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 (*Mean* 1.12 vs -0.12, $p<0.0001$); mental flexibility (*Mean* 0.64 vs 0.04, $p=0.009$); inhibition (*Mean* 0.62 vs 0.04, $p=0.005$); sustained attention (*Mean* 0.96 vs 0.27, $p=0.01$); learning (*Mean*=0.51 vs 0.08,

Author Year Country Study Design Sample Size	Methods	Outcome
	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=0.020); and delayed recall (*Mean* 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=0.010); 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). 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).

Discussion

Novakovic-Agopian et al. (2011) examined the effects of goal-oriented attentional self-regulation training and education in an RCT crossover study. While education was shown to minimally improve memory, specific goals training significantly improved working memory, mental flexibility, learning and delayed recall (Novakovic-Agopian et al., 2011).

Conclusions

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 post ABI individuals compared to receiving the treatment conditions in reverse order (Novakovic-Agopian et al., 2011).

KEY POINTS

- Goal Training may improve memory in individuals with ABI.

Emotional Regulation

TABLE 20 | The Effect of Emotional Regulation Therapy on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Rath et al. (2003) USA RCT PEDro=2 N=46	**Population:** TBI: Mean Age=43.6 yr; Gender: Male=23, Female=37; Mean Time Post Injury=48.2 mo. **Intervention:** Participants 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.	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 ($p<0.01$); and observer ratings of roleplayed scenarios ($p<0.005$).

Discussion

In an RCT, Rath et al. (2003) compared 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 (Rath et al., 2003).

Conclusions

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 (Rath et al., 2003).

KEY POINTS

- Emotional self-regulation therapy may be effective for improving specific elements of memory in individuals with ABI.

Motor Procedural Training

TABLE 21 | The Effect of Motor Procedural Training on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Korman et al. (2018) Israel PCT N=20	**Population:** *Experimental Group (N=10)*: Mean age=30yr; Time post-injury=126.9 days; GCS: 3-12; Mean FIM at admission=53.3. *Control Group (N=10):* Mean age=29.3yr; Time post-injury=118.4 days; GCS: 3-8; Mean FIM at admission=46.8. **Intervention:** Over 2 weeks 5 training sessions took place where the experimental group was trained on a finger to thumb finger sequence task. Neither the TBI control group, nor the healthy control group received any training. All groups were evaluated on this task at two time points. **Outcome Measures:** Number of sequences performed during test time, number of correct sequences performed, performance speed, and number of errors.	*Trained vs Un-trained individuals with TBI* 1. Both groups significantly improved performance speed over the course of testing (p<0.001). With the trained TBI group seeing significantly larger gains (p=0.016). 2. There were no significant changes for either group in the number of errors produced over the testing period. 3. When assessing learning in the TBI group only, significant improvements in speed were seen during the training session (p<0.01). 4. Individual's performance was significantly worse at the end of a session compared to the beginning of a session (p=0.003). *Trained individuals with TBI vs Healthy controls* 1. During pre-training healthy controls completed significantly fewer errors compared to the TBI population (p<0.001). 2. Although both groups improved in performance over training sessions, the healthy control group had significantly greater gains compared to the TBI group (p<0.001). 3. A significant time X group interaction demonstrated that healthy controls had a faster learning trajectory compared to trained individuals with an ABI (p<0.001). 4. Both groups showed a significant decrease in within session gains over the course of testing (p<0.001). No significant differences were seen for between session gains during testing, demonstrating that healthy controls did not significantly out-perform individuals with a TBI who received training.

Discussion

Korman et al. (2018) assessed procedural memory consolidation processes. Participants were trained on motor memory, particularly on a finger to thumb finger sequence task. Individuals who were trained versus untrained on the task showed no significant differences in the number of errors made; however, the trained group saw a significant increase in performance speed compared to the control group. The authors found no correlation in the gains in performance attained during the study and measures of

cognitive abilities, including explicit memory (Korman et al., 2018).

Conclusions

There is level 2 evidence that motor procedural training, compared to no training, may not be effective for improving memory following an ABI (Korman et al., 2018).

KEY POINTS

- Motor procedural training may not improve memory in individuals with ABI.

Attention Training Programs

Attention is required to effectively use higher cognitive functions. Attention training targets attentional functioning in individuals by using repetition (e.g., detecting targets in the presence of distractions, attention shifting) (Michel & Mateer, 2006).

TABLE 22 | The Effect of Attention Training Programs on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Sohlberg et al. (2000) USA RCT PEDro=8 N=14	**Population:** TBI=11, ABI=1, Other=2. *Attention Process Training (APT) Group (n=7)*: Mean Age=33.1 yr; Mean Time Post Injury=7.5 yr; *Control Group (n=7)*: Mean Age=38.1 yr; Mean Time Post Injury=1.6 yr. **Intervention:** Participants 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 participants 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.	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).

Author Year Country Study Design Sample Size	Methods	Outcome
Novack et al. (1996) USA RCT PEDro=5 N=44	**Population:** Severe TBI; *Focused Stimulation Group (n=22)*: Mean Age=28.7 yr; Mean Time Post Injury=5.9 wk. *Unstructured Stimulation Group (n=22)*: Mean Age=26.4 yr; Mean Time Post Injury=6.4 wk **Intervention:** Participants were randomly placed into a focused or unstructured stimulation group. Participants in the focused group received hierarchical attentional learning training (30 min, 5 x/wk). Skills were not taught in a hierarchical or sequential fashion in the unstructured group. **Outcome Measure:** Digit Span and Mental Control subtests of Wechsler Memory Scale-Revised (WMS-R), computer-based simple and choice reaction time tests. *Secondary outcome measures*: Logical Memory I & II, Sentence Repetition, Judgment of Line Orientation, Trail Making A & B, Arithmetic subtest Wide Range Achievement Test-Revised, Visual imperceptions.	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.
Ryan & Ruff (1988) United States RCT PEDro=8 N=20	**Population:** Mean age=32.85yr; Gender: Male=14, Female=6. **Intervention:** The experimental group received attention and spatial integration exercises, and memory retraining in addition to normal therapy. The control group received normal training. **Outcome Measures:** Benton Visual Retention Test (BVRT), Rey-Osterrieth Complex Figure Test (CFT), Taylor Complex Figure Test (TCFT), Selective Reminding Test (SRT), Ruff-Light Trail Learning Test (TLT), Wechsler Memory Scale (WMS), Logical Memory Subtest (WMS).	1. There were no significant differences between groups on any of the outcome measures. 2. A post-hoc analysis showed that those with mild cognitive impairment benefitted more from the intervention than those with moderate or severe cognitive impairment, but not significantly.
Boman et al. (2004) Sweden Pre-Post N=10	**Population:** TBI: Mean age=47.5 yr; Gender: male=5, female=5; Time Post injury=9-40 months. **Intervention:** Each person 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. **Outcome Measures:** Digit Span Test, Claeson-Dahl test, Rivermead Behavioural Memory test (RBMT), Assessment of Motor and Process Skills, European Brain Injury Questionnaire.	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 RMBT were found at the 3-month follow up compared to the RMBT 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

Discussion

With respect to attention process training, it was shown that individuals receiving attention remediation significantly improved in memory measurements compared to controls who had education alone (Sohlberg et al., 2000). Novack et al. (1996) compared focused hierarchical attentional learning with an unstructured non-sequential, non-hierarchical intervention. The authors found no significant group differences in attentional skills, functional skills, or general cognitive abilities. Boman et al. (2004) conducted a study with ten individuals with mild or moderate TBI. Participants completed cognitive training, including attention process training, three times a week for 3 weeks. The authors observed a more pronounced improvement on attention; however, improvements on memory were less distinct and the Rivermead Behavioural Memory Test scores were more pronounced at 3-month follow-up. Ryan and Ruff (1988) found similar results where neither the applied memory training program nor the attentional program significantly improved measures of memory or learning in individuals. Overall, there is weak evidence in support of attention training programs as an effective rehabilitation intervention for memory.

Conclusions

There is level 1b evidence that attention process training may improve memory measurements compared to education alone (Sohlberg et al., 2000).

There is level 1b evidence that attention training program may not improve memory or learning in individuals with ABI (Boman et al., 2004; Novack et al., 1996; Ryan & Ruff, 1988).

KEY POINTS

- Attention training programs may not be effective for improving memory in individuals with ABI.

Hypnosis

Hypnosis involves focused attention and it has been used to treat several conditions such as depression, treatment of phobias, pain, dissociative disorders and psychotic disorders (Vanhaudenhuyse et al., 2014). Hypnosis has also been used as a rehabilitation treatment for individuals with TBI (Vanhaudenhuyse et al., 2015).

TABLE 23 | The Effect of Hypnosis on Memory Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Lindelov et al. (2017) Denmark RCT PEDro=7 N=68	**Population:** TBI=34, Stroke=20, Other=12, NA=2. *Group A (n=27)*: Mean Age=45.2 yr; Gender: Male=12, Female=15; Mean Time Post Injury=5 yr. *Group B (N=22)*: Mean Age=47.0 yr; Gender: males=8, females=25; Mean Time Post Injury=6.5 yr. *Control Group (n=19)*: Mean Age=54.1 yr; Gender: males=8, females=11; Mean Time Post Injury=7 yr. **Intervention:** 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. **Outcome Measures:** Working Memory Index (WMI), B-A Trail Making Index (TMT).	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). 2. After the break, the WMI and MT showed no significant differences for either group 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.

Discussion

Lindelov et al. (2017) examined the effects of hypnosis, as delivered in a targeted or non targeted manner, on memory, attention, and cognitive function in a mixed TBI and stroke population. 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 individuals post brain injury on a continual basis.

Conclusions

There is level 1b evidence that hypnosis compared to no treatment may not be effective at improving memory in individuals with ABI (Lindeløv et al., 2017).

KEY POINTS

-Hypnosis may not be effective at improving memory in individuals with ABI

Dance Therapy

Dance is a performing art that contributes to the integration of mind and body. Dance has been used as therapy for individuals living with TBI and it can potentially help to develop mind-body awareness (Winters Fisher, 2019).

TABLE 24 | The Effect of Dance Therapy on Attention Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Sarkamo et al. (2021) Finland RCT Crossover PEDro=7 N=11	**Population:** *TBI: Moderate-Severe; AB Group (n=6):* Mean Age=36.3yr; Gender: Male=3, Female=3; Mean Time Post Injury=9.2yr. BA *Group (n=5):* Mean Age=33.7yr; Gender: Male=4, Female=1; Mean Time Post Injury=5.8yr. **Intervention:** Participants with TBI were randomized into two groups and received the dance intervention either during the first 3-month phase (AB group) or the second 3-month phase (BA group). The Dual-Assisted Dance Rehabilitation (DARE) featured a combination of dance training and specialized physical therapy, and was provided for 60 min per day, 2 days a week, for 12 weeks. Outcome measures were assessed at the 3- and 6-month stages. **Outcome Measures:** Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Wechsler Adult Intelligence Scale IV (WAIS-IV), Sustained Attention to Response Test (SART), Beck Depression Inventory II (BDI-II).	1. 91% of participants were fully consistent with the protocol, and 83-100% of participants self-adhered to DARE sessions. 2. There was a higher than-average benefit for two domains of the questionnaire on self-reported benefits of DARE: Mobility (p=0.013) and Cognition (p=0.032), as well as for the overall benefit score (p<0.001). 3. The most consistent positive, medium-large effect sizes favouring DARE were observed for the Digit Span (p=0.232), Similarities (p=0.005), and Block Design (p=0.297) subtests of the WAIS-IV, indicating improvement in verbal working memory and reasoning ability. 4. Both groups yielded a significant positive change from baseline to post-intervention in WAIS-IV (p=0.005) and BDI-II (p=0.002).

Discussion

The effectiveness of dance therapy for individuals with severe TBI has been observed previously in case studies (Kullberg-Turtiainen et al., 2019). In an RCT, Sarkamo et al. (2021) examined the feasibility and the effects of a dance-based intervention for individuals living with severe TBI. Sessions involved participants directing their attention to their body parts, mentally scanning their body, and following a dance choreography with music, as well as stretching and relaxing at the end of the session. The intervention demonstrated to be feasible and acceptable. Participants showed meaningful gains in cognitive function, especially short-term and working memory (Sarkamo et al., 2021).

Conclusions

There is level 1a evidence that a dance program is feasible and may improve short-term and working memory in individuals with moderate to severe TBI (Sarkamo et al., 2021).

KEY POINTS

-Dance may be beneficial for individuals with moderate to severe TBI and it is a promising intervention to improve short-term and working memory.

Brain Stimulation Techniques

Cranial Electrotherapy Stimulation

Cranial electrotherapy stimulation (CES) is the application of a low-intensity (1 mA) electrical current to the cranium via electrodes attached around the head, and it has been used to treat a number of clinical disorders including depression, post-traumatic stress disorder, anxiety and insomnia (Brunyé et al., 2021). The effect of CES for the improvement of memory following brain injury has been investigated.

TABLE 25 | The Effect of Cranial Electrotherapy Stimulation on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Michals et al. (1993) USA RCT PEDro=7 N=22	**Population:** Mean Age: 24.8yr; Gender: male=17, female=5; Mean Time Post-Injury: 4.2yr; Condition: TBI. **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. **Outcome Measure** Wechsler Memory Scale-Revised; California Verbal Learning Test, Recurring Figures Test.	1. Results revealed that CES stimulation in brain-injured patients did not improve memory or immediate and delayed recall compared with controls. 2. Repeated trial effects showed significant increase in both intervention and control group, however there was no significant differences between groups.

Discussion

One RCT studied CES stimulation and its effect on memory impairment in individuals with brain injury (Michals et al., 1993). No significant improvements in memory performance were reported. These results suggest that CES stimulation in individuals with TBI 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 (Michals et al. 1993).

KEY POINTS

- Cranial electrotherapy stimulation (CES) is not effective at enhancing memory and recall abilities following TBI.

Transcranial Direct Current Stimulation

Transcranial Direct current Stimulation (tDCS) refers to a non-invasive brain stimulation technique that painlessly delivers electrical currents to specific regions of the brain. These electrical currents modulate neuronal activity through two comparatively large rubber electrodes that are placed on the scalp (S. Li et al., 2015). Two studies examined the effects of tDCS on memory in individuals with TBI.

TABLE 26 | The Effect of Transcranial Direct Current Stimulation on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Rushby et al. (2021) Australia RCT crossover PEDro=8 N=30	**Population:** TBI; Mean Age=50.0±15.1yr; Gender: Male=21, Female=7; Mean Time Post Injury=13.9±12.1yr; Severity: Moderate to Severe. **Intervention:** Participants received a single session anodal (non-invasive transcranial direct current stimulation (tDCS) applied to the left parietal lobe or sham stimulation. Participants were assessed before and after sessions. **Outcome Measures:** N-back task, Hospital Anxiety and Depression scale (HADS), Profile of Mood States (POMS), Alertness and Fatigue Scale.	1. There were no significant differences between active and sham sessions for HADS, POMS, or Fatigue and Alertness Scales (p>0.05). 2. There was a significant difference between active and sham groups on reaction time during the N-back test (1-back task); the active condition performed significantly slower (p=0.044) and had more variable reaction time (p=0.026) than the sham condition. 3. There were no significant differences found on the 2-back task measure.
Lesniak et al. (2014) Poland RCT PEDro=8 N=23	**Population:** Severe TBI=23; Mean Age=28.7yr; Gender: Males=17, Females=6; Mean Time Post Injury=18.1mo. **Intervention:** Participants were randomized to the Treatment Group: transcranial direct current stimulation (tDCS), or the Control Group with sham therapy. Assessments were done at admission, immediately before treatment, after 3wk rehabilitation, and 4mo after completion. **Outcome Measure:** Cambridge Neuropsychological Test Automated Battery (CANTAB), Rey's Auditory Verbal Learning Test (RAVLT), Patter Recognition Memory test (PRM), Paced Auditory Serial Addition Test (PASAT), Spatial Span Test (SSP), Rapid Visual Information Processing (RVP), European Brain Injury Questionnaire (EBIQ).	1. No significant differences between groups post treatment were found on any measures except a moderate improvement in the treatment group on the RVP (p=0.007). 2. At the 4mo follow-up there were no significant differences between groups.

Discussion

Two RCTs examined the effect of tDCS on rehabilitation of memory in individuals living with TBI. Lesniak et al. (2014) randomly allocated participants into two groups. One group received ten minutes of tDCS followed by cognitive rehabilitation for fifteen days, while the control group received tDCS for twenty-

five seconds only sham condition) followed by cognitive rehabilitation. The authors did not find sufficient evidence to support the efficacy of tDCS for improving memory in individuals with severe TBI (Lesniak et al., 2014). Rushby et al. (2021) administered a single session of either anodal tDCS (20 min) or sham tDCS (30 secs) while performing memory tasks. In this study, tDCS did not lead to enhanced working memory in individuals with TBI. A recent systematic review suggested that results obtained by using non-invasive brain stimulation can vary depending on the individual and that combining non-invasive brain stimulation with rehabilitation may contribute to greater improvements (Hara et al., 2021).

Conclusions

There is level 1a evidence that transcranial direct stimulation may not improve memory compared to sham stimulation post TBI (Lesniak et al. 2014; Rushby et al. 2021).

KEY POINTS

- Transcranial Direct Current Stimulation (tDCS) is not effective at enhancing memory abilities following TBI.

Pharmacological Interventions

Donepezil

Donepezil is a centrally acting acetylcholinesterase inhibitor that has been used in the treatment of Alzheimer's disease (AD) and dementia, as well as to enhance cognitive functions in individuals with TBI (Traeger et al., 2020). Donepezil appears to be beneficial in individuals with AD, with higher doses showing greater benefits, and a sustained effect of approximately one year (Takeda et al., 2006). In individuals living with TBI, there is growing support for the use of donepezil to enhance processing speed, attention, functional ability and memory (Swenson et al., 2021). Donepezil's impact on cognitive function and memory in a TBI population is explored in the table below.

TABLE 27 | The Effect of Donepezil on Memory and Cognitive Functioning Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Zhang et al. (2004) USA RCT PEDro=7 N=18	**Population:** TBI; *Group A (n=9)*: Mean Age=33yr; Gender: Male=6, Female=3; Mean GCS=9.3; Mean Time Post Injury=4.6mo; *Group B (n=9)*: Mean Age=31yr; Gender: Male=7, Female=2; Mean GCS=8.9; Mean Time Post Injury=3.9 mo. **Intervention:** Group A received oral donepezil for the	1. At week 10, Group A achieved significantly better scores in AII (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 Group B. 2. This increase in scores in Group A were

Author Year Country Study Design Sample Size	Methods	Outcome
	first 10wk, followed by a washout period of 4 wk. At the conclusion of the washout period, patients received a placebo for 10wk. Group B received the treatments in the opposite order. Donepezil was administered at 5 mg/d for the first 2wk, and at 10 mg/d for the remaining 8wk. **Outcome Measures:** Auditory (AII) and Visual (VII) subtests of Wechsler Memory Scale-III, Paced Auditory Serial Addition Test (PASAT).	sustained after washout and placebo treatment (week 24), leading to no significant differences in AII (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 Group B at study end. 3. Within-group comparisons showed that patients in both Group A and Group B improved significantly in AII and VII (p<0.050), as well as in PASAT (p<0.001), after receiving donepezil.
Khateb et al. (2005) Switzerland Pre-Post $N_{Initial}$=15, N_{Final}=10	**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 2mo. **Outcome Measures:** Stroop test, Trail Making Test (TMT), Rey Auditory Verbal Memory Test (RAVMT), Test for Attentional Performance (TAP).	1. 4 of 15 participants stopped due to side effects within the first week (e.g., nausea, sleep disorders, anxiety, dizziness, etc.). 2. 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). 3. 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 2.9±2.7, p=0.030).
Morey et al. (2003) USA Case Series N=7	**Population:** TBI; Mean Age=30.7yr; Gender: Male=5, Female=2; Mean Time Post Injury=33.3mo. **Intervention:** Following baseline cognitive testing (T1), each participant began a 6mo treatment phase with 5 mg/d donepezil for the first 4wk, then with 10 mg/d for the final 5mo (T2). Washout period then occurred for 6wk (T3). Another 6mo treatment period took place with participants receiving 5 mg/d donepezil for the entire period (T4). **Outcome Measures:** 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.	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.
Masanic et al. (2001) Canada Pre-Post N=4	**Population:** TBI; Age Range=24-35yr; Gender: Male=4, Female=0; GCS Range=3-8; Time Post Injury Range=35-46 mo. **Intervention:** Participants received 5mg donepezil daily for 8wk, 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 Measures:** Rey Auditory Verbal Learning Test	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. 2. Mean scores for short-term and long-term recall on the CFT improved also by 1.56

Author Year Country Study Design Sample Size	Methods	Outcome
	(RAVLT), Complex Figure Test (CFT), Rivermead Behavioural Memory Test (RBMT).	(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. 3. Perceived memory deficit (RBMT) showed a trend toward improvement over the first 12wk, followed by deterioration after the washout period.

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 a study by Masanic et al. (2001) who found that donepezil tended to improve both short- and long-term memory of individuals living with TBI. Improvements in memory were also reported by Morey et al. (2003) in their retrospective study which 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 ($p<0.050$). 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 double-blinded, RCTs that explore the use of donepezil post TBI are needed to determine the efficacy of donepezil on this population. While treatment with donepezil may improve function and cognition in individuals with TBI, there is insufficient evidence on long-term outcomes (Florentino et al., 2022).

Conclusions

There is level 1b evidence that donepezil improves short-term memory post TBI (Masanic et al., 2001; Zhang et al., 2004).

There is level 4 evidence that donepezil may be effective in improving long-term, verbal, and visual memory post TBI (Khateb et al., 2005; Masanic et al., 2001; Morey et al., 2003).

KEY POINTS

- Donepezil likely improves memory following TBI.

Methylphenidate

Methylphenidate is a central nervous stimulant that increases the synaptic and extracellular concentrations of dopamine (Barnett & Reid, 2020). This medication has been used to treat Attention Deficit Hyperactivity Disorder in adults and children (Cândido et al., 2021), as well as to treat mental fatigue and to help improve cognitive function in individuals with TBI (Johansson et al., 2017; Levin et al., 2019). A total of five RCTs examined the efficacy of methylphenidate as a treatment for the recovery of cognitive deficits post ABI.

TABLE 28 | The Effect of Methylphenidate on Learning & Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Jenkins et al., (2019) UK RCT Crossover PEDro=9 $N_{Initial}$=46, N_{Final}=40	**Population:** TBI=40; *Treatment Group (Intervention First; n=20):* Mean Age= 40±12yr; Gender: Male=18, Female=2; Mean Time Post Injury=67±85mo; Severity: Mean GCS=8.3±5.2. *Control Group (Placebo First; n=20):* Mean Age=39±12yr; Gender: Male=16, Female=4; Mean Time Post Injury=67±85mo; Severity: Mean GCS=8.3±5.4. **Intervention:** Participants were randomized to receive 0.3mg/kg of methylphenidate (treatment group) twice a day for 2wk with crossover to placebo (control group) twice a day for 2wk and vice versa. Outcome measures were assessed at baseline, 2 and 4wk. **Outcome Measures:** Choice Reaction Time (CRT) Task, Single-Photon Emission Computed Tomography (SPECT), Trail Making Test (TMT), Stroop Test, People Test, Wechsler Abbreviated Scale for Intelligence (WASI), Lille Apathy Rating Scale (LARS), Visual Analogue Scale for Fatigue (VAS-F), Glasgow Outcome Scale-Extended (GOSE), Hospital Anxiety and Depression Scale (HADS), Frontal Systems Behaviour Scale (FrSBe), Cognitive Failures Questionnaire, Rating Scale of Attentional Behaviour.	1. No significant differences (p>0.05) were observed between groups on several measures: TMT, Stroop, People Test, WASI, FrSBe, GOSE, HADS, Cognitive Failures Questionnaire, Rating Scale of Attentional Behaviour. 2. Participants with low dopamine transporter levels receiving methylphenidate significantly improved on several measures when compared to controls: CRT (p=0.02), LARS self-reported (p=0.03) and caregiver (p=0.02), VAS-F (p=0.007) 3. Participants with normal dopamine transporter levels receiving methylphenidate reported significantly less fatigue when compared to controls (VAS-F, p=0.03).
Dymowski et al. (2017) Australia RCT PEDro=9 $N_{Initial}$=11, N_{Final}=10	**Population:** TBI. *Methylphenidate Group (n=6)*: Mean Age=35yr; Gender: Male=4, Female=2; Mean Time Post Injury=366 d; Mean Worst GCS=4.83. *Placebo Group (n=4)*: Mean Age=32.5yr; 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 were assessed at baseline, 7-wk (on-drug), 8-wk (off-drug), and 9-mo follow-up.	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.

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measures: 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).	
Kim et al. (2012) USA RCT PEDro=7 N=23	**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 Measures:** Visual sustained attention task (VSAT), Two-back task.	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.
Willmott & Ponsford (2009) RCT PEDro=10 N=40	**Population:** TBI; Mean Age=26.93yr; Gender: Male=28, Female=12; Time since injury=68.38 d. **Intervention:** Participants received either methylphenidate (0.3 mg/kg 2 x/d, rounded to the nearest 2.5 mg) or a placebo. Participants were seen for 6 sessions across 2-week period, then crossed-over. **Outcome Measures:** 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.	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).
Kim et al. (2006) Korea RCT PEDro=6 N=18	**Population:** TBI; *Methylphenidate Group (n=9)*: Mean Age=30.1yr; Gender: Male=9, Female=0; Mean Time Post Injury=1.6yr; *Placebo Group (n=9)*: Mean Age=38.3yr; 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 Measures:** Visual sustained attention task (VSAT), Two-back task.	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.
Plenger et al. (1996) USA RCT PEDro=5 N=23	**Population:** TBI; Gender: Male=17, Female=6; *Placebo Group (n=13)*: Mean Age=26.6yr; Mean GCS=8.1; *Methylphenidate Group (n=10)*: Mean Age=31.4yr; Mean GCS=9.3. **Intervention:** Patients were randomly allocated to	1. At 30 d follow-up (n=15), significant differences were obtained on DRS, suggesting better outcome for the methylphenidate group. This difference

Author Year Country Study Design Sample Size	Methods	Outcome
	receive either methylphenidate or placebo. Methylphenidate was administered at 0.3 mg/kg, 2 ×/d, for 30d. **Outcome Measures:** 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).	however was not seen at 90d follow-up (n=11). 2. Significant differences were found on the attention-concentration domain at the 30d 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.
Speech et al. (1993) USA RCT PEDro=7 N=12	**Population:** TBI; Mean Age=27.6yr; 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 ×/d, for 1-wk, followed by 1-wk of placebo, or receive the treatment in a reverse order. **Outcome Measures:** 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.	1. No significant differences were found between methylphenidate and placebo condition in any of the outcome measures studied.
Gualtieri & Evans (1988) United States RCT Crossover PEDro=7 N=15	**Population:** Mean age=24.1yr; Gender: Male=10, Female=5; Mean time post-injury=46.8mo. **Intervention:** Participants were assigned to receive three conditions in randomized order. 1) Placebo; 2) Methylphenidate (0.15mg/kg) twice daily; 3) Methylphenidate (0.30mg/kg) twice daily. Each condition was 12 days long, with 2 days washout between conditions. **Outcome Measures:** Adult Activity Scale self-administered (AAS-S), Adult Activity Scale (administrator)(AAS-O), Examiner's Rating Scale (EXRS), Self-Rating Scale (SRS), Verbal Fluency Test (VFT), Non-verbal Fluency test (NVFT).	1. There was a significant improvement in AAS-S and AAS-O scores between the placebo and high-dose conditions (p<0.05). 2. There was a significant difference in SRS scores between the placebo group and the high-dose condition (p<0.05). 3. On the EXRS there was a significant difference between baseline and low-dose (p=0.012), placebo and low-dose (p=0.025), baseline and high-dose (p=0.012), with higher doses of methylphenidate having improved effects. 4. There was a significant improvement in VFT scores between baseline and the high-dose groups (p=0.017). 5. There was a significant difference on NVFT scores between baseline and placebo (p=0.008), baseline and low-dose (p=0.008), baseline and high-dose (p=0.008), and the placebo and high-dose group (p=0.018), with methylphenidate improving scores.

Discussion

Several RCTs have been conducted to examine the effect of methylphenidate on cognitive functions post ABI. When examining outcomes pertaining to memory, many did not show significant findings. Jenkins et al. (2019) found that the cognitive effects of methylphenidate were only exhibited by individuals with

low caudate dopamine transporter levels. The researchers used the People Test which measured episodic memory and found no significant difference between groups (Jenkins et al., 2019). Results reported by Dymowski et al. (2015) and Speech et al. (1993), indicated no significant difference on any measures related to memory. Plenger et al. (1996) found methylphenidate administration (0.3 mg/kg, 2 x/d, 30 d) significantly improved scores relating to attention and scores on the Porteus Maze and Pursuit Rotor (motor performance and procedural memory) assessments but not those measuring verbal/visual learning and memory (declarative memory). In some studies, methylphenidate showed a positive effect on processing speed and attention; however, the effectiveness of the medication was less prominent in memory tasks (Kim et al., 2012; Willmott & Ponsford, 2009). While in most of the studies, no significant effects were observed in participants when given a dose of 0.3mg/kg, only Kim et al. (2006) reported that a 20mg dose of methylphenidate had a significant effect on reaction time of working memory in individuals with TBI. Appropriate dosing should be further examined to determine the effect of methylphenidate on memory.

Given the potential for side effects, Methylphenidate should be used with caution. . The literature suggests that high doses of methylphenidate can lead to intoxication, causing symptoms such as tachycardia, agitation and hypertension (Hondebrink et al., 2015). A recent systematic review indicated that studies using methylphenidate to improve cognition in individuals with ABI reported that participants experienced increase in heart rate, increased blood pressure, restlessness, depressive symptoms and paroxysmal tachycardia; additionally, the use of methylphenidate must be carefully monitored in individuals with history of seizures (Barnett & Reid, 2020).

Although methylphenidate has been shown to significantly improve measures of attention and processing speed, no reliable effects on learning and memory have been shown specifically in studies examining ABI populations. In a recent meta-analysis, Chien et al., (2019) found that methylphenidate had a positive effect on enhancing processing speed; however, methylphenidate did not have a significantly impact on working memory. This finding aligns with the studies mentioned above. There is a recent systematic review that reported strong evidence that methylphenidate may improve cognitive abilities, including working memory, in individuals with brain injury; however, several studies in this review included participants with mild brain injury (Barnett & Reid, 2020).

Conclusions

There is level 1a evidence that methylphenidate compared to placebo is not effective for improving memory following brain injury for individuals with TBI (Dymowski et al., 2017; Gualtieri & Evans, 1988; Jenkins et al., 2019; Kim et al., 2012; Kim et al., 2006; Plenger et al., 1996; Speech et al., 1993; Willmott & Ponsford, 2009).

KEY POINTS

- **Methylphenidate may not improve memory or learning following an ABI.**

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). Sertraline has been used to treat depression in individuals with TBI, and it still provides the best quality evidence in reduction of depressive symptoms (Narapareddy et al., 2020). However, some studies have shifted focus and begun to evaluate the benefits of sertraline at improving cognitive disorders (Banos et al., 2010).

TABLE 29 | The Effect of Sertraline on Memory and Learning Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Banos et al. (2010) USA RCT PEDro=9 N=99	**Population:** TBI. *Treatment group (n=49)*: Gender: Male=39, Female=10; Mean Age=35.3yr; Mean Time Post Injury=21.5 d; Mean GCS=5.8. *Placebo group (n=50):* Gender: Male=33, Female=17; Mean Age=34.5yr; Mean Time Post Injury=19.2 d; Mean GCS=5.8. **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. **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.	1. More participants 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.

Discussion

The effect of early administration of sertraline on cognitive functioning, intelligence and memory was evaluated by Banos et al. (2010) in a 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. More participants 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. Sertraline has been associated with several side effects, including agitation/anxiety, constipation, diarrhoea, dry mouth, insomnia, nausea, and sleepiness/drowsiness (Cipriani et al., 2010).

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 (Banos et al., 2010).

KEY POINTS

- **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

Amantadine is an antagonist of N-methyl-D-aspartate receptors and an agonist of the dopaminergic system (Liepert, 2016), and it is also considered to work pre- and post-synaptically by increasing the amount of dopamine in the synapse (Napolitano et al., 2005). Amantadine has been used to treat dyskinesia in Parkinson's disease and to facilitate cognitive recovery in individuals with TBI (Loggini et al., 2020). Four studies have been identified that investigate the effectiveness of amantadine as a treatment for the remediation of learning and memory deficits and cognitive functioning following TBI.

TABLE 30 | The Effect of Amantadine on Learning & Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Hammond et al. (2018) United States RCT PEDro= 9 N=119	**Population:** TBI; Mean age=38.6yr; Mean time post-injury=6.2yr; Injury severity: GCS<13. **Intervention:** Individuals were allocated to receive either the placebo or 100mg amantadine twice a day for 60 days. Assessments were completed at baseline, day 28, and day 60. **Outcomes:** Digit-span from Wechsler Memory Scale-III (DS), Trail Making Test (TMT), Controlled Oral Word Association Test (COWAT), Learning/Memory Index (LMI), Attention/Processing Speed Index (APSI).	1. No significant differences were seen on the DS, TMT, COWAT, or the APSI between groups at any time point. 2. The treatment group had significantly lower LMI scores at day 28 compared to the control group (p=0.001), this effect was not present at 60-day follow-up. 3. The treatment group had significantly lower scores on the GCI compared to the control group at day 28 (p=0.002), this effect was not present at day 60 follow-up.
Schneider et al. (1999) USA RCT PEDro=5 N=10	**Population:** TBI; Mean Age=31yr; Gender: Male=7, Female=3; GCS Score Range=3-11. **Intervention:** Patients randomized to either amantadine (50-150 mg 2x/d) or placebo for 2wk in a crossover design with a 2wk washout period. **Outcome Measure:** Battery of Neuropsychological Tests, Neurobehavioural Rating Scale.	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).
Ghalaenovi et al. (2018) Iran RCT PEDro=10	**Population:** TBI; Gender: Male= 37, Female= 3; Mean Ag= 36.77; Mean GCS score AMH group= 7.1; Mean GCS score Placebo group= 6.95.	1. Treatment with amantadine did not show significant effects on memory.

Author Year Country Study Design Sample Size	Methods	Outcome
N=42	**Intervention:** participants were randomly assigned to a group. Individuals received amantadine (AMH) or placebo for 6 weeks (100mg twice a day) **Outcome Measure:** GCS, FOUR score, Mini-mental state examination (MMSE), Glasgow outcome scale (GOS), Disability Rating Scale (DRS), Karnofsky Performance Scale (KPS)	
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 3×/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.	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<0.02). 2. 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).

Discussion

In a large sample RCT by Hammond et al. (2018) individuals either received 200 mg of amantadine or placebo for 60 days. The authors found that there was no significant effect of amantadine on learning and memory, and that the control group had significantly higher scores on the Learning and Memory Index. A smaller RCT by Schneider et al. (1999) and a pre-post study by Kraus et al. (2005) found similar findings; no significant effects of amantadine on learning and memory. Similarly, Ghalaenovi et al. (2018) did not find significant effects on memory. Most of the research using this medication in neurological recovery from brain injury is still preliminary (Ma & Zafonte, 2020), and long-term risks and benefits related to the use of this medication are unclear (Loggini et al., 2020).

Conclusions

There is level 1a evidence that amantadine does not improve learning and memory deficits in individuals with TBI (Ghalaenovi et al., 2018; Hammond et al., 2018; Kraus et al., 2005; Schneider et al., 1999).

KEY POINTS

- **Amantadine is not effective for improving learning and memory deficits post TBI.**

Pramiracetam

Pramiracetam is a nootropic (cognitive) activator 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). Pramiracetam has been used to improve cognitive deficits associated with traumatic injuries, as well as to treat anxiety and aging-related mental impairments (Malykh & Sadaie, 2010). Pramiracetam has been also used in elderly individuals living with cognitive impairment and arterial hypertension (Bachinskaya et al., 2013).

TABLE 31 | The Effect of Pramiracetam on Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
McLean et al. (1991) USA RCT PEDro=5 N=4	**Population:** TBI; Age Range=23-37yr; Gender: Male=4, Female=0. **Intervention:** Patients were treated in two, 3wk blocks of oral pramiracetam (400 mg, 2x/d) and placebo over 12wk. **Outcome Measures:** 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

Discussion

McLean et al. (1991) conducted a study evaluating Pramiracetam in four male participants 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, further studies should be conducted.

Conclusions

There is level 2 evidence that pramiracetam may improve males' memory compared to placebo post TBI (McLean et al., 1991).

KEY POINTS

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

Physostigmine

Physostigmine is a acetylcholinesterase inhibitor that has been used to improve cognition in individuals with Alzheimer's disease (AD), particularly memory and visual-attentional processing (Bentley et al., 2008; Thal et al., 1986). However, recent literature suggests that the use of physostigmine is not recommended in the treatment of AD due to several side effects (Sharma, 2019). Physostigmine has also been used to enhance memory in individuals with brain injury (McLean et al., 1987).

TABLE 32 | The Effect of Physostigmine on Memory Post ABI.

Author Year Country Study Design Sample Size	Methods	Outcome
Cardenas et al. (1994) USA RCT PEDro=6 N=36	**Population:** TBI; Mean Age=29.5yr; Gender: Male=36, Female=0; Mean GCS=5.31; Mean Time Post Injury=4.33yr. **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 Measures**: Selective Reminding Test (SRT), Wechsler Memory Scale I & II, Digit Symbol, Trail Making Test A & B, Memory Questionnaire, Clinical Balance Tests, Serum Cholinesterase Levels.	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.

Discussion

In a double-blind, placebo-controlled randomized trial, oral physostigmine was administered to male participants 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, however additional studies are needed (Cardenas et al., 1994).

KEY POINTS

- Physostigmine may improve long-term memory in men with TBI; however, additional studies are needed.

Bromocriptine

Bromocriptine is a dopaminergic agonist which primarily exerts its actions through binding and activating D_2 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). Dopamine agonists such as Bromocriptine have been used to treat individuals with TBI that present with minimally conscious state (Passler & Riggs, 2001), as well as to facilitate cognitive recovery and rehabilitation in this population (Frenette et al., 2012). Two studies have investigated the use of bromocriptine to promote cognitive recovery in individuals with TBI.

TABLE 33 | The Effect of Bromocriptine on Learning Post TBI.

Author Year Country Study Design Sample Size	Methods	Outcome
McDowell et al. (1998) USA RCT PEDro=4 N=24	**Population:** TBI; Median Age=32.5yr; Gender: Male=20, Female=4; GCS Range=3-8; Time Post injury Range=27 d-300mo. **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. **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.	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=0.050), COWAT (p=0.020), 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).

Author Year Country Study Design Sample Size	Methods	Outcome
Powell et al. (1996) UK Case Series N=11	**Population:** TBI=8, SAH=3; Mean Age=36yr; Gender: Male=6, Female=5; Time Post Injury Range=2 mo-5yr. **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). **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.	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 ($p<0.010$), 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. 3. Bromocriptine was not associated with improvements in mood state.

Discussion

The effect of bromocriptine on learning and memory in individuals with TBI has been explored in one RCT (McDowell et al., 1998), and one case series (Powell et al., 1996). McDowell at al (1998) found that low-dose bromocriptine (2.5 mg daily) improved functioning on tests of executive control it did not significantly influence working memory tasks, only verbal memory. Although the authors demonstrated some benefits following administration of bromocriptine, there was only a single dose administered. 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 participants with TBI or subarachnoid hemorrhage who received bromocriptine. Improvements were found on all measures assessed (i.e., verbal memory, attention, motivation spontaneity) except mood. A recent review suggested that routine use of bromocriptine in individuals with stroke or TBI is not recommended, but there are benefits for individuals presenting with minimally conscious sate and vegetative state post TBI (Kakehi & Tompkins, 2021). Further studies are required to determine the effect of bromocriptine on memory in individuals with TBI.

Conclusions

There is level 2 evidence that bromocriptine may improve verbal memory in individuals with a TBI, however, more studies are required (McDowell et al., 1998).

KEY POINTS

- **More studies are required to determine the effects of bromocriptine on verbal memory in individuals with TBI.**

Cerebrolysin

Cerebrolysin has been demonstrated to have neuroprotective and neurotrophic effects and has been linked to increased cognitive performance in an elderly population. 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 shown protective effects against pathological cascades post neurodegenerative injury or disease, and it has been used to treat stroke, Alzheimer's disease, and TBI (Fiani et al., 2021).

TABLE 34 | The Effect of Cerebrolysin on Memory Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Alvarez et al. (2003) Spain Pre-Post N=20	**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 test (SKT), electroencephalogram (EEG)/brain mapping recordings, and Glasgow Outcome Scale (GOS).	1. Compared to baseline, individuals 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. 2. Significant improvements in SKT performance were noted from pre to post treatment (15.9±2.4 versus 12.0±2.1; $p<0.01$). 3. GOS scores significantly improved from pre to post treatment (3.7±0.3 versus 3.95±0.3; $p<0.05$).

Discussion

In an open-label trial of 20 participants 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 (SKT), consisting of nine subtests was administered to evaluate memory and attentional functions in individuals undergoing treatment with cerebrolysin. There was an overall significant improvement in performance post treatment, suggesting participants experienced cognitive benefits from cerebrolysin treatment. Significant improvements were noted in both Glasgow Outcome Scale (GOS) scores and the SKT performance, including memory (Alvarez et al., 2003). Together these findings suggest that cerebrolysin may represent an effective neuroprotective therapy with tangible cognitive benefits for individuals living with a TBI. Randomized controlled trials are necessary to further explore the efficacy of cerebrolysin for this population.

Conclusions

There is level 4 evidence that cerebrolysin may improve memory function post TBI (Alvarez et al., 2003).

KEY POINTS

- **Cerebrolysin may be beneficial for the improvement of clinical outcome and cognitive functioning, including memory in individuals with TBI; however, randomized controlled trials are needed to further evaluate its efficacy.**

Growth Hormone Replacement Therapy

Following an ABI, it is not uncommon for individuals to be diagnosed with hypopituitarism. TBI is a risk factor for hypopituitarism, often developing in individuals across the brain injury spectrum and affecting cognitive performance, including memory (Pavlovic et al., 2019). Growth hormone replacement therapy (rhGH) is a well-tolerated treatment to reverse the effects of this condition and it has been used to improve function, quality of life and well-being in individuals presenting with GH deficiency post-TBI (Dubiel et al., 2018).

TABLE 35 | The Effect of Growth Hormone on Memory Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
High et al. (2010) USA RCT PEDro=8 N=23	**Population:** TBI. *Placebo* (n=11): Mean Age=39.1yr; Time Post Injury=5.1yr. *Active rhGH* (n=12): Mean Age=36.1yr; Time Post Injury=11yr. **Intervention:** Participants were randomized to either a growth hormone replacement group (rhGH) injection 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, California Verbal Learning Test, Wisconsin Card Sorting Test, Processing Speed Index.	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	**Population**: TBI. Treatment Group (TG, n=23): Mean Age=37.9yr; Gender: Male=19, Female=4; Mean Time	1. Both groups showed significant improvement in instrumental ADL (iADL,

Author Year Country Study Design Sample Size	Methods	Outcome
PCT N=50	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=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).
Reimunde et al. (2011) Spain Cohort N=19	**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).	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).

Discussion

A RCT compared the long term (6 months and 1 year) effects of rhGH administration to placebo in a TBI population (High et al., 2010). Significant within group 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, with no significant between group differences reported. Similar results were reported in PCT by Moreau et al. (2013), who found both groups participant's quality of life, instrumental activities of daily living, attention, memory and visuospatial ability improved over the treatment period but no significant between group differences in memory were found.

Reimunde et al. (2011) performed a cohort study examining the benefits of rhGH administration among those with moderate to severe TBI. Results of the study indicate that those receiving rhGH improved significantly on various cognitive subtests such as: understanding, digits, numbers and incomplete figures ($p<0.05$) as well as "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.

In a recent systematic review, Szarka et al. (2021) found that, regardless of GCS, therapy with growth hormone can potentially enhance quality of life, processing speed and memory in individuals with TBI. Growth hormone therapy showed to improve verbal memory and working memory; however, differences were not significant between the treatment groups and control groups, and working memory did not show improvement in individuals with severe TBI (Szarka et al., 2021). Literature on the benefits of rhGH on individuals with TBI is considered scarce and fragmented, and more studies are needed to further characterize growth hormone deficits and the effect of rhGH in this population (Gasco et al., 2021).

Conclusions

There is level 1b evidence that recombinant human Growth Hormone (rhGH) is similar to placebo for improving memory and learning in individuals with TBI (High et al., 2010; Moreau et al., 2013; Reimunde et al., 2011).

KEY POINTS

- **Growth Hormone Replacement Therapy likely does not improve learning and memory following TBI.**

Rivastigmine

Rivastigmine acts as an acetylcholinesterase inhibitor which prevents the enzyme acetylcholinesterase from breaking down acetylcholine (Liepert, 2016). This increases the concentration of acetylcholine in synapses. Acetylcholine has been most strongly linked with the hippocampus and memory deficits. Similar to donepezil, rivastigmine has been used to treat dementia in Alzheimer's disease and to facilitate cognitive recovery in individuals with TBI (Kakehi & Tompkins, 2021).

TABLE 36 | The Effect of Rivastigmine on Memory Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Silver et al. (2009) USA RCT PEDro=9 N=127	**Population:** TBI. *Ex-Rivastigmine* (n=65): Mean Age=36.9yr; Gender: Male=43, Female=22; Time Post Injury=73.5mo. *Ex-placebo* (n=62): Mean Age=38yr; Gender: Male=42, Female=20; Time Post Injury=100.1mo. **Intervention:** Participants were randomized to receive rivastigmine injections (1.5 mg 2x/d to a max of 12 mg/d) or placebo injection. **Outcome Measure:** Trails A and B, Hopkins verbal learning test (HVLT), Cambridge Neuropsychological Test Automated Batter Rapid Visual Information Processing (CANTAB RVIP A).	1. The mean final dose of rivastigmine was 7.9 mg/day. 2. 40% of patients were responders on CANTAB RVIP A' or HVLT score at week 38. 3. 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). 4. Further sub-analysis controlling for order effects resulted in no significant differences between groups.
Silver et al. (2006) USA RCT PEDro=9 N=123	**Population:** TBI. *Rivastigmine* (n=80): Mean Age=37yr; Gender: Male=53, Female=27. *Placebo* (n=77): Mean Age=37.1yr; 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 4wk, 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 Batter Rapid Visual Information Processing (CANTAB RVIP A).	1. Results of the CANTAB RVIP A' and HVLT found no significant differences between the placebo group and the treatment group. 2. Rivastigmine was found to be well tolerated and safe.

Discussion

In two studies rivastigmine was administered to participants who had sustained a moderate to severe TBI (Silver et al., 2006; Silver et al., 2009). Neither study yielded significant results for any cognitive measures compared to placebo, including memory and verbal learning. Given the availability of alternative treatments, the use of rivastigmine has been generally avoided due to lack of meaningful benefits as reported by RCTs and inconclusive evidence on the use of this medication after stroke and TBI (Kakehi & Tompkins, 2021).

Conclusions

There is level 1a evidence that rivastigmine may not effective when compared to placebo for improving memory in individuals with TBI (Silver et al., 2006; Silver et al., 2009).

KEY POINTS

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

Huperzine A

Huperzine A is a cholinesterase inhibitor derived from Huperzia serrata, an herb commonly referred to as club moss (Zafonte et al., 2020). It has exhibited neuroprotective effects in several models and is a non-competitive antagonist of *N*-methyl-D-aspartate (MDA) receptor (Zafonte et al., 2020).

TABLE 37 | The Effect of Huperzine A on Memory Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Zafonte et al. (2020) USA RCT PEDro=10 $N_{Initial}$=14, N_{Final}=12	**Population:** Moderate to Severe TBI; Mean Age=37.8±15.8yr, Gender: Male=10, Female=4, Mean Time Post Injury=197.1±124.2d. **Intervention:** Participants received Huperzine A (100ug/d for 4d, then increased on a fixed titration schedule up to 300ug, twice per day) or Placebo for 12 weeks. Participants were assessed at baseline and weeks 6, 12, 13, 24 and 52. **Outcome Measures**: California Verbal Learning Test-II (CVLT-II), Beck Depression Index (BDI), British Columbia Post-Concussion Symptom Inventory (BC-PSI), Brief Pain Inventory, Galveston Orientation Amnesia Test (GOAT), Trail Making Test A & B (TMT), Traumatic Brain Injury Quality of Life (TBI-QOL), and Ruff Neurobehavioral Inventory (RBNI) post morbid cognitive domain scale.	1. Improvement in memory performance from baseline to 12wk was found for both groups; however, there were no significant differences found between groups on the CVLT-II total learning (p=0.38), short delay free recall (p=0.38) or long delay free recall (p=0.42). 2. There were no significant differences between groups in self-reports of depression (BDI) at week 12. 3. There was no significant difference in the number of seizures experienced between the groups (p=0.48) or the number of side effects.

Discussion

A RCT by Zafonte et al. (2020) examined the effects of Huperzine A on memory and learning in individuals with moderate-severe TBI. Huperzine A has been hypothesized to exert its neuroprotective effects through the modulation of primary and secondary injury mechanisms that occur in the acute and chronic phases of brain injury. Although promising in animal studies, this study was the first to examine the effects of Huperzine A on memory in humans. Participants received Huperzine A or a placebo for 12 weeks and were evaluated on several occasions and outcome measures. The authors did not find any significant improvements in memory between groups. Further studies are necessary to draw any conclusions.

Conclusions

There is level 1b evidence that Huperzine A may not improve memory following TBI when compared to placebo (Zafonte et al., 2020).

KEY POINTS

- **Huperzine A may not improve memory following TBI.**

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy involves the inhalation of pure oxygen under pressure allowing the lungs to absorb more oxygen per breath. Currently hyperbaric oxygen therapy is used to treat decompression sickness, serious infections, and delayed wound healing as a result of a comorbid illness such as diabetes (The Mayo Clinic, 2019). Hyperbaric oxygen therapy has been used to treat cell death associated with TBI and stroke, and to alleviate memory loss, language difficulties and comprehension deficits in individuals with neurodegenerative diseases (Gonzalez-Portillo et al., 2019).

TABLE 38 | The Effect of Hyperbaric Oxygen Therapy on Learning and Memory Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Hadanny et al. (2018) Israel Case Series N=154	**Population:** Mean age=42.7yr; Gender: Male=58.4%, Female=43.6%; Mean time post-injury=4.6yr; Injury severity: mild=44.8%, moderate=15.6%, severe=39.6%. **Intervention:** All individuals received hyperbaric oxygen therapy (HBOT). Sessions consisted of 60-90 mins of 100% oxygen at 1.5/2 ATA exposure 5 days a week. **Outcomes:** NeuroTrax software subsets: general, memory, executive functions, attention, information processing speed, visual spatial processing, motor skills.	1. On measures of general cognitive functioning there was a significant increase in scores after HBOT treatment ($p<0.0001$). 2. Memory scores significantly increased following HBOT treatment ($p<0.0001$). 3. Executive function scores significantly increased following HBOT treatment ($p<0.0001$). 4. Attentional scores significantly improved following HBOT treatment ($p<0.0001$). 5. Information processing speed significantly increased following HBOT treatment ($p<0.0001$). 6. Visual spatial processing significantly improved following HBOT treatment ($p=0.005$). 7. Motor skills significantly improved following HBOT treatment ($p<0.0001$).

Discussion

One study has evaluated the effects of hyperbaric oxygen therapy on memory deficits post ABI (Hadanny et al., 2018). The results of this study indicated that hyperbaric oxygen therapy may have positive effects on memory as individuals significantly improved on memory scores following 60-90 minutes of exposure five days a week. It should be noted that this study is retrospective and did not have a control group;

therefore, the possibility of spontaneous recovery should be considered. Hyperbaric oxygen therapy can be beneficial for individuals presenting with severe TBI; however, factors such as the heterogenous physiopathology of TBI and the individual's lung status (e.g., ventilator-associated pneumonia), must be considered (Daly et al., 2018).

Conclusions

There is level 4 evidence that hyperbaric oxygen therapy may improve memory following an ABI (Hadanny et al., 2018).

KEY POINTS

- **Hyperbaric oxygen therapy may be promising for improving memory following an ABI; however, more controlled studies are required.**

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