Memory rehabilitation strategies in non-surgical temporal lobe epilepsy: a review

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Abstract

People with temporal lobe epilepsy (TLE) who have not undergone epilepsy surgery often complain of memory deficits. Cognitive rehabilitation is employed as a remedial intervention in clinical settings, but research is limited and findings have been inconsistent concerning efficacy and the criteria for choosing different approaches. We aimed to appraise existing evidence on memory rehabilitation in non-surgical individuals with TLE and to ascertain the effectiveness of specific strategies. A scoping review was preferred over other type of reviews given the heterogeneous nature of the interventions. A comprehensive literature search using MEDLINE, EMBASE, CINAHL, AMED, Scholars Portal/PSYCHinfo, Proceedings First, and ProQuest Dissertations and Theses identified articles published in English before February 2016. The search retrieved 372 abstracts. Out of 25 eligible studies, 6 were included in the final review. None included pediatric populations. Strategies included cognitive training, external memory aids, brain-training, and non-invasive brain stimulation. Selection criteria tended to be general. Overall there was insufficient evidence to make definitive conclusions regarding the efficacy of traditional memory rehabilitation strategies, brain training and non-invasive brain stimulation. The review suggests that cognitive rehabilitation in non-surgical TLE is under-researched and that there is a need for a systematic evaluation in this population.

Key Words: cognitive rehabilitation; external memory aids; cognitive strategies; brain training; non-invasive brain stimulation

1. Introduction

Memory problems are common in people with epilepsy. Declarative memory deficits, defined as those dependent on conscious reflection for acquisition and recall, are the most commonly voiced impairment and have most frequently been associated with focal temporal lobe epilepsy (TLE) . The cognitive signature of mesial TLE is a material specific declarative memory impairment, involving both long-term memory formation and storage. Poor memory in this population is a major cause of academic and occupational difficulties but also leads to problems in daily-life tasks, undermines confidence and lowers levels of self-esteem and satisfaction. Memory impairment is perceived by people with epilepsy as a considerable concern; only anxiety provoked by the fear of having a seizure and driving issues rank higher[1]. Attending physicians in the same study underestimated the concerns generated by memory problems in those they were treating.

Memory deficits have been linked to hippocampal sclerosis – a pathology encompassing a loss of neurons in the hippocampus and associated gliosis, which now appears from neuroimaging to be more widespread, with atrophy involving neocortical temporal lobes, the entorhinal cortex, fornix, parahippocampal gyrus and amygdala. Lateralization of the anatomical lesion usually plays a role in determining the type of deficit. Left temporal lobe abnormalities have been associated with verbal memory deficits[2]. Visuospatial deficits are generally associated with right TLE [3].

Memory rehabilitation strategies

Rehabilitation strategies to improve memory performance encompass a wide range of techniques. Cognitive strategies, external memory aids, computerized mental training and virtual reality training are commonly used in memory rehabilitation. Recently, non-invasive brain stimulation techniques have been explored as a method to enhance physiological memory networks functioning. Application of memory rehabilitation strategies has been extensively reviewed in different neurological diseases (for more comprehensive readings on this topic, please refer to [4-10]).

Cognitive strategies include visual imagery, self-generated images, errorless learning, trial and error learning, vanishing cues or spaced retrieval. Many cognitive strategies are built on the conceptual framework of the “level-of-processing” theory and related research: this has demonstrated that the durability and strength of a mnemonic trace depends on the depth of the initial processing, with shallow encoding (e.g. sensory) generally resulting in weaker memory traces than deeper (e.g. semantic) levels of encoding[11]. In a further development of this theory, elaboration and encoding specificity have been added as other types of processing affecting memory formation and retrieval [12]. Successful recall depends thus on the quality of the encoding process.

Cognitive strategies promote multimodal and semantic encoding. In general, visual imagery involves the translation of verbal information into visual representations: visual association facilitates information recall as more efficient retrieval is possible through access to multiple representations of knowledge (visual and symbolic). Deep or semantic encoding focuses on the meaning of what needs to be remembered and has been shown to improve recall more effectively than shallow, perceptual encoding. Visual imagery has been extensively investigated as a method to optimize encoding and retrieval[9], mainly in stroke and traumatic brain injury (TBI) populations. Visual imagery techniques have been found to be effective in TBI, and in people with mild to moderate memory impairment (i.e. people with multiple sclerosis [13]), but have not been effective in more people with severer memory problems, such as those with Alzheimer [14].

Self-generated images have also been used and have been shown to be beneficial in people with milder memory problems [15] regardless of the etiology of the memory deficit. There is, however, little evidence that this method is of practical value in daily activities or generalizes to new learning situations.

Errorless learning is a procedure in which a positive reward is associated with a learning gain [16]. This approach, originally designed for people with severe anterograde amnesia, has been applied in other populations with unclear (i.e. in Alzheimer disease [17]) or negative results (i.e. in mild memory deficits after brain injury [18]).

Effortful or trial and error learning, vanishing cues or spaced retrieval methods are other interventions directed at the acquisition of specific knowledge relevant to improve functioning in everyday life, for example learning a name [19].

External memory aids are compensatory strategies. They can be used to enhance memory storage or knowledge acquisition. Two main types exist: externally directed or programmed devices (i.e. watch alarms, pill-boxes, etc.), which require minimal cognitive resources and self-managed aids (i.e. notepads or diaries), which need more active involvement and motivation. External memory aids have been deployed in association with other cognitive strategies and have been shown to be effective for people with discrete memory problems [20]. People with more severe memory impairments are less able to use more complex devices.

Computerized and online mental training, also known as "brain training" programs, have been marketed in recent years for their ability to improve cognitive functioning. They often resemble computer games and can be graded for difficulty. Computerized mental training exercises have been shown to enhance performance on the training cognitive tasks in healthy adults but the evidence is limited for translatable gains to other tasks within the same cognitive domain, other cognitive domains, or to measures of everyday function. One study has reported benefits in initial phases of Alzheimer disease [21], but the sample size was small and the results have not been replicated. On line brain training programs are widely available but their efficacy remains equivocal, due in part to the limited transfer of improvements acquired on these programs.

Virtual reality (VR) paradigms can be considered in the broad category of computerized mental training exercises. The user must actively interact with various sensory environments that can be designed to simulate real life scenarios. They are considered to provide a more ecologically valid assessment of everyday cognitive functions and there is the possibility of real-time feedback on performance. VR has been shown to be a valuable tool to assess spatial navigation, providing a better understanding of the mechanisms at play in navigation than more traditional tests. Improved memory function has been described in people with brain injury [22], although effects have been limited in other populations (i.e. Alzheimer) [23].

Non-invasive brain stimulation techniques include transcranial direct stimulation (tDCS), which modulates cortical excitability through weak currents applied via electrodes to the scalp and transcranial magnetic stimulation (TMS), which involves the use of magnetic fields to depolarize neurons. The efficacy of non-invasive brain stimulation techniques for cognitive rehabilitation is controversial. In healthy subjects it has been argued to exert no effect [24], but low to moderate evidence is emerging for its efficacy in people with stroke ([25]), healthy elderly people and individuals with mild cognitive impairment [26].

Recent reviews on memory rehabilitation in stroke [4] and multiple sclerosis (MS) [6] stressed that improvements were subjective and short-term in stroke and more objective and long-term in MS, regardless of the intervention type and setting. A review on cognitive treatments in mild neurocognitive disorder (MND) [5] detected some improvements in the memory domain, but the results could not be interpreted at a group level given the wide methodological variability of the included studies. Given these findings it is unlikely that the underlying pathology plays a determinant role in the effectiveness of interventions.

The available evidence suggests the efficacy of memory rehabilitation strategies is affected by the degree of impairment and age, with people with severe cognitive impairment benefiting most from errorless learning techniques, whereas younger people with less severe deficits seem to benefit most from cognitive strategies. These findings indicate that rehabilitation programs need to be individually tailored to be maximally effective.

Outcomes of rehabilitation studies are most often measured in terms of performance gains on standardized memory tests. These measures, while validated and widely used, do not provide any information on the degree to which the improvements impact on daily life. Poor generalizability is a major issue in cognitive rehabilitation, which has still to be resolved.

Memory rehabilitation strategies in people with temporal lobe epilepsy

Little is known about the impact of memory rehabilitation strategies on memory deficits in people with epilepsy. The potential role of cognitive rehabilitation in epilepsy dates back to Russell Reynolds (1861). The few studies conducted from the seventies in general have supported the benefit of interventions in people with epilepsy [8]. In a recent review of interventions in post-surgical subjects, many papers were rejected due to their poor methodological quality [10]. Nonetheless, cognitive rehabilitation did seem effective in post-surgical epilepsy persons regardless of intervention and setting.

We aim to explore the efficacy of memory remediation in people with temporal lobe epilepsy who have not undergone surgery and to assess whether this assists us to develop a theoretical framework to direct tailored interventions.

2. Methods

A scoping review was conducted [27]. Given the broad range of techniques and methodologies encompassed, this form of review overcomes the diversity of research methodologies and approaches that would have made a traditional systematic review challenging.

The literature was searched for studies, book chapters, conference proceedings, and review/descriptive articles up to February 2016 by two authors (ADF, MM) supported by a Library Officer. A search was completed using the Medical Subject Headings (MeSH) “physiology of memory, spatial memory, memory, long-term memory, short-term memory, memory disorders, episodic memory disorders, partial epilepsy, temporal lobe epilepsy, hippocampal sclerosis, rehabilitation, non-invasive brain stimulation, transcranial magnetic stimulation, computer assisted mental training, computerized mental training, errorless learning, cognitive strategies, external memory aids, cognitive rehabilitation, brain training, epilepsy rehabilitation, audiovisual aids and verbal learning". It was first used on the MEDLINE database and then converted according to the specific database format for each subsequent search. The electronic search strategy included MEDLINE, EMBASE, CINAHL, AMED, Scholars Portal/PSYCHinfo, Proceedings First, and ProQuest Dissertations and Theses. Duplicates were managed by matching findings with MEDLINE retrievals, as already implemented in the majority of searched databases. Reference lists of primary articles were hand searched for additional sources that may have been missed by the electronic search. Only articles in English were included.

One reviewer (ADF) applied inclusion/exclusion criteria to all the retrieved abstracts. Copies of the full articles were obtained for the selected studies. If the relevance of a study was unclear from the abstract, then the full article was obtained.

Inclusion criteria were developed to eliminate articles not answering the central research question (see Appendix 1). They related to the PICOS questions [type of population, intervention, comparator, outcome measures, and setting (primary, secondary or tertiary epilepsy centers, community-based studies)] as detailed below.

Population type: people with temporal lobe epilepsy and no surgical resection, with memory deficits, both pediatric and adults, with a normal cognitive development and cognition and no concomitant psychiatric disorder, with active epilepsy (at least 1 seizure in the previous 5 years), regardless of treatment or pharmaco-resistency.

Intervention: external memory aids (electronic devices, notepads, diaries, calendars); cognitive strategies (visual imagery, first letter mnemonics, rhymes and stories embedding notions to be remembered, spaced retrieval, verbal and visual association, organization of contents, categorization, visualization, anticipation and retrospection); errorless learning; computerized mental training; non-invasive brain stimulation (NIBS) [transcranial magnetic stimulation (TMS), and transcranial current stimulation either direct (tDCS), alternating (tACS) or random noise (tRNCS)].

Comparator: no treatment; other remediation therapy; sham treatment (for NIBS).

Outcome: declarative memory; quality of life questionnaires and subjective memory scales; mood questionnaires; any other measure that authors have developed to test memories. Setting: primary, secondary and tertiary Epilepsy Centers; outpatients and people admitted for pre-surgical evaluation of epilepsy.

All selected publications were then reviewed by two authors (ADF plus MM, MA, AB, and DG alternatively) each using a data charting framework [27] developed by ADF.

3. Results

A total of 372 abstracts were retrieved. Twenty-five eligible studies were selected, of which full length articles were obtained. Six articles were included in the final review. Reasons for exclusion were: unspecific or unclear study population (e.g. pooled data for people with epilepsy and other neurological diseases - 3 papers), no clear intervention on memory (13), aim of the study different from memory rehabilitation (e.g. evaluation of attention deficit, 5), and unclear/unspecific comparators (2). Four studies had more than one reason for exclusion (Table 1).

3.1 Numerical overview

Three studies dealing with cognitive strategies were included, two with external memory aids, two with computerized mental training and two with non-invasive brain stimulation. A combination of methods was used in three studies. There was one case control study, three randomized controlled trials and two observational studies (Table 2).

3.2 Cognitive strategies

One case-control study investigated the compensatory impact on people with left and right TLE of depth of encoding, elaboration of information and use of retrieval cues [28]. Memory performance was tested after learning word lists that promoted either shallow level processing (phonetic lists) or deeper level processing (semantic lists). Phonetic processing did not enhance the performance of those with left TLE, but it did in those with right TLE ($p<0.05$), indicating that people with left TLE have a memory deficit that encompasses difficulties encoding phonetic information. The promotion of semantic processing, however, facilitated the memory performance of the left TLE group ($p<0.05$), while cued recall was associated with improved performance in those with right TLE ($p<0.05$). The combined use of the three strategies was associated with the greatest gains in memory performance.

These results point to a greater difficulty for people with left TLE in engaging spontaneously in encoding processes, whereas those with right TLE might have more difficulties at the retrieval stage. These findings suggest that laterality of the epilepsy could have implications for the choice of cognitive training techniques and that a tailored approach is possible.

Another cognitive strategy explored in one cross-over, randomized trial was the use of self-generated memories [29]. Memory encoding through a self-generated condition required subjects to pair the stimulus to be remembered with a self-generated word of which usually the initial letter was provided. Performance was compared to word learning when the cue word was already provided. The self-generation condition was associated with better performance for cued recall and recognition memory than when the cue word was pre-set ($p<0.001$), with left TLE persons benefitting most. More active processing by the subject at the encoding stage likely improved the consolidation process resulting in more resilient memory formation. Self-generated external cues may increase the likelihood of improved memory and have potential in people with TLE.

Another prospective observational study reported the findings from a more multi-faceted approach that involved the teaching of cognitive strategies, in addition to external aids and computerized mental training [30]. Two main cognitive strategies were taught: visual imagery and semantic encoding. The first involved instruction in creating visual representations of word lists. If participants took to this technique the more complex Method of Loci technique was introduced, in which items to be remembered are visualized on salient places on a familiar route. The second technique, the story method, involved participants learning to embed word lists into a personally created story. Eight of ten individuals with left TLE scored better on verbal memory tests and reported improved everyday memory function after training. These methods were combined with other strategies (i.e. external memory aids and computerized mental training) preventing the determination of the effect of each intervention.

None of the identified articles reported findings on errorless learning, effortful or trial and error learning, vanishing cues or spaced retrieval method.

3.3 External memory aids

Few studies have focused on this strategy in epilepsy. In one prospective observational trial, the intervention covered optimizing diary, calendar, mobile phone and computer use as efficient ways of recording information [30]. Of the ten pre-surgical participants with TLE, eight scored better on verbal memory tests ($p<0.001$) and reported improved subjective ratings of everyday memory performance. The intervention was coupled with cognitive strategies training, thus preventing a conclusion on the efficacy of the exclusive use of external aids.

Another study found that a relatively short group-based strategy training program improved episodic memory test performance and increased memory strategy use ($p<0.05$). The intervention was a 6-week, group-based, psycho-educational and strategy course with a wait list control. In each session different internal and external strategies were presented, including diaries, calendars, alarms and electronic devices among external strategies and repetition, clustering, method of loci among the cognitive strategies. In this study epilepsy types were pooled and data for the TLE group could not be extrapolated [31].

3.4 Computerized mental training

One article on computerized mental training in epilepsy was found[30] and one study focusing on a virtual reality approach [32] .

In the first study, Lumosity, a commercially available on line training program was tested. This package provides mental training exercises targeting memory, concentration, mental flexibility, cognitive control and processing speed. Of the ten pre-operative TLE participants, five were assigned to the Lumosity training group. This training was in addition to instruction in traditional cognitive strategies and use of external memory aids. An effect was observed for the entire cohort (pre and post-operative TLE, $p>0.001$) but changes recorded were in opposite directions for the two memory tests. Verbal recall improved without computerized mental training, while verbal learning improved with computerized mental training. A positive correlation was observed between the number of Lumosity sessions and performance gains on the computerized tests ($p<0.05$). Due to small numbers, there was insufficient power to explore efficacy in the ten pre-operative cases. It was noted that while brain training had positive effects on the Lumosity training tests, evidence was lacking regarding generalizability.

One observational prospective study investigated the efficacy of virtual reality training in memorizing an auditory presented stimulus in healthy university students and a small subgroup of people with focal epilepsy [32]. Participants had to remember items from a shopping list and then find the items in a 360°-VR supermarket, displayed on a circular arrangement of touch-screens. Training took place over five or eight days and learning improved throughout the task in people with focal epilepsy ($Z=0.042$). High levels of engagement with the VR task were seen. Performance gains were associated with scores on a figural spatial memory test ($\rho s = 0.872$, $p = 0.054$). The results also suggested that learning success was greater in those people who became more immersed on the task.

3.5 Non-invasive brain stimulation

These techniques were initially explored for their capacity to control seizures [33] and relatively favorable results have been reported. They have been deployed occasionally in an attempt to boost cognitive function. The limited use for this purpose is due to the fact that the target for cognitive stimulation is usually the same or overlaps with the epileptogenic zone and carries a risk of provoking seizures. Two studies which used tDCS were identified [34, 35].

In the first, a randomized cross-over trial, oscillatory tDCS was applied before a nap to increase sleep spindle density after a memory task [33]. A significant improvement in verbal ($p=0.05$) and spatial memory ($p=0.048$) performance was detected [34]. An associated shift of temporal spindle cortical generators, pathologically distributed in TLE[36], was observed towards more anterior temporal lobe areas ($Z=0.001$).

In the second study, a randomized, parallel group study, continuous tDCS was applied over the left dorsolateral pre-frontal cortex for 20 minutes during wakefulness. This was not associated with improvements in working and episodic verbal memory[35], but with reduced depression scores ($p<0.05$) and modified EEG oscillatory activity (non-significant reduction of delta $p=0.074$, and theta $p=0.072$).

4. Summary and implications for research and clinical practice

We identified studies of memory remediation techniques for people with TLE who had not undergone surgery. The main approaches and their reported efficacy were described. Implications of the findings for rehabilitation practice and research were highlighted and challenges discussed, but the paucity of data prevent from the development of a comprehensive framework from which to tailor interventions.

Relatively few studies were found. The majority of people with epilepsy are not candidates for surgery and yet the literature focuses mostly on memory deficits and subsequent interventions in post-surgical candidates. We highlight this omission and point to a potential wide field of research previously neglected. Some studies were excluded because pre and post-operative cases were pooled. Surgical cases may have more severe deficits and be less likely to benefit from remedial strategies. Most striking was the lack of data in children. This is surprising given the rehabilitation potential of this group and the burden of disability adjusted to life expectancy.

Cognitive strategies were the methods most commonly researched. They have the advantage of being widely available, cost-effective and presentable during group-based training. From this review, the main suggestions relating to cognitive strategies is the potential value of an individual tailored approach, where the complexity of the techniques taught is guided by capacity level and aptitude, with a possible interaction with laterality of the TLE.

External memory aids are one of the more common remedial strategies provided for people with memory problems, but in the population of interest their efficacy could not be determined. The single study [30] investigating this approach did so in combination with other training methods and the specific contribution of external aids could thus not be ascertained. External memory aids appear, from clinical practice, to be one of the most accepted and feasible techniques for helping people minimize the burden of memory difficulties in everyday life.

There was insufficient evidence from the review to draw conclusions regarding computerized cognitive training programs and non-invasive brain stimulation (NIBS). The study exploring the Lumosity program lacked power to assess efficacy in non-surgical cases. A single study deploying tDCS [34] did find significant gains in declarative memory in people with TLE. The underlying neurophysiological correlate – i.e. modulation of location of cortical areas generating sleep spindles – provides a relevant proof of concept of the applicability of neuromodulation to improve cognitive performance in people with epilepsy. These positive results contrasted with those of a second study applying tDCS [35], in which continuous stimulation of the dorsolateral prefrontal cortex during wake did not benefit memory performance. A possible reason for the discordant results is the different stimulation paradigm employed – oscillatory versus continuous – and the association with sleep of the oscillatory tDCS paradigm to boost the sleep learning effect.

The main limitation of the included studies was the lack of data on the degree to which improved function following rehabilitation had any impact on everyday life. The lack of evidence on the generalizability of findings is one of the major criticisms levelled against cognitive rehabilitation research. The problem is intrinsic to neuropsychological testing, which relies on standardized tests administered in a laboratory setting. Validated daily-life indicators of higher cognitive function have yet to be developed. Validated scales measuring the observation of cognitive[37, 38] and memory deficits [39, 40] by family members or caregivers do exist, but they are relatively underused and to our knowledge have not been applied in epilepsy. Another criticism of cognitive rehabilitation studies that was true of the studies considered here is the lack of data on the long-term effects of training. Most studies have assessed outcomes and relatively short intervals after training.

A limitation of the data was the failure to account for the possible detrimental effects of antiepileptic drugs (AEDs) on memory. Another issue not adequately addressed was the relationship of the memory deficit with age and mood. Young and less depressed individuals are reported as usually benefitting more from remediation programs [31].

This review has implications for research. More randomized controlled trials are warranted in non-surgical epilepsy populations, thus complementing the recent emphasis on surgical cohorts[10]. There should be more focus on children, a group previously neglected. Innovative techniques, such as computerized cognitive training methods and NIBS, have also been markedly under-researched and large studies investigating their efficacy are needed. Lastly, traditional cognitive strategies are widely used but a more systematic approach of their relative efficacy should be undertaken taking into account underlying pathology.

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