Memory Rehabilitation Strategies in Nonsurgical 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 concerning efficacy and the criteria for choosing different approaches have been inconsistent. We aimed to appraise existing evidence on memory rehabilitation in nonsurgical individuals with temporal lobe epilepsy and to ascertain the effectiveness of specific strategies. A scoping review was preferred 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. Of 25 eligible studies, six were included in the final review. None included pediatric populations. Strategies included cognitive training, external memory aids, brain training, and noninvasive 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 noninvasive brain stimulation. The review suggests that cognitive rehabilitation in nonsurgical TLE is underresearched and that there is a need for a systematic evaluation in this population.

Key Words: Cognitive Rehabilitation, External Memory Aids, Cognitive Strategies, Brain Training, Noninvasive Brain Stimulation

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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 material-specific declarative memory impairment, involving long-term memory formation and storage.

Poor memory in this population is a major cause of scholastic 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.[1]

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 (VR) training are commonly used in memory rehabilitation. Recently, noninvasive brain stimulation (NIBS) techniques have been explored as a method to enhance physiological memory networks functioning. Application of memory

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rehabilitation strategies has been extensively reviewed in different neurological diseases (for more comprehensive readings on this topic, please refer to these studies[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 depend 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 because a 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 populations. Visual imagery techniques have been found to be effective in traumatic brain injury 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 severe 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 cause 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 patchy (i.e., in Alzheimer disease[17]) or negative results (i.e., in mild memory deficits after traumatic 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 categories 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 trainings, also known as "brain training" programs, have been marketed in recent years for their putative 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. Online brain training programs are widely available, but their efficacy remains equivocal, in part because of the limited transfer of improvements acquired on these programs.

Virtual reality paradigms can be considered in the broad category of computerized mental training exercises. The user must actively interact with various sensory environments, which 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. Virtual reality 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 traumatic brain injury[22] although effects have been limited in other populations (i.e., Alzheimer).[23]

Noninvasive 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 NIBS 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[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[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 studies included. Given these findings, it is unlikely that the underlying pathology plays a determinant role in the effectiveness of interventions.

The available evidence suggests that 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 tailored individually to be maximally effective.

Outcomes of rehabilitation studies are most often measured in terms of performance gains on standardized memory tests. These measures, although 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 postsurgical subjects, many papers were rejected because of their poor methodological quality.[10] Cognitive rehabilitation did seem, however, effective in postsurgical epilepsy persons regardless of intervention and setting.

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

METHODS

We conducted a scoping review.[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, TLE, hippocampal sclerosis, rehabilitation, NIBS, TMS, 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 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 most 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 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.

Exclusion criteria were developed to eliminate articles not answering the central research question (see Appendix 1, http://links.lww.com/PHM/A393). 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 hereafter.

Population types are the following: people with TLE and no surgical resection, with memory deficits, pediatric and adults, with normal cognitive development and cognition and no concomitant psychiatric disorder, with active epilepsy (at least one seizure in the previous five years), regardless of treatment or pharmaco-resistency.

Interventions are the following: 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; noninvasive brain stimulation (NIBS; TMS, and tDCS, alternating or random noise).

Comparators are the following: no treatment, other remediation therapy, and sham treatment (for NIBS).

Outcomes are the following: declarative memory, quality of life questionnaires and subjective memory scales, mood questionnaires, and any other measure developed to test memories. Settings are the following: primary, secondary, and tertiary epilepsy centers; outpatients and people admitted for presurgical 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.

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 the following: 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). T1

Numerical Overview

Three studies dealing with cognitive strategies were included, two with external memory aids, two with computerized mental training, and two with NIBS. 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). T2

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 encompassing difficulties encoding phonetic information. The promotion of semantic processing, however, facilitated the memory performance of the left TLE group ($P < 0.05$), whereas 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.

TABLE 1. Included studies

	Reason for Exclusion	Intervention
Included		
Bresson et al., 2007[28]		Cognitive strategy
Del Felice et al., 2015[29]		tDCS
Grewe et al., 2013[30]		VR
Koorenhof et al., 2012[31]		Memory training session + home adaptations + external memory aids
Liu et al., 2016[32]		tDCS
Schefft et al., 2008[33]		Self-generation encoding procedure
Excluded		
Baker et al., 2009	No intervention	
Carreno et al., 2008	No intervention	
Cohen et al., 2010	Outcome, population (case report, multiple etiologies of memory deficit)	Errorless learning
Conant et al., 2008	Outcome, comparator, population (no subtypes)	Physical exercise
Deak et al., 2011	Outcome, comparator (role of sleep in forgetting: learning motor task, retest after sleep)	Motor learning task + sleep
Engelberts et al., 2002	No intervention	
Farina et al., 2014	No intervention	
Marks et al., 2003	No intervention	
Miller et al., 2014	No intervention	
Poms et al., 2006	No intervention	
Ponds and Hendriks, 2006	No intervention	
Ruehle et al., 2014	No intervention, population (first unprovoked seizure)	
Samson et al., 2010	No intervention	
Schulman et al., 2002	No intervention	
Tudesco et al., 2010	No intervention	
Wedlund et al., 2013	Outcome	Focus group interviews
Wilkinson et al., 2013	No intervention	
Witt et al., 2012	Outcome	Free delayed recall after 1 or 4 wks
Witt et al., 2012	Outcome	Free delayed recall after 1 or 4 wks

These results point to a greater difficulty for people with left TLE in spontaneously engaging in the 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 crossover, randomized trial was the use of self-generated memories.[33] 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 with 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 preset ($P < 0.001$), 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 multifaceted approach that involved the teaching of cognitive strategies, in addition to external aids and computerized mental training.[31] 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.

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.[31] Of the ten presurgical participants with TLE, eight scored better on verbal memory tests ($P < 0.001$) and reported improved subjective ratings of

TABLE 2. Description of included studies

Reference	Study Design	Participants	Methods	Measurement Efficacy	Highlights and Effect Size
Bresson et al., 2007[28]	Case control study	14 LTLE 16 RTLE	Cognitive strategies: Depth of encoding Elaboration of information Use of retrieval cues	Learning word lists: 2 phonetic lists 2 semantic lists	The combined effects of the three aids differed from LTLE to RTLE Phonetic processing: LTLE did not enhance performance what ever the aid. RTLE improved performances with cognitive aids ($P < 0.05$). Semantic processing: L-TLE presented better performance than R-TLE. The memory performance of people with R-TLE was improved by cued recall ($P < 0.05$). Combination of all the three aids offers the larger benefits
Schefft et al., 2008[33]	Randomized controlled trial, crossover	25 LTLE 29 RTLE 2 LFLE 3 RFLE 3 FLE nonspecific	Self-generation encoding procedure: Words to be printed on card, second word self-generated by subject after providing first letter Didactic condition: both words from each pair were printed on the cards	Verbal paired associate free recall, cued recall, and recognition memory.	All participants benefitted from the use of the self-generation condition relative to the didactic condition ($P < 0.001$), with LTLE benefitting the most ($P < 0.001$). Better performance occurred with the self-generation procedure for cued recall and recognition memory test performance ($P < 0.001$), but not free recall.
Koorenhof et al., 2012[31]	Observational, prospective	20 LTLE: 10 completed presurgical, 10 postsurgical 22 healthy controls	3 sessions of memory training max 4 hrs, then homework: -Environmental adaptations -External aids (calendars, watch phone alarms, pill dispensers, diaries, notepods, mobile phones, computer) -Cognitive strategies: visual imagery, method of loci, story method -Computer training homework: Lumosity, a computerized cognitive training program delivered via internet.	-2 verbal memory subtests of BI[illegible]memory information proce[illegible] battery), -The story recall -The list learning tests. -Subjective memory measures: Everyday Memory Failures Questionnaire -HADS -Brain performance index (in Lumosity computer program)	Gains in memory test performance greater than expected from retesting in controls and people with LTLE ($P < 0.001$). Verbal recall showed a greater improvement without computerized mental training ($P < 0.02$). Verbal learning instead improved with computerized mental training ($P < 0.032$), with a positive correlation between the number of sessions and performancegains ($P < 0.05$). In opposite directions, there was no effect of timing of the training program (preoperative versus postoperative delivery).
Grewe et al., 2013[30]	Observational, prospective	1 TLE 1 OLE 1 Hyppocampal sclerosis 2 TPLE	Shopping lists were presented; participants had to remember items and find them in a 360-degree VR supermarket, displayed on a circular arrangement of touchscreens, with a duration of training of 5 or 8 days.	- Time required to buy all the shopping items they remembered - No. correctly picked items - Adjusted number of correctly picked items from the respective list - Length of movement trajectories	Increasing levels of learning throughout the task ($Z = 0.042$) were observed, which correlated with a measure of figural spatial memory ($\rho = 0.872$, $P = 0.054$).

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(Continued on next page)

TABLE 2. *(Continued)*

Reference	Study Design	Participants	Methods	Measurement Efficacy	Highlights and Effect Size
Del Felice et al., 2015[29]	Randomized controlled trial, crossover	12 TLE	Fronto-temporal anodal tDCS over the affected temporal lobe. Sinusoidal oscillating current (0–250 mA, 0.75 Hz) was applied for 30 mins during wake before sleep. After either real or sham stimulation, subjects were allowed to sleep during EEG recording. Verbal and visuospatial memory recall were tested before and after sleep.	-Rey Auditory Verbal Learning Test -Rey Osterrieth Complex Figure Test	tDCS enforces memory encoding through sleep spindles modulation. Oscillatory tDCS was applied before a nap to increase sleep spindle density after a memory task. A significant improvement in verbal ($P = 0.05$) and spatial ($P = 0.048$) memory was detected, associate with a modulation of spindles cortical generators ($Z = 0.001$).
Liu et al., 2016[32]	Double-blinded, sham-controlled, randomized parallel-group study	37 TLE	Left dorsolateral prefrontal cortex tDCS applied for 5 consecutive days at 20 mA for 20 mins/day. Neuropsychological testing and EEG were repeated at baseline, after the 5-days trial, and after 2 and 4 wks from stimulation conclusion	-Rey Auditory Verbal Learning Test -Letters and Numbers Sequencing subtest of the WAIS-III -Digits Span Test subtest from WAIS-III -BDI-II	There was no significant improvement in working memory and episodic verbal memory after tDCS. A reduction the BDI-II ($P < 0.05$) and a modulation of EEG rhythms after stimulation (nonsignificant reduction of δ $P = 0.074$, and θ $P = 0.072$).

BDI-II, Beck Depression Inventory-II; EEG, electroencephalogram; FLE; frontal lobe epilepsy; HADS, Hospital Anxiety and Depression Scale; LTLE, left temporal lobe epilepsy; OLE, occipital lobe epilepsy; RAVLT, Rey Auditory Verbal Learning Test; RTLE, right temporal lobe epilepsy; tDCS, transcranial direct current stimulation; TPLE, temporal-parietal lobe epilepsy; WAIS-III, Wechsler-Adult Intelligence Scale-III.

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-wk, group-based, psychoeducational, 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.[34]

Computerized Mental Training

One article on computerized mental training in epilepsy[31] and one focusing on a VR approach were found.[30]

In the first study, Lumosity, a commercially available online training program, was tested. This package provides mental training exercises targeting memory, concentration, mental flexibility, cognitive control, and processing speed. Of the ten preoperative 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 (preoperative and postoperative TLE, $P > 0.001$) but changes recorded were in opposite directions for the two memory tests. Verbal recall improved without computerized mental training, whereas 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 ($P < 0.05$). Because of small numbers, there was insufficient power to explore efficacy in the ten preoperative cases. It was noted that although brain training had positive effects on the Lumosity training tests, evidence was lacking regarding generalizability.

One observational prospective study investigated the efficacy of VR training in memorizing an auditory presented stimulus in healthy university students and a small subgroup of people with focal epilepsy.[30] Participants had to remember items from a shopping list and then find the items in a 360-degree VR supermarket, displayed on a circular arrangement of touchscreens. Training took place for 5 or 8 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 ($\rho = 0.872$, $P = 0.054$). The results also suggested that learning success was greater in those people who became more immersed on the task.

Noninvasive Brain Stimulation

These techniques were initially explored for their capacity to control seizures,[35] 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.[29,32]

In the first, a randomized crossover trial, oscillatory tDCS was applied before a nap to increase sleep spindle density after a memory task.[35] A significant improvement in verbal ($P = 0.05$) and spatial memory ($P = 0.048$) performance was reported.[29] An associated shift of temporal spindle cortical generators, pathologically distributed in TLE,[36] was observed toward 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 prefrontal cortex for 20 mins during wakefulness. This was not associated with improvements in working and episodic verbal memory,[32] but with reduced depression scores ($P < 0.05$) and modified electroencephalogram oscillatory activity (nonsignificant reduction of δ $P = 0.074$ and θ $P = 0.072$).

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 prevents from the development of a comprehensive framework from which to tailor interventions (Table 3). T3 AQ4

Relatively few studies were found. Most people with epilepsy are not candidates for surgery, and yet the literature focuses mostly on memory deficits and subsequent interventions in postsurgical candidates. We highlight this omission and point to a potential wide field of research previously neglected. Some

TABLE 3. Overview of memory remediation approaches

Cognitive strategies	Internal memory strategies aim to strengthen the acquisition of information into long-term memory. Cognitive strategies Visual imagery: association of the object/fact to be remembered with a visual image (e.g., recalling people's names by making an association between a name and an image). Method of loci: a series of locations are visualized in the order they would be encountered on a familiar journey. First-letter mnemonics: long established technique for learning items; acronyms can also prove useful. Embedding to be remembered information into rhymes and stories: these methods encourage deeper levels of encoding via semantic processing. All these approaches have a good generalization effect, once the techniques are mastered.
External memory aids	These are recommended for people with severe memory impairments. 1. Externally directed and programmed (calendar, agenda, hand-palm computer, mobile telephone). 2. Self-management aids that require individual engagement and motivation. Generalization effects depend on the effective use of these devices, and teaching techniques are not standardized. Ongoing support is another factor that influences a continuous use of electronic devices.
Computerized mental training	There is an increase of computerized and internet-based training programs often classified as brain training packages that are promoted as having memory and other cognitive-enhancing properties. Packages tend to include a range of mental exercises, involving memory, attention and problem solving games usually graded for difficulty, with instant feedback provided regarding performance. The evidence supports improved performance on the mental games with practice, but data relating to support generalization to everyday life are limited.
NIBS	Recent evidence indicates NIBS may be associated with improvements in cognitive function. TMS: modulates cerebro-cerebellar circuits in people with cerebellar cognitive affective disorders or ataxias or for stimulation over the cerebral cortex to compensate for decreased cerebellar drive to this region. tDCS (transcranial current stimulation): cognitive studies have shown that tDCS can enhance human waking performance, including memory, language, computational, and executive function, but results have been sometimes discordant. Generalization to daily life has not yet been reported. Nonetheless, tDCS is an easy-to-use device, and the application of which could be transferred to people with epilepsy.
Domain-specific learning strategies	Interventions directed at the acquisition of specific knowledge, relevant to a certain domain, a particular situation or a class of problems, are essentially aimed at teaching amnesic people relevant information or skills. Errorless learning: recommended as a practice guideline for people with severe acquired memory disorders as a consequence of a stable or progressive disease. In this approach, training promotes success, reducing the likelihood of errors. Research indicates benefits of this to improve performance on specific targeted tasks, but long-term effectiveness and the generalization of results to daily functioning have been variable. Method of vanishing cues: provides partial information for target responses, gradually withdrawn across learning trials. Hierarchical cues method: different types of retrieval cues are varied to find the most effective. Spaced retrieval training: learning technique aimed at achieving long-term retention of newly learned information by systematically increasing the interval between correct recall of target items. Trial-and-error learning: the target response, paired with a retrieval cue in any case, is given to the individual only if an error is produced.

studies were excluded because preoperative and postoperative 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 are 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[31] 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 seem, 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 NIBS. The study exploring the Lumosity program lacked power to assess efficacy in nonsurgical cases. A single study deploying tDCS[29] 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,[32] 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 after rehabilitation had any impact on everyday life. The lack of evidence on the generalizability of findings is one of the major criticisms leveled 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 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.[34]

This review has implications for research. More randomized controlled trials are warranted in nonsurgical 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 underresearched, 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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