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Evidence-based practice recommendations for memory rehabilitation

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Memory impairment is a common consequence of neurological injury or disease, causing significant disability in everyday life, and is therefore a critical target for rehabilitation intervention. Here we report a review of the available evidence on the efficacy of restitution-oriented therapies and compensatory approaches for memory rehabilitation. A total of 110 studies was systematically classified and analyzed in order to generate evidence-based clinical recommendations for treatment providers. Different key aspects, such as types of brain damage, treatments characteristics and outcome measurements guided the evaluation of the literature as to appraise the potential interaction between patients characteristics, interventions and outcomes. The general conclusion is that memory re-training programs and compensatory approaches are probably effective in ameliorating memory disorders in patients with focal brain lesions, with some evidences of changes in memory functioning extending beyond the trained skills. Externally directed assistive devices and specific learning strategies are effective (with a level D and B of evidence, respectively) in retaining information relevant for daily needs also in patients with degenerative diseases. Some methodological concerns, such as the heterogeneity of subjects, interventions and outcomes studied, may limit the generalization of the present recommendations.

KEY WORDS: Memory disorders - Rehabilitation - Practice guidelines as topic.

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Disorders in declarative memory, that is the ability to consciously recollect events or factual information, are a significant cause of disability in everyday life. Amnesic patients fail either in retaining facts or learning experiences occurred after the pathologic event (anterograde amnesia) or in recollecting past events (retrograde amnesia [1]). In particular, memory loss can pertain to personal facts (episodic memory) or to cultural and other concept-based knowledge, unrelated to specific experiences (semantic memory). Disorders in declarative memory can also interfere with the ability to execute an action at a future point in time (prospective memory) thus decreasing effectiveness in performing everyday tasks. While cases of pure amnesia (with no associated impairment in other cognitive processes) are quite rare, being a consequence of a selective damage in the declarative memory neural circuitry, memory disorders often co-occur with deficits in other cognitive skills (such as attention and working memory). This is true either when memory loss is the consequence of a single cerebral assault (trau-

matic brain injury, stroke, etc.), or when amnesia is observed in the context of a progressive cognitive deterioration as in Alzheimer's disease. Memory impairments can also be distinguished according to the type of information to be retained. Indeed, while most of the patients experience analogous difficulties in storing and recollecting both verbal and visuo-spatial information, some patients (depending on lesion lateralization) show exclusive or prevailing memory deficits for either verbal or nonverbal material.

This article is one of a series of publications on evidence-based practice in the rehabilitation of neurogenic cognitive disorders. Specifically, we reviewed the relevant literature on the efficacy of memory rehabilitation as to generate clinical recommendations for treatment providers. Previous clinical practice guidelines on cognitive rehabilitation [2, 3] attested that specific interventions have a differential impact on distinct aspects of memory functioning.[3] Particularly, compensatory memory trainings were rated as possibly effective for patients with relatively mild memory impairment,[3] although factors such as functional independency, as well as the capability and motivation to autonomous strategy use, strongly contributed to effective memory remediation.[3] Specific learning techniques were recommended as probably effective [2] in learning new information essential for definite behaviors, though efficacy depended on the task used, the severity of memory impairment and whether the learning process was measured through explicit recall or via changes in the target behavior.[2] Finally, the compensatory use of memory aids either externally directed - pagers and voice organizers, or self-managed -notebooks and diaries- has been shown to be useful for people with moderate to severe memory impairments in completing everyday activities, even in patients for whom previous interventions were ineffective.[3]

As general recommendations for future researches, the reported guidelines highlighted the need to evaluate the outcome of interventions not only at the impairment level, but also at the disability level;[2] accordingly, it is important to move beyond the simple question of whether cognitive rehabilitation is effective, in order to determine the therapy factors and patients characteristics that optimize the clinical relevance of rehabilitation.[3]

In the current guidelines the issue of whether memory rehabilitation is effective was addressed considering the potential interaction between types of patients, interventions and outcomes; the aim was, in fact, to identify which treatment is most tailored to specific memory deficits as a function of their aetiology and in light of patients' functional goals. Results are presented separately for each therapeutic approach taking also into account whether the memory loss was the consequence of a stable brain damage or a progressive disease. For a detailed description of the considered studies, see [indirizzo sito web]. Methodological concerns (*i.e.,* lack of details on patients' inclusion/exclusion criteria; reduced sample sizes; absence of a control and/or placebo and/or sham treatment group) and the heterogeneity of treatments, subjects and outcomes studied may limit the generalization of the present recommendations.

Materials and methods

Search strategy

In order to identify pertinent studies (published in peer-reviewed journals in a five-year period from 2003 to 2007) the following databases were searched: PubMed, Scopus, PsychINFO, Psychbite, Centre for Reviews and Dissemination, York University and EBM on line. We combined terms describing treatment (rehabilitation, remediation, intervention, treatment, neuro-rehabilitation, therapeutic neuro-rehabilitation) with the term "memory", limiting our search to studies in English and including only those examining adult patients with no psychiatric disorders. Papers published prior 2003 were extracted from existing guidelines on cognitive rehabilitation [2-4] and then integrated with references from pertinent studies. The search resulted in 1 500 studies, afterward narrowed to a total of 110 by applying the exclusion criteria described above and by rejecting, based on the abstract or the complete paper reading, those article that had the following characteristics: theoretical papers or descriptions of treatment approaches; papers without adequate specifications of interventions; reports without empirical data; articles describing pharmacological data and/or addressing normal aging. Studies were then categorized according to the class or type of evidence following the SPREAD (Stroke Prevention and Educational

Awareness Diffusion) method.[5]

The reviewed articles mainly addressed disorders in anterograde and prospective memory, while therapeutic approaches roughly felt into three categories: 1) memory re-training programs (44 studies) essentially aimed at improving the encoding of information into long term memory; 2) trainings focussed on external memory aids (35 papers comprising also electronic aids and assistive technologies) and 3) interventions based on domain specific learning strategies (31 studies).

Evaluation process

Data collection was performed by the complete committee, then members were assigned a therapeutic approach (GAC and CI-memory re-training programs; FP and EB-external memory aids; GAC and FP-domain specific learning strategies) and analysis of evidence was performed independently by each committee member, according to the assignment mentioned above. Any potential disagreement on the level of evidence was discussed until solved, while all recommendations derived from the relative strength of the evidence were reviewed by the entire committee to ensure a 100% consensus.

As stated before, the committee's examination of the literature was guided by different key aspects and subordinate categories as follows: 1) participants' diagnosis and etiology, to evaluate efficacy depending on whether memory loss was the outcome of a focal cerebral accident or the consequence of a neurodegenerative disease; 2) outcomes of the interventions, to determine whether the intervention led to changes: i) restricted to the trained skill; ii) extended to untrained skills; iii) affecting the subjective experience of memory functioning (as measured through self-rating questionnaires) or iv) evident in everyday activities; 3) training duration and frequency, as well as the clinician-to-patients ratio were also taken into account; in addition to 4) study design in order to evaluate the level of evidence.

Results

Memory re-training programs

Several experimental studies on normal subjects demonstrated that encoding and retrieval are intricately linked and that successful information recall depends on the quality of the encoding process.[6, 7] Experimental manipulations aimed at improving the processing and encoding of perceptual inputs for storage and later retrieval comprise visuo-imaginative strategies - in which verbal information is converted into a visual construct - and semantic deep encoding of verbal or visual material. Visual associations or visual elaboration can facilitate recall of verbal information, since a multiple representation of knowledge (*i.e.*, visual and symbolic) leads to a more efficient retrieval.[8] On the other hand, a deep or semantic encoding (centred on the meaning of memorandum) improves recall as compared to a shallow, perceptual coding.[9]

The trainings reviewed here, quite heterogeneous, analyzed the efficacy of methods such as visual imagery [10] and elaborative encoding.[11] These techniques were, in some cases, coupled with interventions on some metacognitive aspects - metamnemonic awareness - to increase clients' knowledge of human memory functioning and strategies, or with the simple reiteration of the memorandum. Taking into account the number of studies reviewed (43), results will not be presented analytically and imagery and elaborative encoding will be considered together.

Nineteen class I [12-30] (Table I), 6 class II [31-36] and 18 class III studies [11, 37-53] - according to SPREAD criteria - were evaluated. Most articles (28) addressed memory disorders with concomitant impairments in other cognitive skills, as a consequence of stable cerebral damage (stroke [3 studies, 18 patients in total], traumatic brain injury [TBI] [9 studies, 89 patients], multiple sclerosis [6 studies, 214 patients], chronic alcoholism [4 studies, 175 patients], mixed etiology [6 studies, 131 patients]). Only few studies (5 including 37 patients) investigated the effectiveness of memory strategies in subjects affected by pure amnesia, while 11 articles addressed patients with memory impairments due to vascular or Alzheimer's dementia (AD) (thus showing a diffuse, progressive cognitive deterioration).

Considering any significant change in the trained task, the effectiveness of memory retraining programs varies according to aetiology and type of brain damage. Indeed, while the intervention improved performance in more than 70% of studies involving patients with a stable brain damage, only 40% of articles supported efficacy of memory re-training

TABLE I.—*Memory retraining programs: addressed population and types of training.*

Author	Class of evidence	Patients (N. and etiology)
Berg *et al.* (1991) [15]	1+	39 severe chronic TBI received either memory strategy training (13) or drill and repetitive practice on memory tasks (13); a control group received no treatment (13)
Cahn-Weiner *et al.* (2003) [24]	1-, RCT	34 AD medicated with a cholinesterase inhibitor (17 blindly assigned to the experimental group, 17 to the control group)
Chiaravallotti *et al.* (2005) [27]	1+, RCT	29 individuals with clinically definite MS (at least one month post most recent exacerbation and/or steroid treatment) with documented learning deficits, randomly assigned to the experimental or control group
Davis *et al.* (2001) [21]	1-, RCT	37 patients (16 men, 21 women) with probable AD, randomly assigned to receive either the cognitive intervention or a mock (placebo) intervention
Doornhein and De Haan (1998) [20]	1+, RCT	12 patients who had suffered a first-time cerebral stroke (TPO: 3-5 mo) with demonstrable memory deficits were randomly assigned to the training program (N.=6) or a non-specific program involving repetitive practice on memory tasks (N.=6)
Dougan and Engel (1984) [12]	1+, RCT	59 chronic alcoholics patients with memory disorders, randomly assigned to the experimental (30) or the control group (29). The experimental group showed more severe (compared to the control group) memory problems
Fraas (2006) [28]	1+	14 patients with acquired brain injury secondary to TBI (N.=9) or stroke (N.=9) for at least one year, 7 in the experimental and 7 in control group (no treatment, then cross-over)
Godfrey and Knight (1985) [13]	1-	12 patients with moderate to severe memory impairment, (7 alcohol amnesic disorder, 2 dementia associated with alcoholism, 2 alcohol dependence, 1 amnesic syndrome) randomly assigned to either an experimental memory training or to a control group
Heiss *et al.* (1994) [19]	1-, RCT	80 AD patients (from mild to moderate) randomly assigned to 4 groups (social support, cognitive training -CT-, CT plus phosphatidylserine, CT plus pyritinol)
Hildebrandt *et al.* (2007) [29]	1+, RCT	Using a single-blinded controlled study design, 42 MS patients were randomised into a treatment group (17) and a control group (25)

Inclusion/exclusion criteria	Types of training
INCL.: at least 9 mo post injury, objective memory disorders as measured through psychometric tests, no other cognitive deficits, no neurological or psychiatric disease prior TBI, age between 18 and 60 EXCL.: -	Individual: meta-mnemonic strategies, encoding strengthening, patient tailored exercises
INCL.: diagnosis of AD EXCL.: other forms of dementia	Group sessions: instructions and extensive practice in multiple mnemonic strategies (organizing stimulus into meaningful categories, organizing ideas and details for remembering everyday text based information, visualizing and associating items to be remembered)
INCL.: clinically definite MS according to the criteria of Poser EXCL.: age over 69, history of neurological disorders (other than MS), alcohol or drug abuse, bipolar disorder, psychotic disorder, or head injury resulting in more than 30 minutes loss of consciousness	Group sessions: the experimental group underwent eight sessions of the Story Memory Technique (visualization i.e., imagery - to facilitate new learning- and context cues -to recall new information), while the control group participated in eight sessions of memory exercises
INCL.: diagnosis of AD EXCL.: -	Individual: a cognitive intervention consisting of training in face-name associations, spaced retrieval, and cognitive stimulation. The placebo treatment consisted of unstructured conversation and questioning by an examiner
INCL.: memory deficits that could be demonstrated on routine neuropsychological assessment (a Dutch version of the Rey auditory learning test) EXCL.: deficits that could interfere with the training program, such as severe aphasia, apraxia, agnosia	Individual: a memory training program comprising two mnemonic strategies ("association" involved training in making verbal and visual associations between, for instance, the name and a characteristics of a person, "organisation" concerned training in reordering/organising the to-be-remembered material, for example putting a shopping list in a logical order)
INCL.: memory disorders in patients with history of alcoholism EXCL.: history of psychiatric or neurological disorders	Group sessions: a memory training program comprising visual and chaining mnemonic strategies; control group: biofeedback training and counselling sessions
INCL.: deficits in recalling face-name pairs EXCL.: aphasia	Individual: computer-assisted training for name-face memory (Memory Works: Names and Faces software); users have one of two strategy options: the Linking Method (visual imagery) or the "Say, Ask, Leave, Test" (SALT) method (study the face, ask for the person's name and use it immediately, leave the situation in order to rehearse, test the subject's memory)
INCL.: memory disorders in patients with history of alcoholism EXCL.: -	Group sessions: associate learning tasks, ROT, picture recognition training, practice in retaining memory for recent events; control group: social skills exercises, card and bingo games, discussion of news, visits outside the hospital
INCL.: diagnosis of AD EXCL.: medicated with other substances active on the CNS	Individual: computerised memory re-training program; control group: conversation and games
INCL.: MS diagnosis, at least four weeks after stopping the treatment with methylprednisolone EXCL.: (1) Expanded Disability Status Scale score >7, (2) current or past medical illness or psychiatric disorder according to the DSM-IV and (3) substance abuse	Individual: home-based computer training focusing on memory (semantic categorization rewarded) and working memory; control group: no intervention

TABLE I.—*Memory retraining programs: addressed population and types of training.*

Author	Class of evidence	Patients (N. and etiology)
Jennett and Lincoln (1991) [16]	1-	10 chronic TBI patients and 8 stroke patients with memory impairments, cross over design
Jonsson *et al.* (1993) [17]	1+, RCT	40 MS patients with mild to moderate cognitive and behavioural impairment (15 yrs PO) randomized to either specific cognitive treatment (20 patients), or to non-specific, mental stimulation (20 pts)
Kaschel *et al.* (2002) [23]	1+, RCT	21 patients in 9 centres (12 TBI, 7 stroke, 1 encephalitis, 1 arachnoid cyst) randomly assigned to the experimental group (imagery-based training) or to the control group (pragmatic memory training)
Koltai *et al.* (2001) [22]	1-	A total of 22 moderate AD were randomly assigned to treatment (14) and waiting-list control conditions (8).
Solari *et al.* (2004) [26]	1-	77 MS patients with subjective complaints of poor attention or memory (score < 80th percentile in at least two tests of the Brief Repeatable Battery of Neuropsychological Tests) 40 in the experimental group and 37 in the control group
Steingass *et al.*(1994) [18]	1+	14 alcoholic patients (abstinent for at least 6 weeks; 34% affected by Korsakoff's syndrome) compared to 15 waiting-list control patients
Tam and Man (2004) [25]	1+	26 persons with brain injury randomly assigned to four age- and gender-matched memory training groups and trained using the related computer software, 8 assigned to a control group
Thickpenny-Davis *et al.* (2007) [30]	1, RCT	12 adults with TBI (N.=10) or stroke (N.=2), a minimum of 12 months post injury. Participants were randomly allocated to waitlist control (6) and experimental conditions (6)
Yohman *et al.* (1988) [14]	1-	3 groups of alcoholic subjects (N.=76) and one group of community non-alcoholic control subjects (N.=36). Alcoholics were divided into three groups: 1 group (N.=25) received 12 h of memory training; a second group (N.=26) received a similar period of training in problem-solving techniques; and a third group (N.=25) received no training during the two-week period

Inclusion/exclusion criteria	Types of training
INCL.: Subjective Memory Questionnaire score>7.5, RBMT score<20, capability to participate in at least 4/6 training sessions EXCL.: -	Group sessions: a variety of memory strategies were taught, and practical advice was provided in the use of external aids
INCL.: MS with cognitive deficits EXCL.: age over 60, neurological and/or psychiatric disorders (other than MS), severe motor or visual problems, too severe cognitive deficits, history of drugs abuse, medicated with psychotropic drugs	Individual memory training: mental imagery and semantic chaining
INCL.: memory problems, age ranging between 20 and 60 years; brain damage documented by CT or MRI scan; at least 6 months following onset; score equal to or less than 15 on the immediate/delayed story recall test from the Rivermead Behavioural Memory Test EXCL.: severe memory problems (standardised profile score of the RBMT of less than 12 points); presence of overt aphasia, neglect, hemianopia, apraxia, agnosia, assessed and ascertained by clinically experienced professionals.	Individual: patients received two training periods: first the patient learned the skill of generating images rapidly given verbal information, e.g.: names of actions (standardised skill acquisition period). In a second stage of training, this skill was transferred to target problems in everyday life, such as remembering verbal information and/or prospective remembering (individualised skill transfer period)
INCL.: (1) age 60 or older; (2) mild to moderate dementia as determined by ratings of 0.5-1.0 on the Clinical Dementia Rating Scale and evidence of cognitive compromise on neurological mental status examination; and (3) adequate language skills EXCL.: -	Group session for 6 participants, individual for the remaining: Memory and Coping Program an integrated intervention program, multiple cognitive, compensatory, and coping strategies to address abilities and adjustment; SR, face-name recall strategy, verbal elaboration, concentration/overt repetition, external aids, coping strategies
INCL.: MS meeting the diagnostic criteria of Poser EXCL.: age less than 18 or over 65 years, MMSE <24, education less than 8 years, ongoing major psychiatric disorder, one or more exacerbations in 3 months prior to enrolment, immunomodulant or immunosuppressant treatment initiated in 4 months prior to enrolment, and cognitive rehabilitation in the 6 months prior to enrolment	Participants were randomized to two computer-assisted retraining interventions: memory and attention (study arm), and visuo-constructional and visuo-motor coordination (control arm)
INCL.: history of alcohol abuse, memory disorders EXCL.: insufficient education	Attentional and memory training (12 training sessions, essentially based on visual imagery and 6 memory-games sessions)
INCL.: age between 18–45 years, with more than three months since TBI, post-brain injury short-term semantic memory impairment, standardized profile score below 15 at the RBMT EXCL.: severe visual defects, impaired physical functions prohibiting the operation of keyboard or mouse, pre-morbid mental retardation or other neurological pathology preceding head injury	Four treatment methods: self-pacing (allowing working at home), feed-back (immediate and non-judgemental), personalized (presentation of actual people, objects and environments), visual presentation (attractive and bright), 4 learning modules: remembering peoples' faces and names; remembering to do something; remembering what people tell; remembering where to put something
INCL.: presence of memory deficits EXCL.: (a) significant impairments that precluded patients from participating in the group (e.g., receptive/expressive aphasia); (b) behavioural problems that would interfere with participation in a group setting (e.g., agitation, aggression); (c) age below 16 years; (d) informed consent not obtainable; and (e) not fluent in English	Group sessions: memory group using a combination of didactic teaching about memory and memory strategies (rehearsal-repetition, multiple coding), small group activities (e.g., brainstorming in pairs), discussions, and both problem solving and practice implementing memory strategies. Errorless learning was used when reviewing material
INCL.: history of alcohol abuse, abstinent, sufficient education, normal IQ EXCL.: neurological diseases	Group sessions: visual imagery for verbal learning and verbal mediation for visual learning

TABLE I.—*Memory retraining programs: aim of the interventions and statistical analysis; post-treatment and follow-up:coutcomes.*

Author	Aim of the interventions	Statistical analysis
Berg *et al.* (1991) [15]	Objective and measurable memory improvement	Inferential: subjective ratings, memory tasks on which an effect of the use of strategies was expected and a reaction time task to control for spontaneous recovery or motivational factors
Cahn-Weiner *et al.* (2003) [24]	To determine whether cognitive interventions can impact cognitively based measures of daily functioning	Inferential: neuropsychological tests, process measures of recall and recognition
Chiaravallotti *et al.* (2005) [27]	To improve new learning and memory performance in MS participants with learning impairment	Inferential: independent samples t -tests were performed to assess baseline equivalency on neuropsychological test performance between the two groups, perceived changes in memory abilities
Davis *et al.* (2001) [21]	To evaluate whether the cognitive intervention would improve face-name recall, recall of personal items and neuropsychological functioning in patients, compared with the mock intervention	Inferential: measures of face-name recall and recall of personal information as well as a battery of neuropsychological tests (administered by examiners blind to treatment condition) and a caregiver rating scale to assess patient quality of life
Doornhein and De Haan (1998) [20]	To evaluate the efficacy of the memory training strategy	Inferential: target memory tasks (practised during the training), control memory tasks (an adaptation of the Rey auditory list learning task, the Oxford Recurring Faces Test), subjective judgments (Memory Questionnaire)
Dougan and Engel (1984) [12]	To improve verbal memory	Inferential: the Dooks Memory Test evaluated the different facets of memory, and the Trail Making Test A and B measured attention and concentration
Fraas (2006) [28]	To train name-face recognition and recall skills	Inferential: Recognition Memory Test (Warrington, 1984), Rivermead Behavioural Memory Test-II, Memory Works: Names and Faces Memory Monitor (Rager, 1996), a self-report assessment

Outcomes of the interventions	FOLLOW-UP	Outcomes at follow up	Grade
Neither treatment procedure showed significant effects on reaction time measures. Both groups subjectively rated the effects of therapy on their everyday memory functioning as highly positive, although significant effects on objective memory performance scores could only be demonstrated in the strategy training group	4 mo after training completion	The observed effects appeared most clearly at the 4-month follow-up	B
No significant effect of group (training vs. control) or time on any outcome measures, nor interactions; modest improvement on recall and recognition of test material presented during the training sessions	8 wks after training completion	None	Null effect, B
When stratifying participants by degree of learning deficits, a significant treatment effect was noted. MS participants with moderate/ severe impairment in learning showed a significant improvement in learning abilities when compared to controls, evident in 88% of participants in the experimental group. Little improvement was noted in MS participants with mild learning impairments. Significant self-reported improvements in memory were noted in MS participants that underwent treatment, but not those that did not undergo treatment	5 wks after training completion	Any treatment gains noted in the experimental group on the HVLT-R total learning score from baseline to follow-up were maintained until the long-term assessment. Over time, the treatment effect documented in the experimental group immediately following treatment is attenuated	B
AD patients showed significant improvement in recall of personal information, face-name recall, and performance on the Verbal Series Attention Test. Improvement did not generalize to additional neuropsychological measures of dementia severity or to caregiver-assessed patient quality of life	NO		Effect limited to the trained skills, B
After a four-week training period retesting showed a significant improvement of the trained memory skills, but there was no improvement on control memory tasks. Subjective ratings of everyday memory functioning did not differ between the two groups.	NO		Effect limited to the trained skills, B
Significant main effect for the Memory Retraining Program. There was also a significant effect of Age and of IQ. No interaction effects between age and treatment, or IQ and treatment. No other independent variables (education, duration, days since last drink, depression) were significant	NO		B
The treatment group demonstrated mean improvement on all tests. The RBMT-II was the only test that proved to be statistically significant (large eta squared effect size). For the group of subjects who did not receive name/face training, no significant differences were found on any of the neuropsychological testing. Significant improvements in self-reports of memory skills, social environment, physical environment, health, and motivation between pre-intervention and post-intervention (large eta squared effect size). No significant changes were noted on any of the memory readiness items for the group who received no training for names and faces	NO		Doubt effect (interaction Group x phase -pre-post intervention- not reported), B

TABLE I.—*Memory retraining programs: aim of the interventions and statistical analysis; post-treatment and follow-up:coutcomes.*

Author	Aim of the interventions	Statistical analysis
Godfrey and Knight (1985) [13]	To compare the two interventions, to assess the extent to which improvement might generalize to memory tasks dissimilar to those used in training and to determine how long treatment gains can be maintained	Inferential: two word-learning tasks, two questionnaires assessing orientation and memory for recent events, a nurse rating of memory ability
Heiss *et al.* (1994) [19]	To evaluate any potential training effect on psychometric measures of memory functioning	Inferential: Verbal and Pictorial Selective Reminding Test
Hildebrandt *et al.* (2007) [29]	To explore the benefits of a home-based cognitive training program for memory and working memory functions in relapsing-remitting MS patients controlling for whole brain and central brain atrophy	Inferential: clinical and cognitive performance, quality of life (QoL), depression and fatigue using self-rating scales
Jennett and Lincoln (1991) [16]	To investigate the effectiveness of group treatment for memory problems	Inferential: RBMT, Rey figure, Subjective memory Questionnaire
Jonsson *et al.* (1993) [17]	To improve memory and cognitive functioning	Inferential: verbal learning (associated word pairs, word lists) and visuo-spatial learning (visual Gestalt learning)
Kaschel *et al.* (2002) [23]	To evaluate the efficacy of a simple visual imagery technique, to compare the efficacy of this imagery training to memory rehabilitation procedures which are currently applied to similar patients with mild memory problems	Inferential: WMS, RBMT, Self-rating Questionnaire, caregivers' ratings of memory functioning
Koltai *et al.* (2001) [22]	A preliminary investigation of the effects of a Memory and Coping Program among patients with mild to moderate dementia who were experiencing difficulty adjusting to their cognitive losses	Inferential: Geriatric Depression Scale, relative GDS, Everyday Memory Questionnaire, relative EMQ, a cognitive screening battery for AD –CERAD–, anosognosia ratings

Outcomes of the interventions	FOLLOW-UP	Outcomes at follow up	Grade
The control group showed the same improvement on most measures, both groups improved significantly on several outcome measures assessing generalization of memory skills	4 wks after training completion	nr	Null effect (improvements in both groups), B
No significant difference between the supportive and the CT group	NO		Null effect (no difference between the experimental and the control group), B
Training had no effect on the neurological status and on QoL or fatigue. However, the treatment group showed better verbal learning, long-delay verbal memory performance, and working memory performance. The impact of treatment on long-delay verbal memory performance was independent from the extent of brain atrophy, whereas for the other findings brain atrophy played a significant role	NO		D
No improvement in memory function was detected on the Behavioural Memory Test or Subjective Memory Questionnaire. Increase in the number of memory aids reported as being used after attending the group. The number of items reported on the Subjective Memory Questionnaire as 'bothering' the patient decreased in frequency after group treatment	NO		Null effect (no difference between the experimental and the control group), B
After short-term treatment, effects on cognitive measures were not convincing, but on the Beck Depression Inventory (BDI) the specific cognitive treatment group reported significantly less depression	6 months after training completion	After 6 months the experimental group showed an effect, since visuo-spatial memory was improved. However, the depression ratings (BDI) were almost maintained from the short-term level. Interestingly, the non-specific treatment group rated themselves as significantly more depressed.	B
Imagery training significantly improved delayed recall of everyday relevant verbal materials (stories, appointments). Frequency of memory problems observed by relatives was reduced	3 mo after training completion	The effects were stable	B
Encouraging trends emerged suggesting improvement among those who received treatment, but group differences did not reach statistical significance. However, participants with insight made significantly greater gains in perceived memory functioning than those without insight	NO		Null effect, B

TABLE I.—*Memory retraining programs: aim of the interventions and statistical analysis; post-treatment and follow-up:coutcomes.*

Author	Aim of the interventions	Statistical analysis
Solari *et al.* (2004) [26]	To assess the efficacy of computer-aided retraining of memory and attention in people with MS impaired in these abilities	Inferential: improvement of 20% or more in at least two BRBNT test scores at 8 weeks compared to baseline (primary end-point). Changes in depression and health-related quality of life
Steingass *et al.* (1994) [18]	To improve learning	Inferential: WMS, word lists learning test, Rey figure, Street map test
Tam and Man (2004) [25]	To test the differences in effectiveness of four different computer-assisted memory training strategies, which were hypothesized to improve different memory skills of persons with brain injury	Inferential: the Rivermead Behavioural Memory Test, a self-efficacy scale and built-up computer performance records
Thickpenny-Davis *et al.* (2007) [30]	To evaluate the impact of an 8-session structured group format memory rehabilitation program on impaired memory functioning	Inferential: neuropsychological assessments of memory and both self-report and significant other report of behaviours indicative of memory difficulties and the use of memory strategies
Yohman *et al.* (1988) [14]	To improve verbal and non-verbal memory	Inferential: a battery of three clusters of neuropsychological tests measuring learning and memory, problem-solving, and perceptual-motor functioning

AD: Alzheimer's Disease; BDI: Beck Depression Inventory; BRBNT: Brief Repeatable Battery of Neuropsychological Tests; CVLT: California Verbal Learning Test; DSM: Diagnostic and Statistical Manual of Mental Disorders; HVLT-R: Hopkins Verbal Learning Test-Revised; IQ: Intelligence Quotient; LTM: Long Term Memory; MCI: Mild Cognitive Impairment; MMS E: Mini-Mental State Evaluation; MQ: Memory Quotient; MS: Multiple Sclerosis; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; PO: Post Onset; QoL: Quality of Life; RAVLT: Rey Auditory Verbal Learning Test; ROT: Reality Orientation Therapy; SR: Spaced Retrieval; STM: Short Term Memory; TBI: Traumatic Brain Injury; TPO: Time Post Injury; WAIS: Wechsler Adult Intelligence Scale; WMS: Wechsler Memory Scale.

programs in demented subjects. This result is even more striking if only randomized control trials (RCT, Class I+ in the SPREAD classification) are considered (4 studies): indeed, while also in this case 70% of studies (11 out of 14) confirmed effectiveness of the training programs in stable patients, no class I evidence sustains the usefulness of mnemonic internal strategies in subjects with degenerative diseases (0 out of 4).

At the outcome level, the effectiveness of memory strategies trainings seems to be narrowed to the trained skill. In fact, independently from aetiology and type of brain damage, a positive effect of memory re-training on the specific memory exercises was reported in 80% of the considered studies. In contrast, improvements extended to untrained skills only in 50% of studies and affected memory functioning in everyday life in a small percentage of evi-

Outcomes of the interventions	FOLLOW-UP	Outcomes at follow up	Grade
An improvement occurred in 45% of study patients vs. 43% of control patients. The study treatment was better than the control treatment only on the word list generation test (explained by regression to the mean since the control arm performed significantly better than the study arm at baseline). For the remaining BRBNT tests, score change differences between the study and control arms were not significant	16 wks after training completion	Between-group comparisons of score changes showed significant differences for the word list and the generation test at both 8 and 16 weeks	Null effect, B
The treated groups showed a small but significant improvement in verbal memory, both immediate and delayed, as well as in reproduction of figures	NO		B
All the four memory training methods showed positive results among the persons with brain injury as compared with a control group, although there was no statistically significant difference among the four training methods. However, clinical improvement was found in all four methods	NO		B
Participation in the memory group increased participants' knowledge of memory and memory strategies as well as use of memory aids and strategies reduced behaviours indicative of memory impairment; and had a positive effect on neuropsychological assessments of memory (e.g., delayed recall for words and figures). All significant improvements exceeded change experienced by waiting-list controls	1 month after training	Significant improvements maintained	Doubt effect (interaction Group x phase -pre-post intervention- not reported), B
All 3 alcoholic groups performed significantly poorer than the control group on all 3 clusters of baseline tests but did not differ from each other on those clusters. Although there was no overall differential improvement on memory tests by the memory-training group, younger subjects in that group improved significantly more than older subjects	NO		Null effect (no difference between the experimental and the control group), B

dences (30%). When only RCTs are considered, the intervention improved the trained skill in all the reviewed studies, while a 44% demonstrated a positive effect on performance in memory tasks other than the trained one, and only 20% of studies reported some improvements at the disability level.

Frequency and duration of training was quite heterogeneous in the considered articles, ranging from one session a week to daily rehabilitation and from 15 days up to 11 months. It is thus, difficult to evaluate the effect of such variable on training efficacy. Nonetheless, trainings lasting less than two months had a positive effect (in RCTs) in approximately 50% of studies, while longer trainings (more than two months) proved to be effective in 60% of evidences. Analogously, interventions delivered more than twice a week demonstrated a differential benefit in 66% of studies in which reha-

bilitation lasted less than two months, and in 57% of evidences reporting a longer training duration. Also the treatment provider-to-patients ratio did not seem to be a crucial factor in predicting the intervention outcome. In fact, individual treatment was effective in 66% of the reviewed RTCs, group therapy determined a benefit in 50% of the considered evidences and computerised rehabilitation had a differential impact on memory dysfunctions in 66% of studies.

Finally, whenever the intervention determined improvements in memory performance, these seem to be long lasting, as all studies in which a follow-up was performed (9) report a maintenance of benefits from one to six months after training completion.

Recommendations

Considerable methodological concerns limit the generalization of the present results. Patients selection and inclusion/exclusion criteria are vaguely described in a number of studies, with no details of the laboratory based measures used or the potential cut-off score set as inclusion criterion. Sample size is, in general, very small, ranging from 12 to 40 patients in RCTs and from 8 to 75 patients in case-control studies. Furthermore, most articles fail to report the severity of memory impairments in the considered sample, or patients are tested using memory measures not widely used by the scientific community; finally, very few studies (6 out of 43) evaluated subjects at the disability level including quantitative data on the functional impairment profile. With regards to study design, blinding was imposed to examiners only in 6 studies and to clinicians in just one article. The majority of studies do not describe treatment providers; in seven articles (out of 10 reporting clinicians' vocational qualification) a psychologist administered the intervention, while a neurologist or unskilled personnel performed rehabilitation in the remaining three studies. When the specific training program was compared to an alternative intervention (class I and II studies), the latter was a placebo treatment in 16 studies. However, in seven articles the differential effect of the experimental intervention could not be established since the control group, on a waiting list, did not receive and alternative treatment. The outcome is generally expressed, in controlled studies, as the difference in the dependent measures between the experimental and the control group; occasionally, efficacy is also reported as the percentage of subjects benefiting from the treatment.

Taking into account the reported methodological biases and based on the current evidence (three class I and several class II and III studies), the committee judged the use of internal memory strategies as probably effective (level B) at improving memory performance in the trained task, in subjects with memory impairments as a consequence of a stable cerebral disease. Only one class I study demonstrated that improvements were maintained six months after training suspension, while one class III study reported performance decline (compared to post-treatment measures) at follow-up. Insufficient evidence supports the effectiveness of memory re-training programs in determining improvements beyond the trained task (14 out of 24, 7 out of 12 RCTs) or any significant change in memory functioning in everyday life (two randomized trials provided contradictory evidences, positive in one study and negative in the other, of potential benefits in everyday activities).

Finally, no evidence supports the usefulness of mnemonic internal strategies training in subjects with degenerative diseases. Indeed, while contradictory evidence subsists regarding a positive effect of memory trainings on specific tasks, most studies (the entirety of RCTs) report a null effect after training completion on non-trained activities and/or memory functioning in meaningful contexts. Based on the current evidence, the committee judged memory re-training programs as not effective (with a level B of evidence) in patients with severe or mild memory impairments as a consequence of vascular or Alzheimer's dementia. Therefore, internal memory strategies are not recommended for patients with a progressive cerebral disease.

No specific recommendations can be made regarding duration and frequency of the considered interventions, nor in favour of an individual or group rehabilitative setting.

External memory aids

There is general consensus that cognitive rehabilitation for neurological patients should aim to improve effective functioning in everyday life.[3] Among

compensatory strategies expressively designed to enhance memory performance in patients with stable or degenerative neurological diseases, external memory aids are particularly useful at the individual point of view, to execute different everyday life activities, and at a social point of view, to promote social role functioning.[54] While such aids are mainly used to compensate disorders in executing daily life activities at a future point in time (prospective memory), they can also be useful in enhancing event memory storage and/or knowledge acquisition and utilisation.[55-83]

There are two main types of memory aids that can be used by rehabilitation providers, depending on patients' functioning profile: 1) those that are externally directed and programmed (pagers and voice recorders), thus requiring minimal cognitive resources for their utilisation; and 2) self-managed aids (notebooks and diaries), that entail the active clients' participation and motivation for independent use.

The committee reviewed a total of 36 studies focussed on the effectiveness of using an external memory aid; these included 4 RCTs (2 with a 1++ class of evidence and 2 with a 1+ level of evidence; Table II), 2 class II+ studies (a case-control study and a cohort study with small alpha levels) 29 class III studies (17 case reports and 12 single cases) and a survey retrospective article.

Most of the reviewed evidences (88.5%) addressed efficacy of external memory aids in compensating prospective memory disorders. In four studies the memory aid was used with a different function: for consolidating episodic memory of autobiographical events (recorded using a wearable camera [56]), for the acquisition of declarative knowledge regarding therapy goals [57] and to successfully navigate in the environment.[58, 59] Furthermore, a follow-up study [60] surveyed patients (two months and four years after training completion) to determine the utility of a palmtop computer to assist memory dependent activities in everyday life. Finally, a preliminarily report of a paging service designed to reduce everyday memory and/or planning problems, provided information on the first 40 clients recruited to the service.[61]

With respect to types of external aids, those aimed to compensate the ability to execute a plan upon the occurrence of the appropriate cues, usually comprised a prompt signal (a beep or some kind of warning sign) indicating patients the right moment in time when the target behaviour had to be performed. A subsequent message (either auditory or visually delivered) informed clients about particulars of the scheduled activity (*e.g.*, medication dosage). Between such types of aids, we can mention the following ones: a portable pager system,[61-65] voice organisers or recorders used by the clients to register messages self-identified as relevant,[57, 58, 66] IC voice recorders programmed by the clinician for delivering spoken messages prompting various daily tasks,[54, 67] electronic memory aids,[68] mobile phones,[69, 70] palmtop computers [60, 71] eventually used as a web-based cueing system to navigate in the environment [59] and alarm clocks.[59] All interventions using such aids were based on external cueing to initiate the target behavior, apart from one study [72] in which a conditioning procedure was used.

Self-managed memory aids requiring participants to store and actively recall the intention to perform an action in the future, included: pocket computers,[72-74] memory books,[75-77] notebooks,[78-82] diaries,[83] palm organisers,[84] paging systems [85] and calendars.[86, 87] For this category of memory aids, specific training programs have been implemented to promote their acquisition and generalization. For example, Sohlberg and Mateer [75, 81, 86] described a structured training sequence for teaching individuals with severe memory impairments to utilise a compensatory memory book. Based on the errorless learning approach, the training consists of three stages: an acquisition phase, in which the patient familiarise with the purpose and use of each different section in the memory book, an application stage, in which the client learns when and where to use a note book, and an adaptation phase in which the patient demonstrates appropriate use in natural settings. Autonomous use of a memory log is achieved also through methods aimed to minimize the tendency to make errors, such as immediate repetition or error prevention,[87, 89] the vanishing cues technique [78] and the spaced retrieval method.[76, 86] Individualized, streamlined memory journals are easier to master.[80, 87]

Considering types of patients, 13 studies addressed subjects with TBI, 13 included clients with different neurological diseases, five investigated memory aid effectiveness in cases of pure amnesia, three in AD samples and one in stroke patients. In general, stage post injury (in stable diseases) varied greatly from one study to the other (ranging from few months to

TABLE I.—*(continued) Memory retraining programs: aim of the interventions and statistical analysis; post-treatment and follow-up:coutcomes.*

Author	Class of evidence	Patients (N. and etiology)
Ownsworth *et al.* (1999) [83]	1+; randomized cohort study	20 long term acquired brain injury GR1 (9 TBI, 1 viral enc., 16.9 yrs PO) GR2 (6 TBI, 2 cerebral tumours 1 stroke, 1 viral enc., 13 yrs PO) + 31 healthy sub. (mean age: 28.1 yrs)
Schmitter-Edgecombe *et al.* (1995) [79]	1+; randomized case-control study	8 TBI, more than 24 months post injury
Wilson *et al.* (2005) [64]	1++; RCT	63 TBI, mean TPO: 5.3 yrs
Wilson *et al.* (2001) [63]	1++; RCT	143 ss (GR-A: 46.8% TBI, 25.5% stroke, 12.8 non progressive acquired BD, 9.6% not reported; GR-B: 38.8% TBI, 24.5% stroke, 18.4% non progressive acquired BD, 2.0% not reported) GR-A: 5.33 (sd 5.8) yrs PO, GR-B: 4.8 (sd 6.94) yrs PO

Author	Aim of the interventions	Statistical analysis
Ownsworth *et al.* (1999) [83]	To improve patients' independence in memory related daily activities, to compare the two training approaches	Inferential: weekly percentage of total diary entries made as a function of the Diary Only (DO) and Self-Instructional Training (SIT) treatment groups
Schmitter-Edgecombe *et al.* (1995) [79]	To examine potential specific effects of the notebook training	Inferential: laboratory-based recall, laboratory-based everyday memory, retrospective reports of everyday memory failures (EMF), observed EMF, symptom distress
Wilson *et al.* (2005)[64]	To see how the TBI patients performed on daily life activities using the NeuroPage	Inferential: mean percentage of targets achieved as a function of intervention phase (baseline, pager or waiting list, pager or aid withdrawal)
Wilson *et al.* (2001)[63]	To evaluate a paging system designed to improve independence in people with memory problems and executive deficits	Inferential: percentage success rate as a function of intervention phase (baseline, pager or waiting list, pager or aid withdrawal)

ACoA: anterior communicating artery; BEHAVE-AD: Behavioural Pathology in Alzheimer's Disease Rating Scale; BI: Brain Injury; EADL: Electronic Aids to Daily Living; EF: Effortful (learning); EL: Errorless Learning; EMA: electronic memory aid.

several years) and the severity of memory impairments (when reported) spanned a wide range.

At the outcome level, all the considered studies demonstrated improved functioning in memory-related activities, in association with the implementation of the external aid. Five articles did not bring strong evidences, since only a proportion of patients benefited from memory aid use,[54, 70, 80] or results

Inclusion/exclusion criteria	Types of training
INCL.: chronic disease, self-reported memory disorders EXCL.: -	Group sessions: two different approaches in training subjects to use a diary to compensate for memory problems: a Diary Only (DO) approach, which emphasized compensation based upon task specific learning, and a Diary and Self-Instructional Training (DSIT)
INCL.: age between 17 and 55, education> 8 yrs, coma duration> 2 days, age at TBI> 15 yrs, TPO> 24 months, IQ (WAIS-R) above the 75th perc, DRS> 133, WMS-R> 89 EXCL.: -	Group sessions: notebook training (incorporating behavioural learning principles and educational strategies) composed of 4 stages: anticipation, acquisition, application and adaptation. A supportive gr therapy as comparison treatment
INCL.: memory and planning disorders as rated by clinical neuropsychologists, occupational therapists, language pathologists, etc., ability to read and to take notes or with a caregiver EXCL.: -	Individual: NeuroPage, paging system to execute daily life activities
INCL.: memory and planning disorders either acquired or developmental as rated by clinical neuropsychologists, occupational therapists, language pathologists, etc., ability to read and to take notes or with a caregiver EXCL.: -	Individual: NeuroPage, paging system to execute daily life activities

Outcomes of the interventions	FOLLOW-UP	Outcomes at follow up	Grade
During the treatment phase, the DSIT group more consistently made diary entries, reported less memory problems, and made more positive ratings associated with treatment efficacy	NO		Included in meta analysis
The notebook training group reported significantly fewer observed EMFs, no significantly changes for the laboratory-based measures	6 mo after notebook implementation	The between group difference in EMFs was no longer significant at follow-up	D
81% were significantly more successful with the pager than they had been in the baseline phase, 6% became worse with the pager and 3% had identical performances	2 weeks after pager withdrawal	When the pager was returned subjects dropped back slightly but were still statistically significantly better than during the baseline (67.23%)	A
More than 80% of those who completed the 16 week trial were significantly more successful in carrying out everyday activities when using the pager in comparison with the baseline period	7 weeks after pager withdrawal	significant improvement (73% success rate) was maintained	A

showed just a trend toward a significant amelioration,[84] or the reported outcome measures were attitude ratings or numbers of entries made in the appointment dairy, rather than the efficacious use of the memory aid.[74] In one study [59] the proposed intervention, an interactive web-based cueing system to provide guidance for a navigation task (case 1) and a complex sequential activity (case 2), was

not effective: in fact, both participants (2 TBI patients, one - case 2 - with signs of cognitive decline) showed just a modest improvement in independent performance after intervention withdrawal.

It is worth mentioning that in the majority of studies (77%) effectiveness was evaluated considering the proportion of target activities successfully performed using the aid. Most studies underscored the importance of measuring the functional impact of the external aid on daily life or on patients' subjective experience of memory functioning as measured through self-rating questionnaires.[78, 80, 84, 86, 88, 89]

When generalization and maintenance of effects were addressed (49% of studies), most evidences showed that patients continued to utilize the devices, even long after initial introduction.[60, 72, 75, 77, 79, 82, 85, 90] On the other hand, improved functioning in memory-related activities resulted to be strongly associated with memory aid implementation and independence in executing daily life activities declined after external aid was withdrawn.[65] Conversely, one study [56] reported a long term (11 months) retention of autobiographical events that were recorded and viewed through a wearable camera (*SenseCam*).

Eight studies assessed effectiveness six or more months after initial memory aid introduction (externally programmed aids;[56, 60, 77] self-managed aids [75, 79, 81, 82, 86]). All studies demonstrated maintenance of memory compensation through external aid use (a memory book;[77] a palmtop computer;[60] a wearable camera [56]). External aids effectively ameliorated patients' quality of life and their independent functioning,[77] increasing clients' confidence [79] and reducing everyday memory failures [81] and/or repetitive questioning,[81] as reported by caregivers.[86] Apart from one class I+ study,[79] the considered studies were case reports (class III) and provided evidences that met the criteria for a practice option.

As for treatment duration or frequency, it is quite difficult to evaluate the effect of such variable on memory aids efficacious use, as total length of therapy and intensity spanned a wide range in the reviewed studies.

Finally, considering clients' satisfaction, external memory aids were, in general, positively rated by users and deemed as effective in improving independence, minimizing everyday memory failures,[79] facilitating vocational reintegration,[78] increasing self-esteem [66, 71, 79] and reducing anxiety [59] or stress.[56, 83] Care-givers as well, often participating in the treatments as trainers and/or supervisors, evaluated positively the use of external memory aids.[56, 63, 65, 69, 70]

Recommendations

As stated before, some methodological concerns may limit the generalization of the reviewed studies. For example, treatment providers were rarely blinded to the treatment-group assignment, while blinding to outcome evaluators was imposed in only two studies.[57, 79] Moreover, in 60% of studies only descriptive and qualitative statistics were reported as to illustrate improvements associated with memory aid implementation. In the remaining 40% of evidences (13 studies) conclusions can be extended beyond the immediate data, since inferential statistics were used; in contrast, the alpha level is very conservative (<0.001) only in a limited proportion of studies (7).

The NeuroPage studies by Wilson *et al.*[63, 64] were the only class I++ studies proving the efficacy of an externally programmed pager system in a large number of stable patients with memory and/or planning/organizational problems. Participants were significantly more successful in carrying out everyday activities when using the pager, but also when the device was returned; this observation suggests that external prompting resulted in establishing the desired behaviour. Based on the current evidence, the committee judged the use of NeuroPage as effective (with a level A of evidence) in patients with not progressive neurological diseases.

Some class III evidences (two case series and one single case) demonstrated that externally managed assistive devices, such as a portable voice organizer or mobile phones, can be considered as effective (with a level D of evidence) also in patients with severe memory impairments as a consequence of neurodegenerative diseases (*e.g.*, AD patients). Memory books or planners (either paper and pencil or electronic) can be considered as effective in compensating memory problems in patients with neurological stable diseases (with a level B of evidence)

Finally, even if a limited proportion of studies evaluated long term outcomes, self-managed memory aids were effective (with a level C of evidence) in compensating memory failures months after aid implementation.

Domain specific learning strategies

Interventions directed at the acquisition of specific knowledge, relevant to a certain domain, a particular situation or class of problems (domain-specific knowledge), are essentially aimed at teaching amnesic patients relevant information and/or skills to ultimately improve functioning in everyday life activities. These interventions are based on the observation that subjects affected by severe memory impairments can acquire a variety of motor, cognitive and perceptual skills, although they may have little or no recollection of the learning episode.[1, 91, 92] Such ability to attain non-declarative forms of knowledge allows amnesic patients to acquire important information for daily needs, like names of people or skills relevant in their present situation.

The key notion behind domain specific learning strategies is that learning is more efficient if participants are prevented from making errors (errorless learning, EL), since the act of producing an error for a certain stimulus can strengthen the incorrect association, while patients cannot recollect the learning experience to self-correct.

When the EL approach is applied to a therapy/remediation program, the task is manipulated so that the subject is unlikely to make mistakes, avoiding the typical situation in which patients' errors are corrected by the therapist. EL, therefore, contrasts with methods in which guessing is encouraged, based on the assumption that effortful retrieval will lead to better performance.[93] EL clinical application entails two different trainings methods: the error elimination condition, in which the task is so easy that errors are very unlikely, and the error reduction condition,[94] in which errors are progressively reduced by increasing retrieval cues or by gradually expanding the delay before recall is required.

Training techniques based on the error reduction approach are the method of vanishing cues, (MVC) which provides partial information for target responses, gradually withdrawn across learning trials, the hierarchical cues method, in which different types of retrieval cues (similar to, conceptually contiguous to, or associated in some way with the target information) are varied in order to find the most effective, and the spaced retrieval training, where the interval between recall opportunities is systematically lengthened until the client demonstrates recall of information in everyday situations.

In the present guidelines the committee reviewed a total of 31 evidences on the effectiveness of domain specific learning strategies: in eight studies the training was performed in the error elimination condition and the EL approach directly compared to effortful or trail and error learning; 12 studies addressed efficacy of the vanishing cues method, and 12 evaluated the spaced retrieval training, explicitly compared to the hierarchical cues method in one study. Results will be presented separately for each technique and focussed on the comparison between the error elimination and the error reduction condition in order to draw conclusions on the potential superiority of one method over the other.

ERRORLESS LEARNING VERSUS EFFORTFUL OR TRIAL AND ERROR LEARNING

The errorless approach capitalizes on amnesic patients' preserved implicit memory abilities and on the "effortless" retrieval of new information by means of the association between a cue (the prompt question) and the target response (either declarative or procedural). In the errorless condition the response (*e.g., "You have to look at your calendar*") is given by the clinician immediately after the prompt question ("*How can you find out what to do today?*") that is later re-presented as a retrieval cue for successful information recall. Conversely, in the effortful (EF) or trail and error learning method (TEL), the target response, paired with a retrieval cue in any case, is given to the patient only if an error is produced.

Among the eight reviewed articles, four directly compared the EL approach to EF or TEL [33, 95-97] while the remaining evidences [98-102] evaluated EL efficacy compared to the effectiveness of domain specific learning techniques in which the error elimination condition was not fulfilled. Two studies [96, 97] found an advantage of EL techniques over TEL, and showed a positive effect on general memory abilities and improved face-name recall in TBI and demented patients. However, in both studies, patients were quite heterogeneous with respect to severity of memory impairment and improvements, measured through laboratory based tests [96] or limited to trained items [97] are not maintained at follow-up.[96]

Two other studies [33, 95] showed that EF and TEL were more effective, compared to EL, in improving face-name recall, events recollection and functional tasks acquisition. The study by Mount *et al.*,[95]

addressing a sample of acute stroke patients with and without explicit memory impairments, showed that while TEL and EL were similarly effective for teaching activities of daily living, TEL facilitated carry-over of acquisition in one out of two functional tasks. Moore *et al*.[33] evaluated the efficacy of teaching procedures, explicitly emphasising rehearsal and effortful recall, for face-name acquisition and events recollection in a sample of mild to moderate AD patients. Results showed improvements in task specific measures - which were sustained for one month after training completion - and slightly improved mood and behavior; in contrast, memory functioning and independence in memory related activities were rated as enhanced by patients' caregivers.

In general, the above-mentioned studies report inconsistent results regarding the advantage of EL techniques over EF and TEL. On the other hand, the four studies addressing the question whether EL or other domain specific learning strategies in the error reduction condition produced better memory performance, attested EL superiority over more effortful techniques. The quantitative meta-analysis performed by Kessel *et al*.[99] considered 11 evidences (for a total of 192 patients with memory impairments from different aetiologies, including psychiatric subjects and patients with bipolar mood disorder) and compared the errorless learning (eight studies, 168 patients) and the vanishing cues method (three studies, 24 patients). Three other class III studies [98, 100, 101] addressed mild to moderate patients with probable AD (for a total of 10 patients quite homogeneous with respect to general cognitive status and severity of memory impairments). The EL approach was proved to be more effective than the MVC in a large population of patients with memory disorders from different aetiologies, as the effect of the intervention was quite robust (0.87, N.=168, P<0.01) compared to the small and non significant size of the vanishing cues method effect (0.27 N.=24, P=ns); EL was also effective in mild to moderate demented patients, when compared to different domain specific learning strategies such as mnemonics, forward cueing or decreased cueing. Efficacy of the EL method extended beyond the trained skills, since probable AD patients showed a general cognitive improvement and functional stabilization,[98] and results were maintained at follow-up in two out of three studies.

Recommendations

In brief, considering immediate benefits after training completion, sufficient scientific evidence (one class I+, one class II++ and four class III studies) suggests the advantage of EL techniques over errorful (TEL and EF) and error reduction strategies (MVC, forward or decreased cueing) in acquiring domain specific knowledge relevant for daily life activities. Therefore, the error elimination approach was rated as effective (with a level B of evidence) in patients with memory impairments as a consequence of a stable or progressive neurological disease. Maintenance of the trained behavior was reported in several class III studies (level D of evidence) up to nine months after training completion, while the potential effect of the EL method in ameliorating daily life functioning was tested in just one study,[98] reporting a null result (level D of evidence).

In conclusion, the EL approach is likely to be effective in teaching domain specific information in a large population of patients, while its long term effectiveness and the generalization of results to daily functioning are unknown and require further researches.

Method of vanishing cues

Several studies hypothesized that repeated priming of responses might produce more durable memory representations, that might eventually support long-term retention of declarative knowledge.[102] Many researches using the word-stem completion paradigm, confirmed that amnesic patients are as likely as normal subjects to produce a previously exposed word to partial cues. Such an effect extends to complex knowledge within a specific domain (for example how to operate a microcomputer [103]) and memory impaired patients are apparently able, if provided with fragmented cues, to attain procedural and new semantic information of factual nature associated with a complex task. Even if the processes involved in the acquisition of new semantic memories through implicit means is not yet clear, it seems likely that factual information within a specific domain might be stored as a series of isolated stimulus-response bonds, subsequently chained backward. Indeed, the so acquired knowledge seems to be hyper specific since the information cannot be recalled if the definitional cues are altered or contexts

are changed or unconstrained, as patients' learning might have been differently represented and not well integrated with prior knowledge structures.[104]

Glisky *et al.*[102] adapted the priming paradigm to teach amnesic patients specific knowledge and devised the Method of Vanishing Cues (MVC) in which subjects are initially given as many letters cues as needed to complete the target word correctly and then provided with progressively weaker cues. Such training method constitutes an EL approach in the error reduction condition.

Overall, the 12 considered studies [102-113] reported a positive effect of MVC. Indeed, the training method was not differentially effective (compared to other mnemonic strategies such as the long term acquisition of face-name pairs in the spaced retrieval condition) in just two studies.[111, 112] In the considered studies, the training was aimed at: teaching patients semantic domain specific information,[110] procedural and semantic knowledge needed to operate on a computer,[102, 105, 106, 108] semantic information on people related to the patients [111-113] and procedural knowledge about the use of a palmtop computer.[113]

Considering types of patients, four studies addressed a mixed sample of neurological patients,[103, 104, 106, 110] four studied patients with amnesic disorders from different etiologies,[105, 107-109] two evaluated the effectiveness of MVC in subjects with memory impairments as a consequence of a TBI [102, 113] and one reported data from a single case affected by AD,[111] tested again three years after training completion.[112]

Evidences addressing a mixed sample of neurological patients (all class III studies) comprised subjects quite heterogeneous with respect to brain damage severity and degree of memory loss, with broad inclusion criteria (as general rule, the difference between the Intelligence Quotient and the Memory Quotient) and minimal exclusion criteria, while training effectiveness was measured considering only potential changes in the trained skills (three studies out of four) and generalization to transfer tasks evaluated in a limited proportion of studies (two out of three). Broad inclusion criteria can give a picture of specific training benefits in patients with different degrees of memory dysfunctions but also restrain the generalization of the reported results beyond the considered sample.

The four single-case studies considering amnesic patients with various degrees of verbal memory impairments usually reported descriptive statistics and evaluated training benefits on the trained tasks; however, maintenance of the acquisitions and generalization of results to transfer tasks was addressed in the majority of studies (three out of four). One case series and a single-case study on TBI patients included subjects on the basis of the mere presence of amnesia, with no exclusion criteria, and reported improvements in the trained task not generalized to transfer tasks, either after training completion [103] or at follow-up.[102] Finally, the single case study on an AD subject [111] showed a robust effect of the MVC in acquiring semantic information, which could be recalled even after nine months from training conclusion, but not at a three year follow-up,[112] due to the patient's cognitive decline.

Recommendations

Considering immediate benefits after training completion, fair scientific evidence (class III studies) demonstrates that the MVC is effective in acquiring domain specific knowledge, although the attained information can not be accessed in altered contexts such as transfer tasks.[103, 108] Thus, relative to post-treatment efficacy, the committee judged the MVC as potentially effective (with a level D of evidence) in learning specific knowledge, which can be eventually maintained over time (level D rating). As for the generalization of results in daily life activities, no scientific evidence supports the effectiveness of the MVC in acquiring information relevant for independent living, while only one class III study [107] (level D of evidence) reported acquisitions transfer over time in functional activities.

Spaced retrieval training

The spaced retrieval method (SR) is a learning technique aimed at achieving long-term retention of new learned information by systematically increasing the interval between correct recall of target items. Some authors referred to spaced retrieval as a shaping procedure applied to memory dysfunctions;[114-116] indeed, during training, the target behavior (long-term retention) is broken into sub-steps that are progressively more demanding (correct recollection after systematically lengthened intervals) until the patient demonstrates recall of information in everyday situations. The technique is thought to rely on non-declarative memory systems such as

procedural memory and capacity for stimulus-response conditioning and probably reinforced by the spacing effect. The latter is the positive effect on recall performance observed when practice is distributed rather than massed, which possibly engages very fundamental and largely automatic memory processes, rather than rehearsal strategies.[117]

In clinical practice, a prompt question is associated with the correct response and the interval between recall opportunities is lengthened (starting with an opening interval of 5 seconds, successively expanded to 10, 20, 40, 60 seconds, with extensions of 30 seconds after the 180 second interval, of 1 minute after the 360 second interval and so on) until the information may be accessed in unconstrained contexts. If the client fails to recall, the correct answer is given and the patient tested again at the interval in which he/she was last successful. The technique is a domain specific learning strategy in the error reduction condition.

The entirety of the reviewed studies [118-129] demonstrate SR effectiveness in learning and retention of target information and its superiority over uniformly spaced practice [126] and the hierarchical cues method.[129] Among the 12 considered studies, eight addressed patients with AD,[118-125, 129] two studied a mixed sample of neurological patients [118-126] and two were performed on subjects affected by memory disorders as a consequence of a TBI.[127, 128] The SR training was aimed at: teaching the association between an auditory cue and a motor response (four studies), retaining semantic information (three articles), improving functional activities (three studies), learning how to use an e-mail service (one study), recalling and playing a new song on the violin (one study).

The studies addressing AD patients (six case series and two single cases) were performed on quite homogeneous samples of subjects respect to severity of memory disorder, while exclusion criteria were not reported in the majority of studies. Sample size was usually restricted, with a mean of 5.1 patients per study, except for the article by Malone *et al.*[129] which investigated SR effectiveness in 66 AD patients. Generally, only descriptive statistics are reported and the outcome typically consists in performance measures (correct recall of the target items). A follow-up was performed in only two studies and generalization of results limited to trained tasks.

The two studies involving a mixed sample of neurological patients (class III) included a small number of non-homogeneous subjects with organic memory disorders, selected without specific exclusion criteria. Reported statistics were descriptive in one study and inferential in the other and results showed performance improvements limited to the trained tasks with no follow-up in both evidences.

Finally, the two studies performed on TBI patients (class III) evaluated SR efficacy (expressed as spaced-retrieval goals maintenance) in fair homogeneous samples of subjects, selected on the basis of inclusion and exclusion criteria quite restrictive in one study, and more broad in the other. Even if only descriptive statistics are reported, training effectiveness was tested on non-trained memory goals and maintenance evaluated one month after training completion using transfer tasks.

Recommendations

Several studies demonstrated that the SR training is potentially effective in teaching patients with memory disorders from different aetiologies, specific information. Since the evidence for immediate benefits after training completion comes essentially from class III studies and only one class II+ article,[129] the committee assigned a grade D recommendation to SR. Only one class II+ study [129] (grade D recommendation) addressed maintenance of results six months after training suspension, demonstrating that SR was more effective, compared to the hierarchical cues method, for long-term acquisition. Thus, the evidence needs to be replicated before SR can be considered a specific technique for long-term retention of new information. None of the reviewed studies evaluated SR efficacy in ameliorating patients' independency and effective functioning in meaningful contexts, therefore no evidences support a recommendation that SR be considered a practice option for reducing patients' disability in everyday life.

General recommendations for domain specific learning strategies

Overall, the efficacy of domain specific learning strategies was investigated in several studies addressing a total of 451 patients, allocated as follows: 284 trained with the EL approach, 42 with the MVC and 125 with the SR method.

Even if the above mentioned techniques significantly improved the performance of severe amnesic patients in specific tasks, their differential effectiveness is not supported, at present, by consistent and good quality scientific evidences. Specifically, the effectiveness of the EL methods in the error reduction condition (MVC and SR) has been tested so far only on small samples of patients, while both techniques did not produce significant and persisting improvements in contexts different from the experimental setting. Only the EL approach in the error elimination condition (validated through a grade B meta analysis) can be considered a practice guideline for people with acquired memory disorders as a consequence of a stable or progressive disease.

Conclusions

In the present guidelines we addressed the question of whether memory rehabilitation is effective, considering which types of patients would preferably benefit from specific interventions and taking into account different outcome measures. The reviewed studies generally support the practice of memory rehabilitation to improve memory performance in specific tasks, but lack sufficient data to demonstrate the effects of memory trainings on relevant functional outcomes.

Specifically, internal memory strategies, aimed to strengthen the acquisition of information into long-term memory, proved to be effective at increasing memory performance in trained tasks and are therefore recommended as a practice guideline for subjects with memory impairments as a consequence of a stable cerebral disease. Conversely, such methods are unlikely to be beneficial for patients with a progressive cerebral disease, as high quality evidences reported inconsistent effects on performance in specific tasks, or null results on non-trained activities and/or memory functioning. Finally, the effectiveness of internal memory strategies in determining significant changes in daily life memory functioning is unknown, since good quality studies provided inconsistent evidence of potential benefits in everyday activities.

The effectiveness of other compensatory strategies, such as external memory aids, varies according to types of aids and types of patients. Externally directed and programmed aids, such as portable pagers, can be recommended, based on two high quality evidences, as a practice standard for patients with no progressive neurological diseases. Particularly, the NeuroPage by Wilson and colleagues [63, 64] was effective in a large number of stable patients with memory and/or planning/organizational problems, in improving daily life functioning even after the device was returned. On the other hand, the effectiveness of externally programmed memory aids in patients with severe memory impairments as a consequence of neurodegenerative diseases (*e.g.*, AD patients) is supported by little scientific evidence. Self-managed external aids, entailing clients' participation and motivation for independent use, can be recommended as a practice guideline for patients with not progressive disease, while little scientific evidence suggests their effectiveness in compensating memory failures months after aid implementation.

Finally, the differential effectiveness of domain specific learning strategies in determining long-term acquisition of information relevant for daily needs is not supported, at present, by consistent and good quality scientific evidences. Only the EL approach, in the error elimination condition, can be recommended as a practice guideline for people with acquired memory disorders as a consequence of a stable or progressive disease.

In conclusion, future researches on memory rehabilitation should evaluate the effectiveness of well-defined memory rehabilitation programs not only at the impairment level, but also considering the effects of specific trainings on patients' social and vocational reinstatement and functional independence. Large scale RCTs should be conducted in order to replicate interventions that have already demonstrated effectiveness, as to extend previous results to broader samples of patients. Future studies should also aim at a better clinical and pathological definition of the patients included in the trials since the degree and nature of persistent memory deficits vary among people with brain injury, while trainings efficacy might depend on the severity of memory impairments[2]. There is also a clear need for good quality studies evaluating factors that contribute to maintenance of results over time, since little scientific evidence support the effectiveness of memory rehabilitation in producing significant and persisting improvements.

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