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Improving Memory in Patients with Epilepsy: Considering the Impact of Anti-Epileptic Drugs, Low Mood and/or Surgery on Memory Training Program Outcomes

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Abstract

Aim: To determine whether epilepsy treatments (number of antiepileptic drugs and surgical history) and/or depressed mood would influence the ability to benefit from memory training of outpatients with epilepsy who participated in a group-based, six-week, Memory Training Program. We also investigated the relationships between symptoms of depression, performance on a new objective measure of association memory and subjective memory ratings.

Method: Forty-seven adults with epilepsy and memory complaints completed the training with pre- and post-training assessments. Scores included (1) number correct on a new Identity Association Memory Test; (2) subjective self-rating of memory function; (3) number of reported strategies used for memory support. Two way (Group x Time) Repeated Measures Analyses of Variance were used to look for differences on the association-learning task. Pearson correlation analyses were used to examine the relationships between number of anti-epileptic drugs, subjective memory ratings, and presence of depression and objective memory scores.

Results: Repeated measures ANOVAs demonstrated that training resulted in significant improvements of the total score on the Association Memory Test regardless of number of antiepileptic drugs ($F=6.5, p=.01$), surgical status ($F=6, p=.02$) or mood ($F=7.4, p<.01$). Although the depressed group rated their memory as lower overall (Group main effect $F=4.8, p<.05$), both groups showed similar improvements as a result of the training, (Test-time main effect: $F=8.0, p<.01$). Although depression level was correlated with lower self-ratings of memory (pre: $r=-.3$, $p=.02$; post: $r=-.3$, $p=.05$), depression scores were not correlated with objective memory performance at either test time.

Conclusion: This study contributes to evidence that memory rehabilitation benefits people with epilepsy. We found significant pre- to post-training improvements on subjective as well as objective measures of association learning. Furthermore, we found that the gains on all three outcome measures were unaffected by higher levels of antiepileptic drugs, previous surgical treatment or depressed mood.

Keywords: Antiepileptic drugs; Depression; Epilepsy; Memory; Neuropsychology; Rehabilitation

Abbreviations: AEDs: Antiepileptic Drugs; ATL: Anterior Temporal Lobectomy; ANOVA: Analysis of Variance; DASS: Depression, Anxiety, Stress Scales; PWE: People with epilepsy; RPA-IAM: Royal Prince Alfred-Identity Association Memory Test; SEM: Standard Error of the Mean

Introduction

Multiple cognitive disturbances are associated with epilepsy, including impairments in attention, concentration, psychomotor speed, language, executive functioning and memory [1]. Possibly as a result of a combination of these disorders, people with epilepsy (PWE) often complain about their everyday memory [2,3] and memory deficits are frequently detected on formal neuropsychological evaluation [4-7]. Many people with epilepsy ask for help to improve their memory, but until recently, few studies have collected empirical data to guide such remediation. In 2011, Radford et al., showed that PWE who complain of everyday memory problems benefit from a six-week, group-based, manualised, strategy training course [8,9]. More specifically, whereas patients showed no changes over repeated *baseline* assessments conducted 3 months apart, they showed significant pre- to post, training-related gains on word-list learning, word list delayed recall, self-report everyday prospective memory and strategy use. In the present study, we sought to re-evaluate this memory training program in additional groups of PWE and to determine its impact on association learning with a new outcome measure. We were particularly interested in determining whether specific baseline factors might have an impact on training outcomes.

PWE often attribute everyday cognitive problems to side-effects of anti-epileptic drugs (AEDs) [10]. Numerous studies have investigated the cognitive effects of AEDs and extensive reviews are available [11,12]. For the most part, neuropsychological testing has tended to find that the cognitive effects of AEDs involve reductions in attentional abilities and psychomotor processing speed [12]. For those people taking multiple AEDs (polytherapy) the association with cognitive impairment, and memory problems in particular, is even more prevalent [13]. However, the direct influence polytherapy (as opposed to monotherapy) may have on the ability to benefit from memory rehabilitation has seldom been investigated. Radford et al. [9] found that the number of prescribed AEDs correlated negatively with gains in memory post-training on only one measure out of eight, a word-list learning task.

Similarly, the extent to which post-surgical patients may benefit

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from memory rehabilitation has received limited attention. Temporal lobe epilepsy surgery is the most successful surgery for refractory epilepsy, but it can sometimes result in increased memory difficulties [14,15]. It is well established that patients undergoing left anterior temporal lobectomy (ATL) are likely to have significant memory deficits before surgery, with postoperative worsening of both verbal learning and memory. Deficits after right ATL are less consistently identified, but up to 25% may show permanent visual-spatial memory deficits [1]. One study of group-based memory training for patients who had recently undergone selective ATL was conducted by Helmstaedter and colleagues [16]. They found significant improvement in verbal, but not visual, anterograde memory following an intensive (month-long), multidisciplinary rehabilitation program, which incorporated five 1-hour memory group sessions, in comparison to no rehabilitation. These results need to be interpreted with care, however, as there may have been systematic bias. Specifically, outcomes for patients from one epilepsy centre that offered rehabilitation were compared to patients from another that did not. It is also not known whether rehabilitation would have benefited those without surgery to the same (or possibly to a greater) extent.

Depression can also impact negatively on aspects of cognition, including memory [13,14, 17,18] and depression is now recognized as the most common psychiatric condition to be experienced by patients with epilepsy [19]. Rates of depression in epilepsy are very high when compared to both the general population and other chronic illnesses [20,21], with recent data suggesting that between 25-48% of epilepsy sufferers met criteria for a depressive disorder [22,23]. One might expect depressed patients to show fewer benefits from memory training as well. However, in a previous study of PWE, Radford et al. [8] found that higher symptoms of depression suppressed training-related gains on only a few of their outcome measures.

Interestingly, whereas the correlation between neuropsychological test performance and subjective memory complaints in epilepsy patients tends to be weak, subjective reports of memory tend to vary with level of depression rather than objectively measured memory abilities [24,25]. Consistent with (and extending) this pattern, Radford et al. [9,26] found that for neurological patients (and specifically for those with epilepsy) lower levels of depression at baseline were associated with greater gains after memory strategy training on self-report memory inventories. In contrast, mood was not found to influence training outcome on objective measures, such as anterograde word-list memory and prospective memory.

In this study we sought to determine whether two epilepsy treatment factors (i.e., number of AEDs and surgical history) and/or depressed mood would influence the ability to benefit from memory training in outpatients with epilepsy who participated in the Radford et al. [8] group-based Memory Training Program. In addition we investigated the relationships between symptoms of depression, performance on a new objective measure of association memory and subjective memory ratings.

Method

Participants

Participants in the memory training course were mainly patients who had been referred for assessment to one of three Neuropsychology Units at hospital-based epilepsy units in Sydney, Australia. There were also a small number of self-referrals coming from community epilepsy support groups. The course offered to patients who met the selection criteria, was voluntary and was provided free of charge. Selection criteria were (1) history of seizure disorder, (2) memory complaints, (3) English as their language of choice, (4) proximity to the hospital where the course was offered and (5) age between 18 and 70. Patients with a history of psychiatric (other than mood) disorders and those with progressive lesions were excluded. Only data from participants who attended at least 4 of the 6 memory training sessions were included. Forty seven (25 men) met all the criteria. Of these, 26 were receiving polytherapy; 15 had undergone cortical resection (14 ATL) for management of seizures; 27 were classified as depressed according to their baseline score on the Depression, Anxiety and Stress Scales (DASS-21) [27].

Materials

Measures:

Royal Prince Alfred-Identity Association Memory Test (RPA-IAM)

A new test of face-name-profession association learning was developed for this study. Participants initially completed an example trial where they had 1 minute to study (and try to remember) 2 faces presented on a single page, accompanied by names and professions (Figure 1). Immediately after collecting the to-be-learned stimuli, each participant was given a new page with a total of 4 faces (2 target, 2 novel). They were instructed to indicate which faces they had seen before and to fill in the names and professions. Following this example, in the actual test, participants were given 2 minutes to study 6 faces presented on a single page, accompanied by names and professions. Immediately after collecting the stimulus sheet, each subject was given 2 pages with a total of 12 faces (6 target, 6 novel). They were instructed to indicate which faces they had seen before and to write each name and profession that they could remember. The recall score comprised the number of correct individual elements (face, first name, surname, profession) plus associations (face-name, face-profession, name-profession) (max=42).

Two alternative versions of the test with different face-name-professions were developed for randomised use, pre- and post-training. These two versions were piloted on a group of 20 healthy young adults who completed both versions of the test in counterbalanced order with a half an hour interval in between. No significant difference in mean recall scores were found between the two versions (V1=37.3, V2=38.2; t(1,19)=-1.217, p=.238).

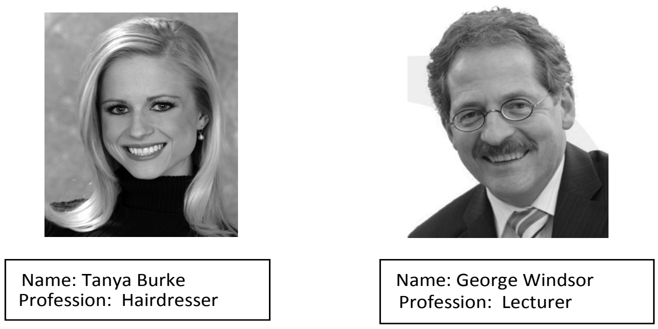

Figure 1: Practice trial for RPA-IAM.

Strategy Use

On a single piece of paper, subjects were asked to write down all of the internal (mental) strategies and secondly, all of the external

I would rate my memory as

1 Very Poor	2	3 Average	4	5 Very Good

Figure 2: Overall self-rating of memory function scale.

memory aids that they used to support their memory. The total number of different techniques used was taken as the score.

Overall self-rating of memory function

Using the simple graphic shown in Figure 2, subjects provided a subjective self-rating of their overall memory function. Scores ranged from 1 being very poor to 5 being very good.

DASS 21-item version

From the Depression Anxiety and Stress Scales [DASS; 27] the score from the depression scale was obtained. This questionnaire requires the subject to respond to statements (e.g. I felt downhearted and blue.) by circling a number to indicate how much the statement applied to them over the past week (0= never, 1= sometimes, 2= often, 3= almost always). The responses from the seven items pertaining to the Depression Scale (DASS-D) were multiplied by two (to convert to the original DASS 42-item version scores). Higher scores were indicative of more frequent depressive symptoms. Based on the descriptions provided in the manual, scores above 9 were classified as indicative of depression for this study.

Memory training program: The memory intervention involved six weekly two-hour strategy training sessions (fully described in Radford et al., [8]). Each session involved education about memory and life-style factors influencing memory function and training in the use of compensatory strategies (both internal/mental strategies and external memory aids). Group exercises and discussion were used and homework tasks were set to encourage practice and generalization of strategy use between sessions. Groups of 5-10 participants were run by facilitators in different hospital settings using the memory training manual.

Procedure

The effects of training were evaluated with two assessments, conducted at the beginning of the first and at the end of the last session of the training program. The measures described above were administered on both occasions. In addition, the following demographic information was gathered in the first session on a questionnaire: age, educational level, history of neurosurgery and current number of AEDs.

Statistical analyses

All data were analysed using SPSS (version 21.0). α levels for all analyses were set at $\alpha < 0.05$ and Cohen's d effect sizes are shown. One way analyses of variance were used to compare groups on the bases of age and education level. Two-way analyses of variance (ANOVAs) (Group x Test-time) examined the impact of the variables under consideration on each measure. Pearson correlation tests were used to look for relationships between the number of AEDs and the change scores pre- to post-training and for relationships between the baseline level of depression, baseline memory scores and the change scores pre- to post-training.

Results

When divided on the basis of medication level, surgery status and depression level, the groups all proved to be well matched, there being no significant differences in age or educational level (Table 1).

	Mean Age (yrs) (SD)	Mean Education (yrs) (SD)
AEDs		
Polytherapy n=26	45 (11.6)	13 (2.7)
Monotherapy n=15	49 (17.2)	12 (2.4)
Surgical status		
Operated n=15	44 (11.8)	11 (2.1)
Unoperated n=31	48 (14.8)	13 (2.8)
Mood		
Depressed n=27	45 (11.5)	12 (1.9)
Not Depressed n=20	48 (16.8)	13 (3.2)

Table 1: Group demographics.

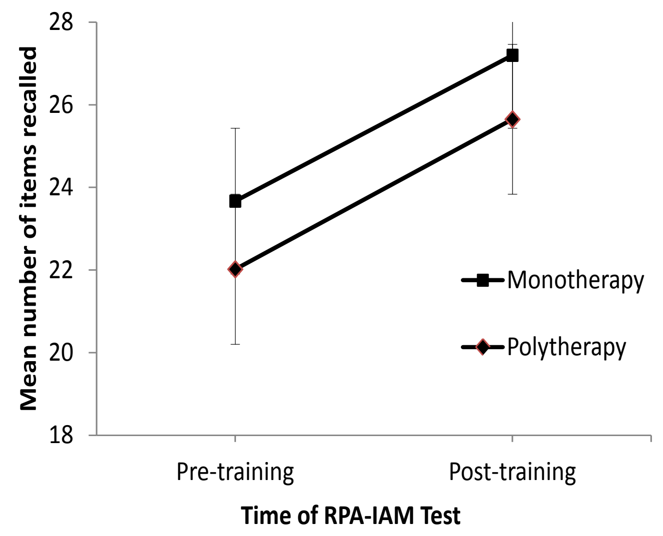

Figure 3: Objective memory performance: Represents improvements in number of items recalled on the new association memory test, the RPA-IAM, from the pre- to post-training irrespective of patients' AED group. Error bars represent the SEM.

Impact of AEDs

Two-way Group x Test-time repeated measures ANOVA was used to look for differences between those on mono versus polytherapy (the 6 patients taking no AEDs were dropped from these analyses). There was no interaction or main effect of Group. However, a significant effect of Test-time was found ($F(1,39)=6.5$, $p=.01$; $d=.35$); there was a mean improvement in the total score on the RPA-IAM test from pre-training to post-training testing (Figure 3). Furthermore, there was no significant correlation ($r(1,41)=-.001$, $p=1$) between the number of AEDs and the change score (i.e. the difference between the number of correct items recalled pre- and post-training).

Strategy use was examined using two way repeated measures ANOVA. Significant effects were found only for Test-time (no main effect of Group or interaction); the number of strategies reported increased from pre-training to post-training (Figure 4) ($F(1,39)=36.4$, $p<.001$; $d=1.16$). Furthermore, there was no significant correlation

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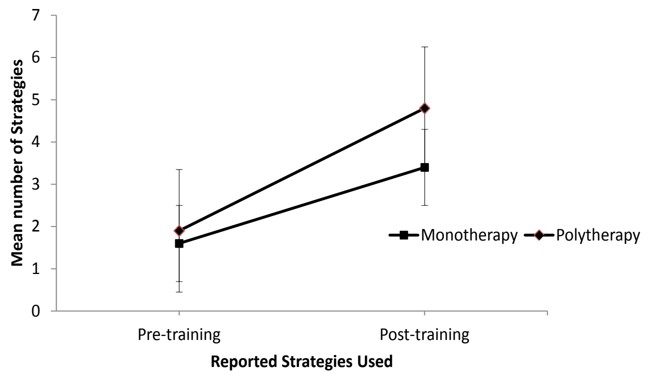

Figure 4: Reported strategy use: Mean number of reported strategies increased from pre-training assessment to post-training assessment regardless of the patients' AED group membership. Error bars represent the SEM.

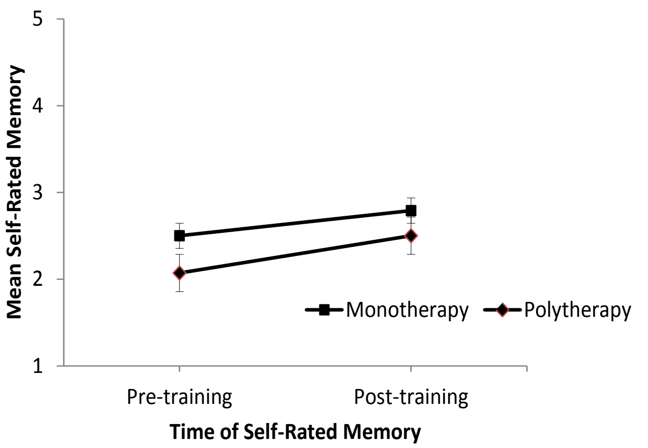

Figure 5: Subjective self-rated memory function: Higher scores indicate better overall function. Patients' overall self-ratings improved following training regardless of their AED group. Error bars represent the SEM.

(r(1,41)=-.2, p=.2) between the number of AEDs and the change in strategies used score (i.e., the difference between the number of strategies participants reported using pre- and post-training).

In the case of participant self-rated memory, again there was no significant interaction and no main effect of Group found when participants were divided according to AED mono- versus polytherapy. However, the main effect of Test-time reached significance (F(1,34)=6.0, p=.02, d=.42); there being an improvement in participants' self-rated memory performance following training (Figure 5). There were no significant correlations (r(1,36)=.08, p=.6) between the number of AEDs prescribed at baseline and the change in self-rated memory after training.

Impact of surgical resection

When participants were divided on the basis of surgical treatment (resection or no resection), Group x Test-time repeated measures ANOVA revealed no interaction or Group main effect on the RPA-IAM. A significant effect was found for Test-time, (F(1,44)=6,p=.02, d=.37) with participants recalling a greater number of items on the RPA-IAM test at post-training testing (Figure 6) regardless of their surgical treatment status.

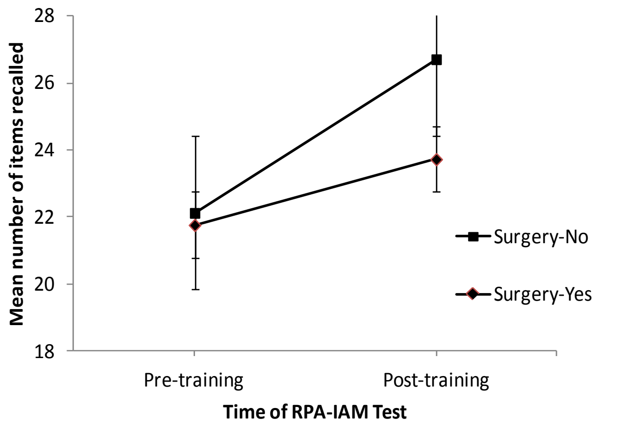

Figure 6: Objective memory performance: Increase in the mean number of items recalled on the new association memory test, the RPA-IAM, from pre- to post-training in patients with or without surgical intervention for the treatment of epilepsy. Error bars represent SEM.

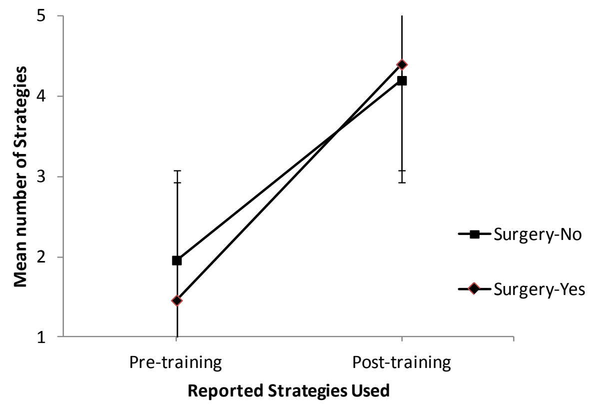

Figure 7: Reported strategy use: Mean number of reported strategies increased from pre- to post-training in patients with or without surgical treatment for the control of epilepsy. Error bars represent SEM.

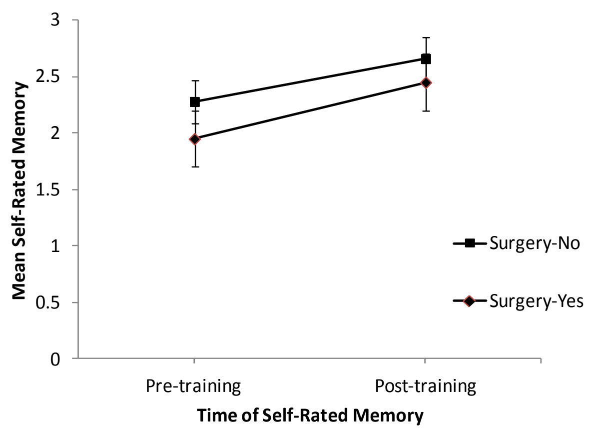

Figure 8: Subjective self-rated memory function: Higher scores indicate better overall function. Patients' overall self-ratings improved following training regardless of their surgical status, (resection or no resection for treatment of epilepsy). Error bars represent SEM.

Strategy use was also examined using two way repeated measures ANOVA. Again, this demonstrated no Interaction or Group effect for patients divided on the basis of surgical treatment. A significant effect was found for Test-time ($F(1,44)=45.4, p<.001$, d=1.17), with an increase in the number of strategies reported as used by participants pre-training to post-training (Figure 7).

When we examined the operated versus unoperated participants' perceptions of their memory, again there was no significant interaction found between Group and Test-time and no main effect of Group, but the effect of Test-time reached significance ($F(1,38)=7.7$, p=<.01, d=.49) (Figure 8).

Impact of baseline symptoms of depression

The influence of depression on face-name-profession association memory was examined using two way repeated measures ANOVA. There was no significant interaction or main effect of Group. There was a main effect of Test-time ($F(1,44)=7.4, p<.01$, d=.37); both the depressed and non-depressed groups showed significant and similar pre- to post-training gains on the RPA-IAM test (Figure 9). Consistent with the insignificant interaction result, no correlation ($r(1,47)=-.2$, p=.2) was found between the baseline DASS-depression score and RPA-IAM change scores (i.e., the difference between the total score pre- and post-training).

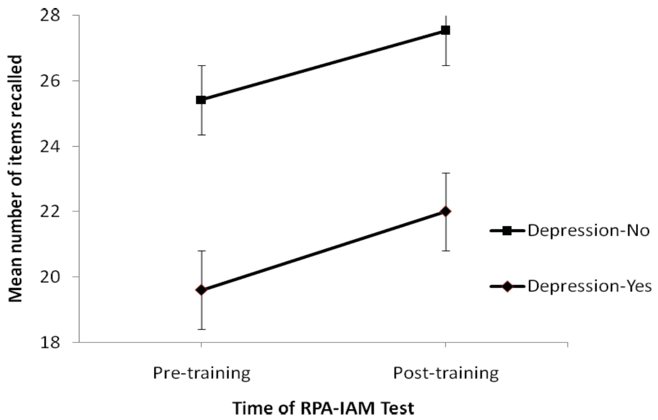

Figure 9: Objective memory performance: Increase in the mean number of items recalled on the new association memory tests, the RPA-IAM, from pre- to post-training in patients with or without depression. Error bars represent SEM.

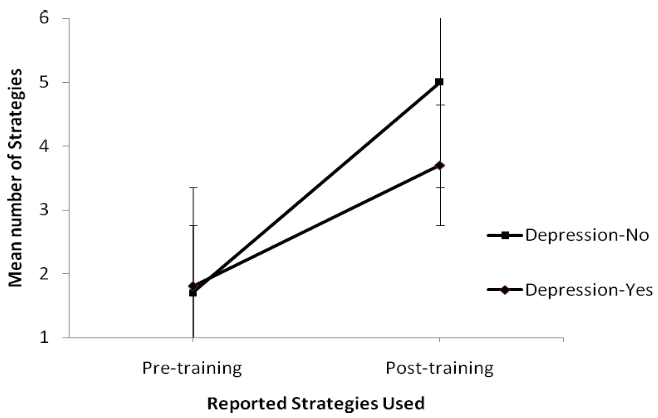

Figure 10: Reported strategy use: Mean number of reported strategies increased from pre- to post-training for all patients regardless of their depression status (depression or no depression). Error bars represent SEM.

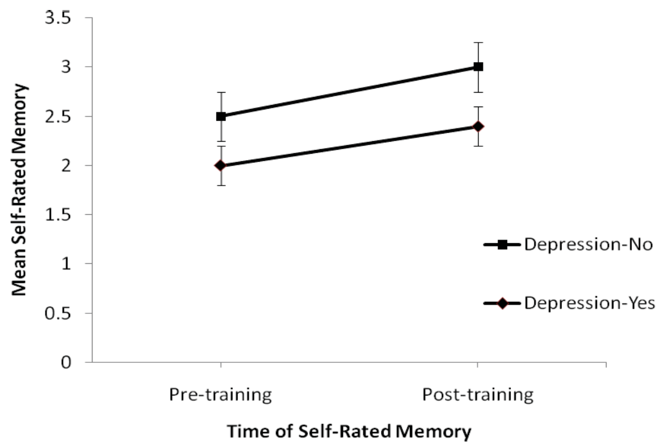

Figure 11: Subjective self-rated memory function: Higher scores indicate better overall function. Patients' overall self-ratings improved following training regardless of their depression status (depression or no depression). Error bars represent SEM.

Effects of depression on gains in strategy use were also examined using two way repeated measures ANOVA, which demonstrated no Interaction or Group effect. A significant effect was found for Test-time, ($f=1,44)=54.2$, $p < .001$, d=1.17) with an increase in score occurring after training, (Figure 10). No significant correlation was found between baseline depression status and change in strategy use ($r(1,46)=-.2$, p=.2).

The depressed group rated their memory as lower overall (main effect of Group: $F(1,38)=4.8, p<.05$) , but both groups showed similar improvements as a result of the training, (Test-time main effect: $F(1,38)=8.0, p<.01$, d=.49) with the interaction failing to reach significance (Figure 11). No significant correlation ($r(1,40)=.1$, p=.5) was found between pre-training raw DASS-depression score and the changes in the self-rating of their memory functioning pre- to post-training.

At both testing times depression level was correlated with lower self-ratings of memory (pre: $r(1,46) =-.3$, p=.02; post: $r(1,40)=-.3$, p=.05). However, depression scores were not correlated with objective memory performance (RPA-IAM) at either test time (Pre: $r(1,47)=-.2$,p=.1; post: $r(1,46)=-.07$,p=.6).

Discussion

The present study contributes to the growing body of evidence [9,16,28] that memory rehabilitation benefits PWE. We have extended previous results demonstrating the effectiveness of Radford et al's. [8] Memory Training Program using new outcome measures. We found significant pre- to post-training improvements on subjective measures as well as a new objective measure of association learning. In addition, we found that the gains on all three outcome measures were unaffected by higher levels of AEDs, previous surgical treatment or depressed mood.

It is interesting that we found training related gains on the RPA-IAM, given its visual content. Some other rehabilitation studies have found gains in verbal memory but not visual [16,29]. It may be that the RPA-IAM was more sensitive to training gains because it involved both visual and verbal information or because it involved association learning. Determining which of these aspects was more important to its success as an outcome measure depends on further research. In either case, it is clear that improving face-name association memory would be very helpful in everyday life. It should be noted that although the memory training program did teach some strategies for associating names and faces and also for recalling names, the type of stimuli used in the RPA-IAM were never used in the training. Hence, the subjects learned strategies rather than how to perform tests in the program and gains on this measure are likely to reflect generalisation of what they have learned.

The benefits derived from the six week training program were not influenced by the number of AEDs people were prescribed or by the history of cortical resection for the control of seizures, which is similar to previous findings [7]. Therefore neither polytherapy nor resection represents a barrier to benefiting from training in cognitive rehabilitation strategies or at least in specific memory rehabilitation strategies. Furthermore, the presence of depression did not influence the extent of improvement seen after the training on either objective or subjective memory measures.

Although our study indicated that low mood did not prevent PWE benefitting from a memory strategy training program, we also found that the participants' self-reports of memory problems were more highly correlated with mood than with their objective memory performance. This has been reported before both in epilepsy research [9,24] and also in non-epilepsy populations [30].Thus the trends in our data are similar to previous research and emphasise that depression is an important factor for understanding memory complaints in people with epilepsy [5,9,24].

We recognise that our current study had some limitations. Gains from training were based on test-retest comparisons and this raises the possibility of practice effects. We note that Radford et al. [8] found no practice effects when similar patients were re-tested (with no intervening training) in her original study, but in that case the interval was three months (rather than six weeks) and different measures were considered. In the present study, effort was made to reduce practice effects by using alternative versions of the RPA-IAM before and after training. In addition, whether or not the gains were in part due to practice effects, we would point out that our main aim (to investigate whether baseline factors influenced outcome) is not compromised by this possibility. There are a number of other epilepsy variables (e.g., seizure frequency, length of time since onset or epilepsy syndrome) that may influence outcome and were not considered in the current study. These factors have been covered in previous research [9,16,28]. Furthermore, our numbers were relatively small with larger groups it may have been possible to examine the effects on cognition of specific anti-epileptic medications. Finally, we had only one post-training evaluation, which was carried out immediately following the training program, which does not permit evaluation of any lasting benefit of this course. Again this has been addressed in previous studies using the same memory strategy training program and benefits have been shown to persist for at least three months post–training [9,26,29].

In conclusion this study yielded evidence that people with epilepsy show benefits, on objective memory measures, after undergoing a six-week group-based memory training program. Furthermore these benefits are irrespective of their AED level, cortical resection status or self-reported depression symptoms.

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