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Distinct memory impairments following electroconvulsive therapy and imipramine

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SYNOPSIS Memory functioning was assessed in 26 unmedicated patients with major depressive disorder (DSM-III) who were then administered either bilateral electroconvulsive therapy (ECT) ($N = 16$) or imipramine 200 mg per day ($N = 10$). The subjects were retested following seven ECT administrations or 21 days of imipramine treatment respectively. The retrograde memory tasks included recall of public and autobiographic events. The anterograde memory tasks included an immediate memory task, a verbal paired-associates recall task, and a non-verbal figure reproduction task. Depression was significantly improved in the ECT-treated subjects but not in those administered imipramine. Both ECT- and imipramine-treated patients showed a deficit in recent anterograde memory relative to their pretreatment performance, but no deficit in immediate memory. ECT-treated patients also had a significant and well-characterized impairment in retrograde remote memory. By contrast, imipramine-treated patients did not show a retrograde memory impairment which could be explained by treatment. The results suggest qualitatively different memory deficits produced by ECT and imipramine.

INTRODUCTION

Although electroconvulsive therapy (ECT) is widely recognized as an intervention of choice in severely depressed patients (Frith *et al.* 1983; Squire, 1984, 1986*a*; Squire and Slater, 1983; Weiner, 1984), adverse effects on memory remain an important limitation of the treatment. The pattern of anterograde and retrograde memory impairments induced by ECT has been well characterized in an extensive series of studies (Chronholm & Ottosson, 1961; Cohen & Squire, 1981; Daniel & Crowitz, 1983; Frith *et al.* 1983; Jackson, 1978; Steif *et al.* 1986; Squire, 1975, 1977, 1984, 1986*a*: Squire & Chace, 1975; Squire & Slater, 1978, 1983; Squire *et al.* 1975, 1981; Weiner, 1984).

Whereas the deficits caused by ECT are well characterized, the effects of tricyclic antidepressants on memory have not been comprehensively evaluated. Some studies report improved mnemonic and cognitive performance (Glass *et al.* 1981; Staton *et al.* 1981) following treatment with these agents, while others show no change or an impairment of functioning (Legg & Stiff, 1976; McNair *et al.* 1984; Moskovitz & Burns, 1986). The disparate findings may be better understood if various intersecting influences are taken into consideration. Since most tricyclic antidepressants have anticholinergic effects which impair memory functions (Crow & Grove-White, 1973; Safer & Allen, 1970; Snyder & Yamahura, 1977), some degree of impairment might logically be suspected on this basis. On the other hand, the untreated depressive state is itself associated with memory impairment (Sternberg & Jarvik, 1976) and lifting of depressive symptoms would be suspected to alleviate these state-related deficits. In order to investigate the net effect of tricyclic antidepressants on memory, it is therefore necessary to control experimentally depression levels, e.g. by considering only subjects in whom the depressive state is not affected by treatment, or by using normal individuals as subjects.

The present study aimed at evaluating and

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comparing the pure effects of both ECT and the tricyclic antidepressant, imipramine, on a comprehensive battery of tests of memory. The tasks included measures of anterograde (post-treatment) immediate and recent memory, and retrograde (pre-treatment) remote memory. One question which may be answered by this design is whether those memory faculties which are affected by ECT are also affected by imipramine? Another question which the present study aimed to clarify was whether deficits induced by both ECT and imipramine differ in magnitude for the two treatment modalities?

In approaching these questions it is reasonable to hypothesize that imipramine treated patients will have recent anterograde memory deficits. This hypothesis is based on the following evidence derived from previous studies on the effect of tricyclic antidepressants on memory function: (1) Branconnier *et al.* (1982) studied normal individuals (whose clinical state had not changed during treatment), and found that another tricyclic drug, amitryptyline, impaired anterograde memory tasks ('secondary memory'), but not immediate tasks ('primary memory'); (2) studies in which depressive symptoms improved on tricyclic treatment did not show a corresponding improvement in anterograde recent memory tasks (Belmont *et al.* 1963; Henry *et al.* 1973; Sternberg & Jarvik, 1976; Zung *et al.* 1968), thus suggesting a residual memory impairment; (3) some studies showed deteriorated anterograde memory performance on treatment, although there was an improvement in the depressive symptoms manifested (Legg & Stiff, 1976; McNair *et al.* 1984); and (4) we have not been able to find any study reporting an improved anterograde recent memory performance other than immediate memory (Legg & Stiff, 1976; McNair *et al.* 1984), which is known to be least affected in cases of organic amnesia. Hypotheses relating to retrograde memory tasks are, however, more difficult to formulate since we have not found studies using such tasks to examine the effects of imipramine. Their inclusion in the present study may thus be revealing in terms of the influence of imipramine on retrieval and storage of well encoded information.

A second purpose of the present study was to find out whether a similar pattern of memory impairment would be induced by minimal suprathreshold electrical stimulation using a dosage titration procedure as by conventional ECT not employing this methodology. There is consistent (Sackeim *et al.* 1986; Squire & Zouzournis, 1986), although not universal (Frith *et al.* 1983; Fromm-Auch, 1982), support for the pattern of ECT-induced antetrograde and retrograde deficits summarized above. A different pattern of deficits in the present study would support a role for electrical current intensity in producing ECT-related memory impairments.

METHODS

Subjects

Twenty-six patients suffering from major depressive disorder participated in the study. All patients had been diagnosed according to Research Diagnostic Criteria (RDC) (Spitzer *et al.* 1977), and their diagnoses were reconfirmed using the Diagnostic and Statistical Manual of Mental Disorders, DSM-III (American Psychiatric Association, 1986). Patients admitted to the Resistant Depression Unit of the hospital were assessed as to whether tricyclic antidepressants could be of benefit for them. If such treatment was contra-indicated due to medical reasons, or recently attempted without success, other forms of treatment were considered. ECT was prescribed in cases in which other drugs such as monoamine oxidase (MAO) inhibitors were considered inappropriate and in cases in which there was prior evidence for fast relief with this treatment. As a result of these clinical procedures 16 patients (five males and 11 females were prescribed ECT, and 10 (four males and six females) imipramine. None of the patients had received ECT during the previous year. All patients were drug free for at least 2 weeks before treatment commenced. No patient had observable brain damage, hearing impairment, or a history of alcohol or drug misuse or psychosurgery. None was in an observable hallucinatory state at the time of testing. All available patients were considered for the study, and there were no refusals. Table 1 presents the results of this sampling procedure in respect of age, estimated current cognitive functioning (as assessed by a Hebrew Version of the Quick Test, Form 1; (Ammons & Ammons, 1962)),

Table 1. *Background characteristics of subjects*

	ECT-treated patients Mean	(S.D.)	Imipramine-treated patients Mean	(S.D.)
Age (years)	60·40	(9·03)	54·40	(14·06)
Quick Test Performance	86·00	(24·05)	91·00	(11·70)
Bender–Gestalt Test*	10·40	(5·91)	9·00	(3·65)
Hamilton Depression Scale	29·92	(5·50)	24·11	(7·70)

* Scores using Hutt's (1977) criteria giving either 1 or 0 for each figure.

estimated 'organicity' (as assessed by the Hutt's Scoring of the Bender Gestalt Task), and estimated severity of depressive symptoms (as assessed by the Hamilton Depression Scale). Although patient assignment was non-random, none of the differences between ECT- and imipramine-treated patients reached significance. Ten normal controls of low-medium socioeconomic class (firemen) (age: Mean = 45·40, S.D. = 7·86) were used as controls. They were tested on the Personal Memory Questionnaire only.

Treatment procedure

1. *ECT administration*

ECT was administered using a MECTA (Mecta, Inc.) constant-current apparatus. It was a bilateral, brief-pulse treatment, according to a dosage titration procedure (Sackheim *et al.* 1986). This procedure ensures that stimulus intensity does not substantially exceed the level required for seizure elicitation. Bilateral (with fronto-temporal electrode placement) rather than unilateral treatment was chosen because the antidepressant efficacy of this modality is universally accepted (Abrams, 1982). Anaesthesia was induced with thipentone sodium (Pentothal) (2–3 mg/kg) and succinyl choline (0·75 mg/kg). EEG and ECG were recorded during treatments. Prior to succinyl choline administration a tourniquet was applied to one of the lower limbs at calf level to prevent paralysis of the limb and to permit monitoring of peripheral seizure length. All ECT treatments followed the same procedure. The number of treatments was dictated by clinical considerations. However, all patients received at least seven treatments after which assessments were made.

2. *Imipramine treatment*

Patients who received imipramine were given 200 mg per day, throughout the study period. No toxicity due to this treatment was observed.

Materials

Two tests were used to assess retrograde memory performance, that is, memory for materials learned before treatment commenced.

The Famous Events Questionnaire

This questionnaire constructed along the lines described by Squire *et al.* (1981) is known to be sensitive to amnesia. Its three forms (constructed using a raffle procedure from the pool of items), were given in counterbalanced order in the three test sessions. It has been adapted to Israeli culture and covered the last 12 years. The six time periods equally represented were: 1973–80, 1981, 1982, 1983, 1984, 1985. The questionnaire included details about the Israeli political figures, national events, noteworthy economic events etc. This questionnaire allows testing the relative strength of memory as a function of time prior to treatment. As retrograde amnesia may differ in severity as a function of time (Squire *et al.* 1981), thus constituting a continuum with anterograde amnesia, such a time-recall function was of major importance for the present study. However, this questionnaire has the disadvantage that many events may be unfamiliar to the subject because of lack of interest and lack of exposure to media. For these reasons this questionnaire constitutes a complementary tool to the Personal Memory Questionnaire.

Personal Memory Questionnaire

This measure of autobiographic memory has been adapted from Weiner & Davidson (1985),

using the most recently modified version. It has proved most sensitive in detecting long-lasting memory deficits after ECT (Weiner & Davidson, 1985). The Hebrew modified version of the questionnaire included questions about the present illness, residence, neighbours, family members, friends, events transpiring during the subject's last birthday, the last Passover, the last overnight trip out of town, the favourite TV show, the last movie seen, the current hospitalization and recent outstanding experiences. At the first baseline session all questions were asked. Following treatment only those questions which were responded to at the baseline session were repeated. The same set of questions was repeated at follow-up. If at a subsequent testing responses differed from the baseline session, attempts were made to establish which of the two responses was perceived by the scorer as correct, as a form of self-corroboration. The score in terms of percentage remembered out of the baseline assessments was extracted.

Three tests were used to assess anterograde memory performance.

Verbal Paired-Associates Retention Task

This task is particularly sensitive to detecting anterograde memory deficits (Squire, 1977; Squire & Chace, 1975). It consists of a list of 10 pairs of unrelated nouns. These pairs are presented sequentially on cards on a stand at a distance of about 50 cm and the subject is instructed to read them aloud to ensure that their processing is both auditory and visual. Following presentation, the subject is instructed to recall the second word of each pair when presented with the first word only. The subject is given the correct response if wrong. The list is presented three times during the first session, the last trial not including feedback. It is presented a fourth time at a second session the next day after 18–21 hours, to evaluate delayed recall, which is most sensitive to memory deficit (Squire & Chace, 1975). The word lists consisted of Hebrew, unrelated 1 to 3-syllable nouns sampled from newspapers with perfect agreement of two independent raters (with a background in education) that they were as easy as 'primary school difficulty level standards'. They had also a high frequency of eight or more on Belgur's (1968) frequency norms in Hebrew. The words were placed in the different lists randomly (using a raffle procedure) and the lists thus constituted equivalent forms. The forms of these lists were given in a counterbalanced order to minimize possible list effects.

Complex Figure Reproduction Task

This nonverbal task which is sensitive to right hemisphere temporal lobe dysfunction (Squire & Chace, 1975), has been used as a measure sensitive to ECT effects on memory (e.g. unilateral *v.* bilateral ECT (Squire & Slater 1978)). It consists of the Rey-Ostereith and the Taylor and Ritchie figures used as parallel forms. (The Ritchie figure was recently developed as a parallel form by Dr Squire and he granted permission for us to use it.) In this test, the subject is initially represented with the complex figure and asked to copy it on a sheet of paper. Then the figure is taken away and the subject is instructed to reproduce it from memory. On each occasion, at session 2 (18–21 hours later), the subject is asked to reproduce the figure for a second time in order to evaluate the effect of ECT or imipramine on delayed recall. The forms were given in a random alternating order to minimize specific figure effects.

Immediate Memory Span

This test requires the subject to repeat a series of digits vocally presented, immediately after presentation. It requires short-term retention dependent on echoic memory or rehearsal. This sort of memory is little affected by amnesia (Albert *et al.* 1981). The different forms are taken from the Wechsler Adult Intelligence Scale and Wechsler Memory Scale. This task was administered to patients as a control task. The purpose of its administration was to show that post-treatment deficits are not generalized cognitive deficits (Chapman & Chapman, 1978), but specific amnesic phenomena.

Procedure

The tests were administered in random order to patients first at baseline and then in either 18–21 hours after the seventh ECT treatment or during the fourth week of imipramine treatment. No other drugs were given during the study period.

Data analysis

Data were analysed using parametric tests (ANOVA and t tests), and within subjects designs. The memory scores used were arcsin of proportion of items recalled or forgotten. This transformation was necessary to minimize effects of deviation from 50% accuracy and from normality which characterize amnesic patients. Due to circumstantial problems, not all patients were able to complete all tasks. The actual number of subjects used in each analysis can be easily inferred from degrees of freedom reported in the Results section.

RESULTS

Clinical state

The depressive symptoms of ECT treated patients had significantly improved with treatments ($t = 5{\cdot}430$, df 11, $P < 0{\cdot}0002$). Clinical improvement was positively correlated with total seizure length produced by all ECT treatments ($r = 0{\cdot}468$, $P < 0{\cdot}046$). By contrast, the depressive symptoms of imipramine treated patients had not changed significantly ($t = 1{\cdot}143$, df 6, NS). As stated in the introduction to this paper, neither an improvement nor lack of improvement, only deterioration in depressive symptoms can explain a memory deficit. Therefore, the memory deficits to be reported next are genuine results of treatment, and cannot be explained by the changes in depressive symptoms.

Retrograde memory performance

(a) Famous Events Recall

The recall of famous events by imipramine-treated patients remained unchanged when on treatment relative to baseline ($t = 0{\cdot}319$, df 9, NS). By contrast, the performance of ECT-treated patients was significantly poorer after treatment than before treatment ($t = 3{\cdot}656$, df 11, $P < 0{\cdot}0038$). The inspection of raw data showed that their performance was 31·27% of that of baseline. An analysis of variance showed a significant interaction effect ($F = 11{\cdot}981$, df 1,20; $P < 0{\cdot}0089$), supporting this difference between groups. No evidence of an amnesic gradient, that is, better recall for the distant past than the more recent past, emerged either in patients treated with imipramine ($F = 2{\cdot}839$, df 5,55; NS) or those on ECT ($F = 0{\cdot}751$, df 5,55, NS). This finding is not surprising, as this gradient is expected to be mainly due to forgetting of the last one or two years (Cohen & Squire, 1981; Squire 1986*b*; Squire *et al.* 1981). As the study period was long (about 2 years), and the questions were not readjusted, many patients were not tested for recent public events, and so the chance of finding an amnesic gradient had diminished. This chance was not diminished in the Personal Memory Questionnaire to be reported next.

(b) Personal memory

Imipramine-treated patients forgot far less autobiographic information than did ECT-treated patients ($t = 2{\cdot}600$; df 21, $P < 0{\cdot}017$). The raw data showed they forgot 15·31% less than ECT patients. However, normal controls forgot even less information than patients ($F = 15{\cdot}373$; df 2,30; $P < 0{\cdot}00009$). Imipramine-treated patients recalled 85·45% of that recalled by normals, and ECT patients recalled 70·09%. The deficit imipramine-treated patients had relative to normals, could of course, have pre-existed and been caused by depression. When the three early (more than 2 years) and the three late (last year) time periods (for which the number of patients not having missing data exceeded 4) were considered (Fig. 1), it was found that forgetting

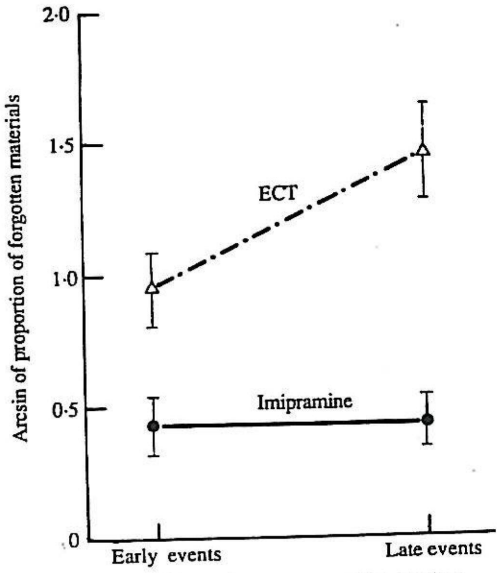

FIG. 1. Personal memory: amnestic gradient.

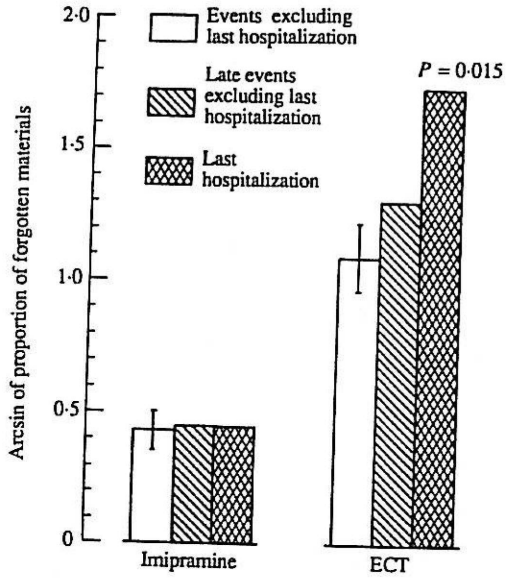

FIG. 2. Personal memory: forgetting of events related to the last hospitalization.

of late events (last birthday, last Passover, last hospitalization) by ECT patients was much higher than that of early events (neighbours, friends, family members) ($F = 6{\cdot}548$; df 1,15, $P < 0{\cdot}021$; 44·01% and 21·12% respectively by raw data). Further, as imipramine-treated patients showed equivalent forgetting for both early and late events, this selective forgetting effect could be ascribed to ECT, thus confirming an amnesic gradient for these patients. This also resulted in a marginally significant interaction effect ($F = 4{\cdot}193$, df: 1,15; $P < 0{\cdot}058$). A test of the hypothesis that this amnesic gradient was in part due to excessive forgetting of events related to the last hospitalization is presented in Fig. 2. It shows that for ECT, but not for imipramine-treated patients, these events were forgotten substantially more (57% by raw data) than the rest of the late events (39% by raw data, $P <$ 0·05 by confidence interval. The significance level shown in Fig. 2 represents the fact that this test mean was also significantly different from all other five tests, taken together).

Anterograde memory performance

(a) *Paired-associates immediate and delayed recall*

Both imipramine-treated and ECT-treated patients remembered fewer words when tested on

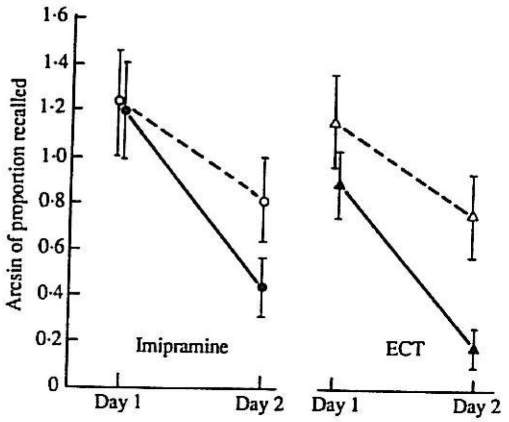

FIG. 3. Paired-associates recall performance; (---) baseline; (—) treatment.

treatment (Fig. 3), than before treatment ($F =$ 21·08; df 1,9; $P < 0{\cdot}0014$; and $F = 28{\cdot}501$; df 1,13; $P < 0{\cdot}0001$, respectively). This was to a large extent due to the fact that the rate of forgetting from one day to another was significantly more rapid after treatment than before treatment for both imipramine ($F =$ 5·877; df 1,9; $P < 0{\cdot}039$, for the interaction) and ECT ($F = 5{\cdot}767$; df 1,13; $P < 0{\cdot}032$, for the interaction) treated patients. The raw data for ECT showed 53·1% forgetting before treatment and 94·2% forgetting after treatment; for imipramine: 51·7% forgetting before treatment and 82·5% forgetting after treatment. Imipramine- and ECT-treated patients performed alike ($F = 0{\cdot}773$, df 1,22; NS).

(b) *Complex figure immediate and delayed reproduction*

Unlike the verbal task, this nonverbal recall task (the scores of which were corrected for graphic ability, by taking the proportion recalled out of the copying score of the figures) showed (Fig. 4) neither significant changes in performance when on treatment as compared with the performance before treatment ($F = 1{\cdot}797$; df 1,9; NS for imipramine, and $F = 3{\cdot}226$; df 1,14, NS, for ECT), nor different forgetting rates from one day to another ($F = 0{\cdot}372$, df 1,9; NS and $F =$ 0·349, df 1,14; NS, respectively). The raw data for ECT showed 23·4% forgetting before treatment and 27·4% forgetting after treatment; for imipramine, 13·5% forgetting before treatment and 21·4% after treatment. An analysis of variance including both imipramine- and ECT-

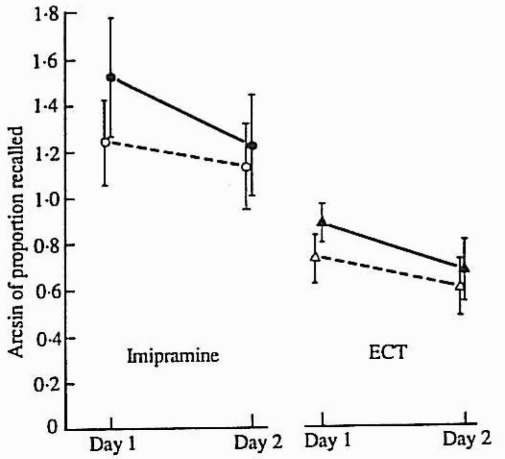

FIG. 4. Complex figure reproduction from memory; (---) baseline; (—) treatment.

treated patients showed better overall performance for imipramine than ECT-treated patients ($F = 15{\cdot}118$; df 1,23; $P < 0{\cdot}0008$). This combination of the data from these two groups also gave an effect of forgetting from one day to another ($F = 4{\cdot}865$; df 1,23; $P < 0{\cdot}038$). However, performance was not significantly affected by the treatment ($F = 1{\cdot}335$; df 1,23; NS).

(*c*) *Immediate recall* (*digits span*)

Neither of the two treatments significantly affected immediate digits recall, resulting in a combined nonsignificant effect of the two treatments ($F = 1{\cdot}384$; df 1,23; NS). Also, there was no significant difference between ECT and imipramine treated patients ($F = 2{\cdot}737$; df 1,23; NS). These data were not transformed before analysis as they did not appreciably deviate from 50% accuracy.

(*d*) *Control measures and memory*

Total seizure length, total electric current, total succinyl choline dose, and total Pentothal dose were not significantly correlated with any memory measure, in ECT-treated patients. These were, therefore, not treated as confounding variables.

DISCUSSION

The results show that both ECT and imipramine treatment cause memory impairment in depressed patients. The deficits are, however, distinct. Whereas ECT-treated patients manifest both anterograde and retrograde memory deficits, imipramine-treated patients show anterograde memory deficits only. The ECT- and imipramine-induced anterograde memory defects appear to be of similar nature and magnitude. This suggests a qualitatively different pattern of deficits resulting from these two treatments, rather than quantitative differences in the relative impairments produced.

The results for imipramine-treated patients replicate former findings in showing deficits in long-term anterograde memory and no deficit in immediate memory (Glass *et al.* 1981; Legg & Stiff, 1976; McNair *et al.* 1984; Moskovitz & Burns, 1986; Staton *et al.* 1981). They are, however, novel in showing rapid forgetting of newly acquired information, which is known to be both a classical amnesic sign (Butters & Meliotis, 1985) and due to anticholinergic effects (Drachman & Levitt, 1974). As the results do not support a residual memory deficit in any of the other tasks used (considering also the fact that depressive symptoms had not improved significantly), one can conclude that rapid forgetting of verbal material is the main positive finding of the present study in imipramine treated patients. As the hypothesized reason for the amnesic effects of imipramine is its anticholinergic activity, one can conclude that this activity interferes with late-stage consolidation or retrieval of newly acquired information more than with early-stage retrieval. This may be due either to interference with the consolidation process (Squire 1986*a*, *b*), or to lack of activation of a retrieval plan (Mandler, 1967; Wicklegren, 1979).

Inspection of the rest of the results may highlight the correct explanation. For this purpose one has to take into account the other novel finding of the present study, that is, no retrograde memory deficit caused by imipramine. As this finding suggests no memory problem, one can conclude that it is not retrieval *per se* that is adversely affected by imipramine, but retrieval of newly acquired information (anterograde tasks) only. This suggests that it is the consolidation rather than the retrieval process that is adversely affected by the anticholinergic activity of imipramine. As this sort of deficit has been localized to the medial temporal region of the brain (Squire, 1981), this

finding may be of neurophysiological importance.

It is important to note that there was no corresponding nonverbal deficit in the imipramine-treated patients and no rapid forgetting for this task. As the general performance of this task by the imipramine-treated patients was not as impaired as that of ECT patients, it is unlikely that this was due to a floor effect. There are several possible reasons for the lack of positive finding: (*a*) the non-verbal task is less sensitive to amnesia than the verbal task; (*b*) imipramine affects verbal more than nonverbal tasks; and (*c*) this is an accidental finding. Since the literature review suggests that (*a*) and (*b*) are quite unlikely (Squire, 1984, 1986*a*; Squire *et al.* 1981; Weiner, 1984), one is left with the third possibility, (*c*). One would, therefore, recommend a replication before considering other than methodological reasons for this negative finding.

With regard to the ECT-treated patients, the results of the study suggest that minimum dose, brief-pulse ECT administered according to a titration procedure (Sackeim *et al.* 1986) causes the same types of deficit previously reported, using conventional procedures (Squire, 1984, 1986*a*). However, in the present study the anterograde memory deficit produced by ECT was only as large as that caused by imipramine, and this is known to be a relatively mild deficit (Glass *et al.* 1981; Legg & Stiff, 1976: McNair *et al.* 1984; Moskovitz & Burns, 1986; Staton *et al.* 1981). This may suggest relatively mild anterograde memory problems when using the titration procedure (Squire & Zouzournis, 1986). However, a study directly comparing the two procedures is of major importance in confirming this tentative conclusion.

In other respects, the results support former findings regarding the memory deficit produced by ECT. They show (*a*) a deficit and an amnesic gradient in autobiographic retrograde memory (Squire *et al.* 1981), (*b*) a deficit in public events recall (Cohen & Squire, 1981; Squire, 1975 ; Squire *et al.* 1975, 1981), (*c*) rapid forgetting in verbal retrograde memory (Squire, 1977, 1986*a*; Squire & Chace, 1975), and (*d*) no deficit in the control task of immediate memory (Chronholm & Ottosson, 1961; Weiner, 1984), namely digit span. Only two findings did not replicate former results. These were the findings (*a*) of lack of non-verbal memory deficit which has been discussed above, and (*b*) of no amnesic gradient in public events recall, which may be explained by the fact that the study period was too long for showing the latest periods in which a disruption of the consolidation process and forgetting is very pronounced (Cohen & Squire, 1981; Squire 1986*b*; Squire *et al.* 1975, 1981). By the time the study ended 'last year' became 'three years ago'. This reasoning is supported by the fact that when one used the personal memory questionnaire in which later periods were readjusted according to each subject's life, this gradient did emerge.

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