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Influence of ACTH 4-10 and Unilateral ECT on Primary and Secondary Memory in Depressive Patients

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Summary. Primary and secondary memory were tested in depressive patients by means of immediate free recall of lists of words in a double blind intraindividual cross-over comparison between ACTH 4–10 in a single s.c. dose and placebo, in connection with the second and third unilateral electroconvulsive treatment (ECT).

The results of the study did not show any memory facilitating effect of ACTH 4–10 in immediate recall from primary and secondary memory, after ECT.

The results indicate a negative effect of ECT on delayed recall from secondary memory 120 min after ECT.

Key words: Primary and secondary memory – ACTH 4–10 – ECT – Depressive patients

Introduction

Immediate free recall of lists of words longer than the memory span characteristically shows a pronounced serial position effect. The plot of the probability of recall as a function of the position of the words is U-shaped, with the beginning peak usually lower than the end peak.

It is hypothesized that the U-shaped serial position consists of two curves, each representing output from separate storage mechanisms (Glanzer and Cunitz 1966; Murdock 1967; Postman and Keppel 1968). The words recalled from the beginning of the list are primarily an output from the long-term storage ("primacy effect"), while words recalled from the end of the list are considered as an output from short-term storage ("recency effect") (Glanzer and Cunitz 1966; Underwood 1976).

Evidence has been accumulated that short-term and long-term memory operate separately and independently from each other (Glanzer 1971). Short-term memory is characterized by a limited capacity and short duration (measurable in terms of digit span, i.e., number of digits correctly repeated by a subject) estimated in the region of 20–30 s. Long-term memory, on the contrary, has under optimal conditions, an unlimited capacity store.

Amnesics have normal short-term memory since they are able to repeat sentences shorter than digit span efficiently immediately after presentation (Drachman and Arbit 1966; Baddeley and Warrington 1970), i.e., they show a normal "recency effect", but are impaired for recall of words coming earlier in the list, i.e., they show an impaired "primacy effect". If normal subjects are requested to recall word lists, words heard last are more likely to be recalled ("recency effect"). However, this effect disappears if recall is delayed for some 20–30 s.

There is unfortunately some conceptual confusion about the distinction between short-term and long-term memory (Wough and Norman 1965). In order to avoid it, in accordance with Wough and Norman (1965) we prefer the terms "primary memory" (which corresponds to short-term memory) and "secondary memory" (which corresponds to long-term memory). Items in primary memory are still "in mind" and they are maintained in primary memory by a process of continuous rehearsal until they are displaced by other incoming material. Defined in this way primary memory holds only two to four verbal items (Watkins 1974). Primary memory is thus viewed more as a temporary holding and organizing process, than a structured memory store. Secondary memory items have been absent from consciousness at some point and are coded in a permanent memory store from which they must be retrieved even in an immediate retention test. Primary memory and secondary memory are here considered as two parts of the U-shaped curve of recalled words.

Adrenocorticotrophic hormone (ACTH) and its structural analogues are known to interfere with the acquisition and maintainance of behavior in many animal experiments (Rigter and v. Reizen 1978; review in d'Elia and Frederiksen 1984).

Hypotheses aimed at defining the physiological nature of the behavioral effects of ACTH analogues have focused on motivation, attention, arousal, and memory as the target functions possibly affected (d'Elia and Frederiksen 1984). Human studies have failed to support a memory facilitating effect of ACTH 4–10, at dosage varying between 10 and 30 mg s.c. Similarly, no consistent findings support the hypothesis that ACTH 4–10 may attenuate amnesic disorders in humans (Dornbush and Volavka 1976; Ferris et al. 1976; Small et al. 1977; Branconnier et al. 1978; Draper et al. 1978; d'Elia and Frederiksen 1980a, 1980b). However, memory tests employed in these studies have mainly measured aspects of the secondary memory.

The present study is part of a research project into possible memory facilitating effects of ACTH analogues in psychiatric patients. In previous studies effects of ACTH 4–10 on consolidation and retrieval of material in secondary memory were considered (d'Elia and Frederiksen 1980a, 1980b). The aim of the present study is to answer the following questions:

1. Does electroconvulsive therapy (ECT) influence primary and/or secondary memory?

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2. Can a single dose of ACTH 4–10 alleviate anterograde dysmnesic effects of ECT on primary and/or secondary memory?

Patients and Methods

The Design and Subjects. The investigation was carried out as a double blind intraindividual cross-over comparison between ACTH 4–10 and placebo in an anterograde design, in connection with the second and the third unilateral ECT (d'Elia 1970). Each patient was tested for immediate recall four times i.e., before and after the second and the third ECT in a treatment series (Study I and II). In order to test the hypothesis of a negative effect of ECT on secondary memory, delayed recall of a word-list was studied in an intraindividual cross-over comparison before and after ECT (Study III).

In *study I* the patients (n = 16) were tested 60 min before ECT. They were then tested again 180 min after ECT, 150 min after the injection of ACTH 4–10 or placebo. The aim of this schedule was to discover a possible longer lasting effect of the peptide.

In *study II* the patients (n = 12) were tested 60 min before ECT, as in study I. They were tested again 120 min after ECT, but only 30 min after the injection of ACTH 4–10 or placebo. The aim of this schedule was to discover a possible short lived effect of the peptide.

The ACTH 4–10 was administered s.c. at a dose of 30 mg. For details see d'Elia and Frederiksen (1980a, 1980b). A total of 28 patients (10 males and 18 females) aged 21–50 years referred for ECT by their treating doctors, participated in studies I and II. Older patients were not included in order to eliminate the possible influence of age on memory. Half of the patients started at random with ACTH 4–10, the other half with placebo. On the second day of investigation, the alternative treatment was given.

In *study III* the patients (n = 10, 6 female and 4 male, aged 26–47 years), who did not participate to the ACTH 4–10 study, were tested with a modified test procedure. The patients were instructed to recall words of the list with a delay of 30 s, during which the patient counted backwards in two s from two digit numbers presented by the examiner, immediately after the last word. In order to minimize the effects of output interference, nonverbal signal for recall was given. This procedure will be indicated as delayed recall. The procedure previously described in the paper is indicated as immediate recall.

Half of the patients started at random on the second ECT treatment with delayed recall, the other half with immediate recall. The two test procedures were alternated on the third ECT treatment, 60 min before and 120 min after ECT.

The Test Instrument: Forty different lists of 10 unconnected words each, and at each test occasion 10 lists were used. Lists were composed of 10 items only in consideration of the need for a simple and easy instrument to be used by depressive patients. The word lists were composed of 400 bisyllabic abstract and concrete Swedish substantives of different categories, taken from the vocabulary edited by the Swedish Academy (Svenska Akademins Ordlista över Svenska Språket, Stockholm 1950). The material is probably not homogeneous with respect to concreteness and imagery values. The lists were previously tested on a group of 40 medical students. High frequent and low frequent words were substituted with more usual ones. The list was read by the examiner at a rate of 1 word every 2 s. The patients were instructed to recall immediately after the last word in the list was pronounced, as many words as possible, in any order. The procedure for delayed recall has been described above.

Statistical method. Differences in memory score were tested by means of t-test for paired comparison (two-tailed values). Adjustment procedure according to Holm (1979) and described by Abt (1983) was used in order to counteract the "α inflation", i.e., the inflation of the probability for Type 1 error due to the multitude of significance tests. Thus, the 1-P values are rank ordered and compared to nominal significance levels. As long as a 1-P value is smaller than the nominal significance level, the null hypothesis is rejected.

Results

The mean number of words immediately recalled by all patients in studies I and II (n = 28) before and after the third ECT, are plotted in function of their order of presentation. Figure 1 shows the typical U-shaped curve with an almost complete recall of the last item and a lower peak at the beginning of the curve. After ECT there is a slightly lower recall at the beginning of the curve, suggesting a weak negative effect on secondary memory. Primary memory is uneffected.

Differences between treatments (ACTH 4–10 and placebo) in studies I and II are shown in Tables 1 and 2. The data indicate a U-shaped distribution of correctly recalled items at each test occasion. In study I (Table 1) no difference between treatment was found. In study II (Table 2) significantly fewer words were correctly recalled after placebo, thus suggesting a possible effect of the peptide on primary memory.

With delayed recall primary memory (or "recency effect") does not appear, as expected, leaving a stable secondary

Table 1. Study I. Mean number of words correctly recalled according to treatments and to serial positions

	Serial position	ACTH 4–10	Placebo	t (15 df)
60 min before ECT	1	4.1	3.9	0.18
	2	3.1	3.1	0.00
	3	2.8	2.6	0.21
	4	1.5	1.7	0.18
	5	1.6	2.0	1.00
	6	1.7	2.2	0.94
	7	3.0	3.5	1.16
	8	4.5	3.7	1.64
	9	8.2	8.0	0.91
	10	9.0	8.7	0.46
180 min after ECT	1	3.6	4.0	0.46
	2	2.5	2.5	0.00
	3	1.9	1.6	0.34
	4	1.0	1.8	1.61
	5	1.2	1.6	1.10
	6	1.6	1.9	0.09
	7	3.0	2.9	0.12
	8	5.3	4.9	0.43
	9	8.5	7.9	1.16
	10	8.5	9.1	1.43

Table 2. Study II. Mean number of words correctly recalled according to treatments and to serial positions

	Serial position	ACTH 4–10	Placebo	t (11 df)
60 min before ECT	1	5.2	4.6	1.41
	2	1.9	2.2	0.86
	3	2.1	2.3	0.14
	4	2.8	2.0	1.10
	5	2.0	2.3	0.46
	6	2.3	2.8	0.56
	7	3.6	4.0	0.81
	8	4.9	4.8	0.09
	9	7.8	7.4	0.61
	10	9.5	9.2	1.01
120 min after ECT	1	4.1	5.6	2.26
	2	1.4	1.9	0.21
	3	1.6	1.5	0.11
	4	1.6	1.6	0.00
	5	2.0	2.1	0.13
	6	2.4	2.1	0.29
	7	3.9	3.2	1.05
	8	4.7	5.2	1.17
	9	7.5	6.1	2.72*
	10	8.5	9.2	1.83

* $P < 0.05$

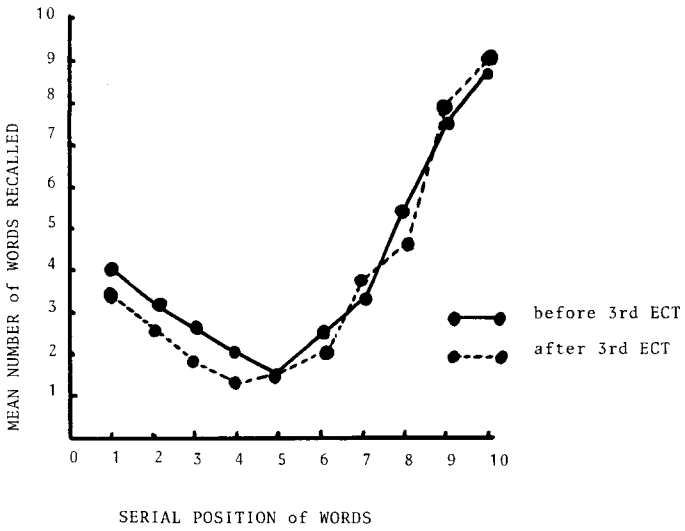

Fig. 1. Immediate recall

memory component (the "primacy effect"). Figure 2 shows a deficit in secondary memory after as compared to before ECT. The difference in total number of words recalled for word positions 1–10 was statistically significant (before ECT $\bar{x} = 26.6$, after ECT $\bar{x} = 14.1$, $t = 4.33$, $P < 0.01$). Thus ECT appears to have a negative effect on delayed recall from secondary memory. The results of immediate recall are almost identical to these shown in Fig. 1.

Discussion

Sources of Error. When a list of verbal items is presented for immediate recall, the level of retrieval increases progressively

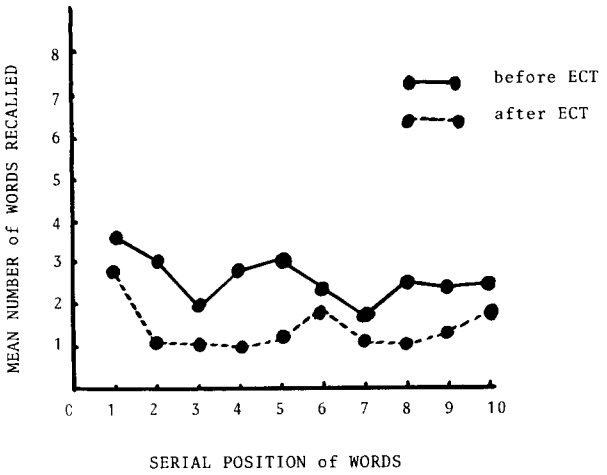

Fig. 2. Delayed recall. 4. $t = 4.25$, $P < 0.01$; 5. $t = 3.15$, $P < 0.02$; 8. $t = 3.01$, $P < 0.02$

over the sixth or seventh item. A striking feature of this effect is its general appearance under different experimental conditions. The probability of recall of items presented at earlier serial positions depends, on the contrary, on a large number of experimental variables, such as list length, presentation rate, frequency of occurrence in the language, semantic association, phonological similarity (Glanzer 1971; Watkins 1974).

The lists of verbal items used in this study are quite short and the items themselves are not homogeneous with respect to concreteness and imagery values. Practical consideration influenced the composition of the lists. Firstly the need for a short, simple test to be used by depressive patients. Secondly, the shortness of bisyllabic words in the Swedish vocabulary. In consideration of the special conditions for which the tests were composed and used, the results of the present study cannot be generalized to other patients.

There are different methods for distinguishing between the primary and secondary memory components of free recall. The simplest one is that proposed by Tulving and Patterson (1968). They attribute each recalled item to either primary or secondary memory according to whether it had been presented at one of the last four serial positions or at an earlier serial position. This method has the advantage of being very simple. Further, evidence has been presented that the technique is efficient in dividing recall in two components which differ in their properties (Watkins 1974). One objection, however, is that not all recency items are necessarily attributed to primary memory. Tulving and Colotla (1970) suggested a more sophisticated type of estimate of primary memory based on the count of all items that are recalled with no more than seven input and/or output items intervening since presentations. The selection of seven as the number of intervening items is based on the extent of the recency effect. Other investigators have chosen five (Roberts 1969) or six (Craik 1970; Watkins and Watkins 1974). It cannot be excluded that somewhat different results might be obtained with methods other than the one used in this study.

Comments on the Results. The technique used in this study is the immediate free recall of lists of words. The bimodal serial position curve in free recall represents output from the two storage systems involved in primary and secondary memory. When the subject listens to a list of words, items at the begin-

ning and at the end of the list are most easily recorded. The first few items in the list can be recalled because they have been transferred to the secondary memory store before the primary one becomes too overloaded with material. Items at the end of the list are easily rehearsed on immediate recall because they are still present in consciousness, or, if we want, in primary memory store. Items in the middle of the list will be easily lost, because they tend to be squeezed out of primary memory store before they can be transferred to secondary memory store.

From previous studies it is known that ECT interferes specifically with delayed recall of memory, while the learning of new material is not influenced or only influenced to a lesser extent (Cronholm and Ottosson 1961; d'Elia 1970). A specific effect of ECT on secondary memory is therefore not surprising. The results of this study show that recall from secondary memory may be nearly "normal" in an immediate recall situation, but is deficient in a delayed recall situation.

The lowering of the secondary memory component in the delayed recall situation may be interpreted in at least two different ways, either as a rapid loss from secondary memory store, or as difficulty in retrieval. Reversible difficulty in retrieval has been described on the basis of personal experience of ECT treatment (Anonymous 1965), and is supported by experimental findings (Weiskrantz 1966). However, on the basis of our present knowledge, only speculative answers can be given (Piercy 1977; Williams 1977). The findings of this study suggest that one effect of ECT on memory material is exerted at the early phase of encoding in the permanent memory store.

ACTH 4–10 was not shown to facilitate immediate recall from primary memory. In agreement with previous studies concerning other aspects of memory (d'Elia and Frederiksen 1984), ACTH 4–10 did not show any antidysmnesic effect on secondary memory in ECT treated patients.

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