JAMES L. McGAUGH / MICHAEL J. HERZ

MEMORY CONSOLIDATION

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JAMES L. McGAUGH *Department of Psychobiology, University of California, Irvine*

MICHAEL J. HERZ *Laboratory of Psychobiology, Langley Porter Neuropsychiatric Institute; University of California, San Francisco*

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PREFACE

One of the most obvious features of behavior in man and the other animals is that it is changed by experience. We learn, we remember, and we forget. Since the behavior of most animals, and man in particular, depends so heavily on memory, an understanding of memory has obvious practical, as well as theoretical, consequences. For these reasons research on the neurobiological bases of memory has surged in recent years.

Although we know a great deal about learning and memory from a behavioral perspective, we do not yet understand the *bases* of these processes. We know relatively little about the neurobiological mechanisms that underly our ability to learn, remember, and forget. There are, of course, many theories of memory, as well as a wealth of facts. However, the facts do not yet provide a coherent view of how the molecules, cells, and neural systems of the brain enable us to learn and remember.

The study of the bases of memory is approached in a variety of ways. For example, there is considerable effort to find neurobiological *correlates* of memory. Changes are known to occur in both the electrical and the biochemical activity of neural tissue when animals are trained [see reviews by John, 1967; Glassman, 1967, 1970]. Evidence that these changes or correlates are *involved* in memory processes will, when obtained, be an extremely important contribution to understanding memory.

Another major approach to memory, the one examined in this book, employs the strategy of experimentally modifying the neural processes initiated by a training experience. This approach is guided by the assumption that knowledge of the way in which the development of memory processes can be impaired or enhanced by various treatments that modify neural functioning will provide important clues concerning the neural bases of memory.

Part One of this book examines current facts and theories related to the consolidation hypothesis and some of the major empirical and theoretical issues regarding time-dependent processes in memory storage.

The readings in Part Two are reasonably representative of research in this general area. However, since the published research findings are as extensive as they are controversial, any review is of necessity selective [see reviews by Zeigler, 1957; Glickman, 1961; McGaugh, 1966; John, 1967; Deutsch, 1969; Lewis, 1969; Rosenzweig and Leiman, 1969; Deweer, 1970; Sheer, 1970]. Part Three is an extensive bibliography of works in the field. All citations in both Part One and the readings are cross referenced to this bibliography.

The consolidation hypothesis was originally proposed on the basis of studies of memory in humans. However, because most of the controversies center on findings from experiments with infrahuman subjects, we have not included any analysis of research on memory consolidation in humans. It should be noted that there is renewed interest in the implications of the consolidation theory for human memory [Milner, 1966; Barbizet, 1970; Drachman and Arbit, 1966; Pribram and Broadbent, 1970].

Numerous laboratories are actively involved in investigation of time-dependent processes in memory storage in animals. In our interpretations of contemporary theory we have been strongly influenced by many of our colleagues. In particular we should like to thank Murray Jarvik, Lewis Petrinovich, Harman Peeke, Everett Wyers, Arthur Cherkin, Steven Zornetzer, Gerry Dawson, Paul Gold, and Philip Landfield for their contributions to our thinking about memory-storage processes and for their comments on earlier drafts of Part One.

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PART ONE

CURRENT ISSUES IN MEMORY CONSOLIDATION

THE CONSOLIDATION HYPOTHESIS OF MEMORY

The first formal consideration of the possibility that an experience is not permanently recorded in memory until some time after it occurred is credited to Müller and Pilzecker [1900]. They proposed that the neural processes that underlie memory "perseverate" in a labile form after an experience and become "fixed" or "consolidated" later with time. That is, the formation of long-term or permanent memory is based on processes that are time dependent. This *perseveration-consolidation hypothesis*, or simply *consolidation hypothesis*, is supported by evidence from numerous clinical and experimental studies conducted since the turn of the century. However, many of the findings have raised serious questions concerning the adequacy of the hypothesis, and as a consequence it has been surrounded by controversy in recent years.

The consolidation hypothesis was initially proposed as an explanation of *retroactive inhibition* in human memory, the observation that the interpolation of new information interferes with the retention of previous learning. This interference was thought to be caused by interference with neural processes involved in memory consolidation. McDougall [1901] was quick to point out that Müller and Pilzecker's hypothesis provided an explanation of the retroactive amnesia observed with head injuries. As noted by Burnham [1903] and later discussed more extensively by Russell and Nathan [1946], head injuries often produce amnesia for events that occurred shortly before them. In a survey of head-injury cases Russell and Nathan found that approximately 75 percent of the patients had amnesia for events occurring up to half an hour before the trauma. In about 50 percent of the cases the patient was unable to remember only the last few moments before the accident. In many cases, however, there was permanent retrograde amnesia for experiences that had occurred minutes, hours, or even days prior to the injury. These clinical observations of retrograde amnesia are generally consistent with the consolidation hypothesis.

Although the results of both clinical and experimental studies of human memory were interpreted in terms of the consolidation hypothesis, a specific theory of memory consolidation was not put forth

until a little over two decades ago, when Hebb [1949] and Gerard [1949, 1955] proposed a *dual-trace hypothesis* of memory storage. According to this view the neural activity initiated by an experience persists for a period of time after the experience, and this reverberating activity in the neural circuits serves as a basis for perseveration by sustaining the memory for a period until "permanent storage" occurs. This shortlasting reverberating trace was assumed not only to provide a basis for short-term memory, but also to produce the neural changes necessary for the consolidation of long-term memory. Thus the hypothesized dual-trace mechanism accounted for the development of permanent or long-term memory and at the same time allowed for an initial "labile" period during which the neural processes underlying memory are subject to interference.

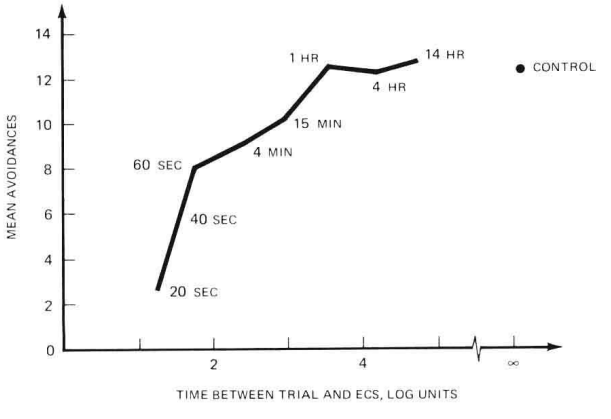
The dual-trace hypothesis was based on neurophysiological and neuroanatomical evidence available at that time. For example, Lashley [1929] investigated the effect of removing portions of the rat's cerebral cortex and found that within given structural regions the degree of interference with memory produced by a lesion depended on the total amount of tissue destroyed. The results of Lashley's early investigations suggested that memory traces may involve large numbers of cells widely spread throughout the cerebral cortex. Lorente de No's discovery [1938] of closed circuits of neurons connected by internuncial fibers suggested the possibility of self-reexciting (that is, reverberating) groups of cells, and these were considered by Hilgard and Marquis [1940] as one possible basis of memory. In later studies Burns [1954, 1958] demonstrated that a single electrical stimulus train can initiate bursts of electrical activity in slabs of isolated cortex which may last 30 min or longer. Whereas such bursts can be interrupted by subsequent massive electrical stimulation, their elicitation becomes easier with repeated stimulation. Verzeano and Negishi [1960] and Verzeano et al. [1970] recorded recurrent patterns of discharge of single cells in the thalamus of monkeys with permanently implanted microelectrodes. Such patterns followed sensory stimulation and appeared to vary with changes in the stimulus. Although it has not yet been shown that such electrophysiological activity has a specific role in memory storage, the recurrent patterns could provide a basis for the neural perseveration postulated by the dual-trace hypothesis.

Thus there appear to be neural processes which *could* serve as a basis for a dual-trace mechanism. The question, however, is whether such a mechanism is needed. Is there clear evidence that recent memory is labile and that the development of long-term memory is time dependent? Let us consider the evidence on this issue.

Although numerous early behavioral and clinical observations suggested that a variety of treatments administered shortly after an experience could disrupt memory of the experience, systematically controlled laboratory investigations of memory mechanisms had to await the development of an experimental tool. In 1938 Cerletti and Bini introduced electroconvulsive shock (ECS) as a treatment for mental illness. Within a few years the results of several studies indicated that ECS produced retrograde amnesia in human patients [Flescher, 1941; Mayer-Gross, 1943; Zubin and Barrera, 1941]. An ECS treatment (or ECT, electroconvulsive shock therapy) consists of passing electric current through the subject's head for a brief period of time. Current of sufficient intensity and duration produces a convulsion unless the subject is first given a drug which prevents the convulsion [for details see McGaugh, 1968*b*].

It remained for Duncan [1949] to take the technique into the animal laboratory, where more adequate control could be exerted. In this now classical study Duncan trained groups of rats to avoid footshock in an active-avoidance task by giving them one training trial followed by ECS every day for 18 days. The ECS was delivered through electrodes attached to the rats' pinnae, with the current of sufficient intensity and duration to elicit convulsions. Animals in different groups were given ECS either 20 sec, 40 sec, 60 sec, 4 min, 15 min, 1 hr, 4 hr, or 14 hr after each of the daily trials. Control subjects were given no ECS. The results indicated that in the groups administered ECS within 15 min after each training trial learning was markedly slower than in the other ECS and nonconvulsed control groups (see Figure 1). The effect was

FIGURE 1 ***Mean avoidance responses by rats on 18 daily trials in an active-avoidance task as a function of the trial-ECS interval (expressed in log units). ECS was administered 20 sec, 40 sec, 60 sec, 4 min, 15 min, 1 hr, 4 hr, or 14 hr after each trial.*** [***Duncan, 1949***]



graded: animals given ECS 20 sec after each training trial showed almost no learning, and the longer the interval between training and ECS treatment, the better the learning. Thus ECS appeared to produce a retrograde-amnesia gradient similar to that seen in human patients with head injuries.

Duncan's study was a milestone in the development of the consolidation theory of memory. His investigation marked the transition from reliance on clinical observation to careful laboratory experimentation, and his findings stimulated great interest in the problem of memory consolidation. The appearance in the same year of the first specific hypothesis of consolidation [Hebb, 1949; Gerard, 1949] indicates that the problem was simultaneously under attack on several fronts.

However, Duncan's research was not above reproach. His study raised a number of very important questions, some of which are not yet resolved. The primary question concerns the *basis* of the retrograde amnesia produced by ECS. Are the learning deficits observed in animals administered ECS shortly after each trial the result of retroactive interference with memory processes, or are they caused by the punishing effects of ECS or by some other general effect of the treatment? Are the ECS-produced deficits in learning permanent, or are they merely transient effects? Are they due to the accompanying behavioral convulsion or to interference with neural, electrical, or biochemical activity? Does the graded amnesic effect obtained by Duncan reflect the "true course" of the consolidation process, or were these results specific to the particular conditions of his study? These are only a few of the issues raised by Duncan's findings.

Questions such as these can be answered only by the kind of detailed laboratory research that gradually results in a sizable and reliable body of empirical evidence. It should be emphasized that although most of the research on consolidation has employed ECS as an amnesic agent, many other treatments have been investigated. Of course, many of the controversial issues concerning the amnesia produced by ECS apply to most, if not all, of the other treatments used in experimental studies of memory storage.

During the decade following the publication of Duncan's study, Thompson and his colleagues [Thompson and Dean, 1955; Thompson and Pryer, 1956; Thompson, 1957*a*, 1957*b*; Thompson and Pennington, 1957; Thompson et al., 1958] conducted systematic and detailed series of investigations of the generality of the amnesic effects of ECS in rats. Thompson was apparently the first to suggest that multiple convulsions (one after each training trial, as in Duncan's study) might have a cumulative effect on behavior. As an alternative approach he gave animals a single ECS at various intervals after a series of training trials. He then retrained them on the same task and inferred the degree of interference produced by ECS from the savings that were attained

during retraining. The results of these experiments provided further evidence that a single posttraining ECS treatment produced retrograde amnesia. Under some conditions interference was obtained even when an hour elapsed between the end of training and the treatment [Thompson and Dean, 1955]. Additional studies indicated that the amnesic effects of ECS were more severe in young rats than in old ones [Thompson, 1957*b*; Thompson et al., 1958] and that the effectiveness of ECS decreased with increasing degrees of distribution of practice in the original learning [Thompson and Pennington, 1957]. However, with the procedures used in these studies (25 trials, with intervals of 1 min or longer preceding ECS) some consolidation might have occurred prior to the administration of ECS. Thus it is difficult to compare Thompson's results directly with Duncan's.

The results of one study by Thompson [1958*a**] show the differential effectiveness of ECS delivered at various intervals after varying amounts of training in tasks of varying degrees of difficulty. Since most of the conclusions concerning ECS-induced retrograde amnesia are based on experiments utilizing avoidance learning of some kind, it is important to note the effect on different types of tasks. In this study Thompson administered ECS to rats after varying amounts of massed training trials on a visual-discrimination task. Contrary to what might be expected if ECS effects were due solely to some gross or general interfering effects on performance, ECS administered very early in training (after only 10 trials) produced amnesia only if it was delivered within 30 sec after the last trial. With additional training (20 trials) interference was produced by ECS administered as long as 30 min after the last trial, but with still further training (30 to 40 trials) it was produced only by ECS delivered within a few minutes after training. That is, the gradient of retrograde amnesia seemed to vary with the degree of training. In a second part of the same study Thompson demonstrated that ECS produced greater degrees of amnesia for complex learning than for simple discrimination tasks. In general his findings have been strongly supported by subsequent research.

ALTERNATIVE INTERPRETATIONS OF RETROGRADE AMNESIA

The findings of Duncan, Thompson, and others in the late 1940s and 1950s provided strong evidence that memory-storage processes are time dependent. However, it was apparent at that time that there might

*The articles included as readings in Part Two are denoted in this discussion by an asterisk.

be other interpretations of the data. The alternative explanations fall into two general categories. One thesis is that the treatments do affect memory processes, but that the graded amnesic effects are not due to effects of the treatment on time-dependent consolidation processes. The other is that the treatments which appear to produce retrograde amnesia do not in fact impair memory; rather, they produce other effects that are mistakenly regarded as evidence of memory impairment. Several hypotheses of this latter type have been proposed in recent years.

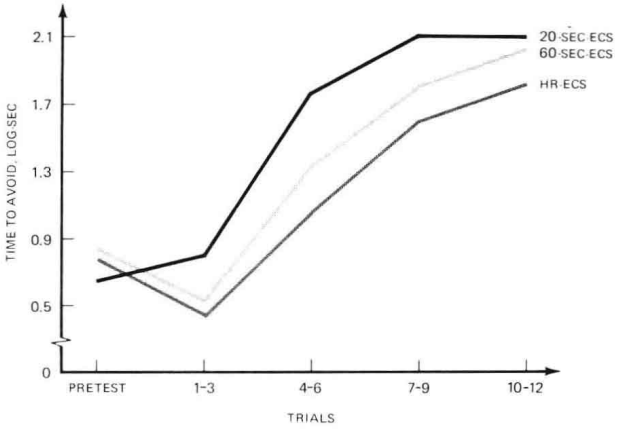
DEVELOPMENT OF FEAR

Many investigators [Stainbrook and Lowenbach, 1942; Siegal, 1943; Hayes, 1948; Friedman, 1953] observed signs of fear in rats that were given several ECS treatments. Duncan included controls for the possible punishing effects of ECS in his original study. He reported that learning was not significantly impaired in rats given intense electroshock stimulation of the hindlegs (which did not produce convulsions) shortly after each trial, but the possibility of punishing effects had not been completely ruled out. Coons and Miller [1960] argued that the poor learning observed when ECS treatment closely followed learning trials could also be explained in terms of an ECS-induced fear of the goal, with a resulting conflict that interfered with performance. The active-avoidance task used in Duncan's experiments clearly makes his results susceptible to such an interpretation, and the issue is a critical one. If the effects of ECS are due simply to punishment, they are irrelevant to the problem of memory storage; if punishment can be ruled out as a source of interference, then the findings of ECS studies are relevant for theories of memory consolidation.

The results of Coons and Miller's first experiment confirmed most of Duncan's findings but also indicated that rats given ECS soon after learning trials showed increased fear, as measured by their urination and defecation scores. A second experiment was designed to distinguish between the aversive and the amnesic effects of ECS. The animals were first trained in an active-avoidance task to avoid the shocked side of a grid, and then the conditions were reversed, with shock introduced on the previously "safe" side of the grid. Under these conditions the sooner ECS followed each learning trial, the *faster* was the rate of learning (see Figure 2).

The Coons and Miller study [1960] raised quite explicitly the first of many controversial issues concerning the consolidation theory of

FIGURE 2 ***Mean response latencies (log seconds) as a function of trial-ECS interval. Rats were first trained to avoid shock on one side of a grid. They were then shocked for entering the previously safe side. ECS was administered 20 sec, 60 sec, or 1 hr after each daily trial; each point is the average of three trials. Learning of the inhibitory response improved (as indicated by longer avoidance times) with decreasing intervals between each training trial and ECS.*** [*Coons and Miller, 1960*]



memory. In both Duncan's study and this one the animals were given one learning trial and one ECS a day for as many as 17 days. Because of the possibility that ECS might have aversive effects when it is administered repeatedly—a problem that had also been considered by Thompson and his colleagues—investigators began to employ one-trial learning tasks [Pearlman et al., 1959, 1961*] followed by a single ECS to minimize the cumulative effects of multiple convulsions. Many experimenters attempted to distinguish the effect of a single ECS from that of multiple ECS treatments [King, 1965, 1967; Madsen and McGaugh, 1961; McGaugh and Madsen, 1964; Hudspeth et al., 1964; Chorover and Schiller, 1965]. Hudspeth et al. [1964], for example, gave rats repeated trials in a step-down inhibitory-avoidance learning situation (often called passive avoidance). In this task the animals are punished for making a response, and retention is indicated by their reluctance to make the same response on a retention test. The rats received one learning trial and one ECS each day for eight days. As shown in Figure 3, although aversive effects of ECS appeared in later trials regardless of whether the ECS was proceeded by footshock, only amnesic effects resulted from a single convulsion. Chorover and Schiller [1965] obtained similar results. Furthermore, in a study with a discriminated inhibitory-avoidance task McGaugh and Madsen [1964] found only amnesic effects in early trials, whereas with repeated treatments the animals tended to avoid the place in a maze where ECS was administered.

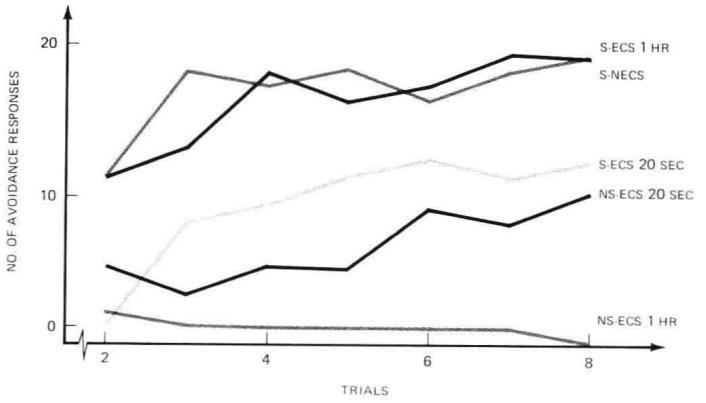


FIGURE 3 ***Avoidance responses made by rats on trials 2 to 8 in an inhibitory-avoidance task. The ECS groups were administered ECS either 20 sec or 1 hr after each daily trial. S indicates groups that were given footshock avoidance training. NS indicates no shock avoidance training [Hudspeth et al., 1964]***

If ECS modifies behavior simply because its effects are aversive, an ECS treatment given after each extinction trial should facilitate extinction; this is essentially what Coons and Miller [1960] reported. Several studies have shown, however, that ECS interferes with extinction of responses based on both appetitive and aversive learning [Madsen and Luttges, 1963; Gerbrandt and Thomson, 1964; Greenough and Schwitzgebel, 1966]. In an early study Friedman [1953] reported that rats developed no aversion to as many as eight ECS treatments administered twice a day for four days if the behavioral convulsions were prevented by ether anesthesia given prior to the ECS. Thus it appears likely that some correlate of the convulsion, and not simply the passage of current through the brain, is the basis of the aversive quality of ECS. Kesner et al. [1970] recently reported that repeated ECS treatments are not punishing if the current is delivered through cortical electrodes instead of ear-clip electrodes. They suggest that the rats' pinnae may become sensitive following repeated ECS administration via ear clips. This might account for the observation [Dawson and Pryor, 1965; McGaugh and Madsen, 1964] that rats given repeated ECS treatments via ear-clip electrodes avoided the place in a two-compartment box where the ECS was administered.

As these findings show, methods used to investigate a problem may very easily complicate it further. ECS treatments undoubtedly have diverse effects on brain function and behavior. According to the consolidation hypothesis one effect is interference with memory-storage processes. An alternative suggestion is that the amnesic effects